Oscillatory Activity in Parietal and Dorsolateral Prefrontal Cortex During Retention in Visual Short-Term Memory: Additive Effects of Spatial Attention and Memory Load

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Abstract: We used whole-head magnetoencephalography to study the representation of objects in visual short-term memory (VSTM) in the human brain. Subjects remembered the location and color of either two or four colored disks that were encoded from the left or right visual field (equal number of distractors in the other visual hemifield). The data were analyzed using time-frequency methods, which enabled us to discover a strong oscillatory activity in the 8–15 Hz band during the retention interval. The study of the alpha power variation revealed two types of responses, in different brain regions. The first was a decrease in alpha power in parietal cortex, contralateral to the stimuli, with no load effect. The second was an increase of alpha power in parietal and lateral prefrontal cortex, as memory load increased, but without interaction with the hemifield of the encoded stimuli. The absence of interaction between side of encoded stimuli and memory load suggests that these effects reflect distinct underlying mechanisms. A novel method to localize the neural generators of load-related oscillatory activity was devised, using cortically-constrained distributed source-localization methods. Some activations were found in the inferior intraparietal sulcus (IPS) and intraoccipital sulcus (IOS). Importantly, strong oscillatory activity was also found in dorsolateral prefrontal cortex (DLPFC). Alpha oscillatory activity in DLPFC was synchronized with the activity in parietal regions, suggesting that VSTM functions in the human brain may be implemented via a network that includes bilateral DLPFC and bilateral IOS/IPS as key nodes. *Hum Brain Mapp* 30:3378–3392, 2009. © 2009 Wiley-Liss, Inc.

Key words: visual short-term memory; MEG; induced activity; source localization; IMF; synchronization

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INTRODUCTION

In contrast to the high processing capacity of early vision, our capacity to retain information in visual short-term memory (VSTM) is limited to about three or four objects [Stevanovski and Jolicoeur, 2007; Vogel et al., 2001]. Klaver et al. [1999] used electroencephalography (EEG) to record brain activity during the encoding and retention of visual shapes. They found an event-related potential (ERP) that was more negative over the contralateral side of the brain (relative to the position of the stimuli) relative to the ipsilateral side and that was relatively sharply focused over posterior scalp regions. We will refer to this ERP as the sustained posterior contralateral negativity [SPCN; Jolicoeur et al., 2006a, 2006b, 2007]. Klaver et al. [1999] suggested that visual information was memorized by the brain hemisphere contralateral to the side of presentation.

Vogel and Machizawa [2004] used EEG recordings with a paradigm adapted from Luck and Vogel [1997] and Vogel et al. [2001], which consisted of retaining colored squares, encoded from either the left or right visual field. They also found an SPCN during the retention period for this task. Most interestingly, the amplitude of the SPCN response increased with the number of squares to be memorized, but only up to the capacity of VSTM (about 3 or 4 items). Moreover Vogel and Machizawa [2004] found a significant correlation between an individual's memory capacity [Cowan's coefficient K: Cowan, 2001] and the increase in amplitude of the SPCN between two and four items. These results provided powerful arguments linking the SPCN to brain mechanisms specifically related to VSTM [see also McCollough et al., 2007].

Importantly, the SPCN has also been observed in tasks that likely require encoding representations in VSTM but are not specifically designed to be memory tasks, such as in the attentional blink paradigm [Dell'Acqua et al., 2006; Jolicoeur et al., 2006a, 2006b; Robitaille and Jolicoeur, 2006] or the psychological refractory period paradigm [Brisson and Jolicoeur, 2007a,b,c]. Also, in a visual-letter memory task, Predovan et al. [2008] found that the amplitude of the SPCN was influenced by the lexical status of letter strings. All these results suggest that the SPCN will be a useful tool to understand the involvement of VSTM in a number of different situations.

With the use of functional magnetic resonance imaging (fMRI), Todd and Marois [2004] identified brain regions involved in the encoding and maintenance of information in VSTM (in a similar task to the one used by Vogel et al., 2004, with the main difference being that subjects encoded all disks present in the visual field). The bilateral intraparietal sulcus (IPS) and intraoccipital sulcus (IOS) cortex was isolated as the sole cerebral regions showing an increase of activation level as the numbers of items maintained in VSTM increased [see also Song et al., 2006; Xu and Chun, 2006].

Oscillatory activity during the maintenance of visual objects in VSTM has been studied by several authors. Thut et al. [2006], Wyart and Tallon-Baudry [2008], and Meden-

dorp et al., [2007] reported a contralateral (relative to the stimulus side) suppression of alpha power in the parietal regions or posterior sensors. The authors concluded that this suppression could be the consequence of the spatial attention or anticipation of the target. An increase in alpha activity (local synchronization) during the retention interval, in memory tasks, was found in a number of studies [Busch and Herrmann, 2003; Cooper et al., 2003; Jensen et al., 2002; Klimesch et al. 1999; Sauseng et al., 2005; Schack and Klimesch, 2002; see Klimesch et al., 2007, for a review]. Sustained oscillatory activity in the beta and gamma bands during the delay period of a match-to-sample task was also observed [Tallon-Baudry et al., 1999a,b]. The authors suggested that this activity could reflect the maintenance of visual object representations in VSTM. We note, however, that some previous work that studied effects of memory load used variants of the Sternberg task or paradigm, typically with letter or digit stimuli that were presented sequentially during the encoding phase of each trial [Klimesch et al., 1999; Jensen et al., 2002; Schack and Klimesch, 2002]. In our paradigm (see below), all the stimuli were presented simultaneously, briefly, and were colored disk. The simultaneous and very brief presentation, the brief retention period, and the use of nonverbal stimuli make it unlikely that our stimuli were recoded into verbal memory, which could happen when digits or letters are presented sequentially [Vogel et al., 2001]. Furthermore, the load manipulation (number of colored disks) and the attention manipulation (encoding from left or right visual field) were performed simultaneously and orthogonally in our design, which was not the case for others studies of VSTM.

In the present study we combined the methods used by Vogel and Machizawa [2004] with the time-frequency analysis techniques to have a better understanding of the oscillatory activity produced during the retention of information in VSTM (during the occurrence of the SPCN). We isolated the brain regions that produced this activity. Brain activity was recorded using whole-head high-density magnetoencephalography (MEG) and EEG electrodes at sites selected to measure the SPCN concurrently.

METHODS

Subjects and Recordings

Twenty-seven adult subjects with normal vision who reported no neurological or psychiatric problems participated in the experiment, after giving informed consent, and received 25\$ Canadian upon completion of the experiment. Subjects sat upright in a chair and looked at a screen on which the visual stimuli were back-projected by a liquid-crystal data projector. Magnetic brain activity was recorded while subjects performed a VSTM task (described in the next section) using a whole-head CTF-VSM 275 sensors MEG system. The sampling rate was 240 Hz. Vertical and horizontal electro-oculogram and electro-cardiogram were also recorded (HEOG-VEOG-ECG), as well as

electroencephalographic activity using electrodes at sites PO7 and PO8, referenced to average mastoids. Analyses of event-related magnetic fields (ERMFs) and ERPs, reported elsewhere (Robitaille et al., 2008) confirmed the presence of an SPCN in the EEG and of the magnetic equivalent in the ERMFs. For five subjects, high-quality anatomical MRI images were obtained on a 3T MRI Siemens Trio scanner.

Experimental Design

The paradigm was adapted from Vogel and Machizawa [2004] and is illustrated in Figure 1. Subjects had to press a button to initiate each trial. A central fixation cross appeared and remained on the screen during the entire duration of the trial. Two greater-than or less-than signs (in the form of arrow heads, one above and one below the fixation cross) appeared between 300 and 1000 ms after the start of the trial, and remained on the screen for 400 ms, pointing either to the left or right. The arrow heads cued the subject to encode the objects displayed on the indicated side (and to ignore objects in the other hemifield). From 400 to 1100 ms after the offset of the arrow cues, either 2 or 4 colored disks were presented on each side of the fixation point for a duration of 200 ms. The color and the position of the disk within the hemifield was randomly selected (without replacement) on each trial. The screen was then blank (except for the fixation cross) for a retention interval of 1200 ms, following which a

probe disk was presented at the location of one of the encoded disks (along with a distractor disk in the other visual field). The probe and distractor remained in view until the subject's response. The task was to decide whether the color of the probe disk was the same or different as the one shown at encoding. Subject pressed a button (with their index finger) if the probe disk was identical and another button (with their middle finger) if the probe disk was different. A feedback symbol (a plus sign for a correct response, or a minus sign for an incorrect response) then appeared in place of the fixation cross, and remained on the screen until the next trial. There were 192 trials in each of the 4 conditions defined as two encoding sides (left vs. right), and two memory loads (2 vs. 4 colored disks). These 768 trials were presented in blocks of 64 trials. The randomization process created 8 sequences of 8 trials for every block. Each sequence of 8 trials consisted of 2 trials in each condition (encoding side [2], by load [2]), one showing a difference at the test and one not showing a difference at the test. Subjects could not anticipate the conditions for the forthcoming trial and they could not determine which response they would make until the probe stimulus was presented. Response times in this task were usually longer than 600 ms, and thus activity associated with motor preparation or execution could not contaminate the recorded activity during the retention interval [Cheyne et al., 2006].

The colored disks had a diameter of 1.44° and they were presented within two $5.28^\circ \times 7.21^\circ$ rectangular regions that were centered 4.81° to the left and the right of the central fixation cross on a gray background. Each disk was selected at random from a set of eight highly discriminable colors, and a given color could not appear more than twice in any given display (once on each side). Disk position was randomized over each trial, with the constraint that the distance between disks within a hemifield was at least 1.92° (center to center).

Figure 1.
Sequence of events in each trial of the experiment.

MEG Analysis

Third-order gradient noise reduction (computed with CTF software) was applied to all MEG signals that were then segmented (-200 to $+1,750$ ms) and baseline-corrected based on the mean activity during the 200 ms before the onset of the memory array. Trials with eye blinks or eye movements were removed by visual inspection of the VEOG and HEOG traces. Trials with large artifacts (e.g., head movement, or external noise) were also removed. Signals were not filtered beyond the low-pass hardware antialiasing filter imposed during the original recording. In our case, the filter was a 60 Hz low pass filter with a slope of 30 db per octave.

Time Frequency Analysis

We performed time-frequency analyses using the software *fast_tf* (<http://cogimage.dsi.cnrs.fr/logiciels/index.htm>)

(LENA-CNRS-UPR640, Cognitive Neuroscience and Cerebral imaging Laboratory). This analysis first computes the convolution of a complex wavelet $w(t,f)$ with the signal $s(t)$ [described in Tallon-Baudry et al., 1997]:

$$W(t,f) = w(t,f) \otimes s(t),$$

from which we obtain the time-frequency energy

$$E(t,f) = |W(t,f)|^2.$$

For our analysis, we used Morlet's complex wavelets. Morlet wavelets have a Gaussian shape both in the time domain (SD σ_t) and in the frequency domain (SD σ_f) around the central frequency f :

$$w(t,f) = (\sigma_t \sqrt{\pi})^{1/2} \exp(-t^2/2\sigma_t^2) \exp(2i\pi ft).$$

We fixed the ratio $\frac{f}{\sigma_f}$ to 10. We also computed z-score maps. For trial i , the z-score at time t and frequency f is:

$$\text{z-score}_i(t,f) = (E_i(t,f) - m_i)/\sigma_i,$$

where m_i and σ_i are the mean and the standard deviation of the power at that frequency, during the baseline period. Wavelet transforms were computed frequency by frequency, trial by trial, based on a prememory stimulus period of 200 ms. The final mean z-score(t,f) map was the mean of $\text{z-score}_i(t,f)$ over all the trials.

The phase locking of oscillatory activity in the time-frequency domain was also evaluated. The normalized complex time-frequency coefficient $W(t,f)/|W(t,f)|$ for each single trial was calculated for all points in the time-frequency maps prior to averaging across trials, leading to a complex value describing the phase distribution of the time-frequency region centered on t and f . The modulus of this complex value, ranging from zero (nonphase-locked activity) to one (strictly phase-locked activity), is called the phase-locking factor. Average time-frequency maps (power, z-score, and phase locking factor) (over trials) were calculated for each MEG sensor, each condition, for each subject. Grand average time-frequency maps were also computed by averaging over subjects.

Localization Analysis of Oscillatory Activity

The Maximun of Entropy on the Mean method, MEM [Amblard et al., 2004, Grova et al., 2006] was used to perform source localization of the time-varying MEG signals. This method is a cortically-constrained source-localization approach. The cortical surface (we used the white matter/gray matter boundary) was segmented from each anatomical MRI scan using BrainVisa [Mangin et al., 1995a,b; Rivier et al., 2002] software (http://brainvisa.info/index_f.html). Approximately 4000 sources, oriented perpendicularly relative to the cortical surface, were distrib-

uted roughly evenly over the entire cortical surface, and these local sources were used in distributed source localization analyses.

Source localizations were performed based on the spatial distribution of induced oscillatory activity. The mathematical basis of distributed source-localization methods is to find an inverse of the forward problem (determining the distribution of activity at the sensor level from a known source at a given point in the brain). Source localization cannot be done from the energy as mentioned before (power, which is a squared quantity). This problem was solved by devising a novel method to localize oscillatory activity while remaining in the original (linear) signal space.

We will refer to the spatial distribution of induced oscillatory activity as the induced magnetic field (IMF). The IMF was calculated by performing the following steps (cf. Fig. 1 in Supporting Information). A window in time and frequency was selected (width in time: Δt ; width in frequency: Δf) in the time-frequency map where induced activity was found (step 1). The mean of the power during this window of interest was estimated for each MEG sensor. A spatial map of this mean power was computed. The sensor with the peak power within each focal region was selected (step 2). This sensor was called the event-alignment sensor (note that we also performed similar calculations using other event-alignment sensors, and found remarkable reproducibility of the results across different choices of event-alignment sensors). For this sensor, for each trial, the time point for which the time signal (original sensor signal filtered in Δf) reached a positive peak within the time window was marked (step 3). Then, the IMF was computed as an ERMF (on the unfiltered signal) but using the time at which maximum peak (which is indeed the point of maximal power) had been reached as the event of interest (step 4). Generators of induced activity were estimated using source localization methods on the newly computed IMF (step 5).

Group Analysis

To perform a group analysis of the localizations performed on a subject-wise basis, the following procedure was used:

1. First we performed MEM source localization on the cortical surface, for each of the four experimental conditions (2L, 2R, 4L, 4R), for each subject.
2. Next, we calculated difference maps for the effect of memory load, for each subject, for each side (i.e., 4L-2L and 4R-2R) from the localisation maps computed in step 1.
3. Difference maps (calculated on the cortical surface) were interpolated in the volume MRI image of each subject.
4. All the images for each subject were normalized to a common template in Talairach space [Talairach and Tournoux, 1988] with SPM2 tools.

5. Each of the normalized contrast images was smoothed using a gaussian filter with a 12 mm FWHM).
6. All the images were averaged.

We then computed a statistical map for the group image using the following procedure:

1. We evaluated the H_0 hypothesis group map (null hypothesis, i.e. no difference between the load 2 and load 4 conditions) by calculating a group image (see previously) with a random permutation of the four conditions for each subject before the calculation of the difference maps (step 2 of the localization procedure). We calculated 1,000 H_0 group maps, in order to estimate the average and standard deviation under the Null hypothesis, H_0 .
2. We compared the true group image (based on the original difference maps, no permutation) with the 1,000 permuted group images.
3. A threshold ($P < 0.05$) mask was built by keeping only the voxels in the true group image that had an amplitude that was in the top 5% (top 50) of the 1,000 maps computed under the Null Hypothesis). This voxel threshold was then used to identify which voxels from the actual group contrast map (no permutation) showed a significantly greater load effect than what would be expected by chance ($P < 0.05$).

Regions with strong local activations were identified using the atlas of Talairach and Tournoux [1988], the atlas of Duvernoy [1999], and an automatic algorithm implemented in the BrainVisa software package [Rivière et al., 2002].

RESULTS

Subject Selection

Data from 4 subjects were rejected because they moved their eyes in the direction of the stimuli to be encoded on a high proportion of trials [based on the HEOG results; Lins, 1993]. Data from 3 subjects were lost because of breathing artifacts. Data from 4 subjects contained MEG and/or EEG signals with noise levels that precluded meaningful analysis. The analyses were based on data from the 16 remaining subjects (11 females, aged between 19 and 24 years, average 22).

The analyses were focused in a time window that ensured that the observed brain activity would reflect, primarily, retention in VSTM, namely in a period that started at 600 ms after the onset of the memory array and ended at the time of presentation of the memory probe (1,400 ms), and thus we excluded early visual evoked responses. The SPCN, ERPs, and ERFs were examined and confirmed that this component was present in the EEG and MEG results. Detailed descriptions and interpretations of these results can be found in Robitaille et al. (2008), see

Figure 2.

Event-related magnetic fields corresponding to the SPCM. Maps of the interaction between load and side, calculated as $(4L-2L)$ minus $(4R-2R)$, for the retention period (400–1400 ms). Sensors with a significant interaction of Load and Side are shown in white. The waveforms for these sensors, for each of the four conditions, indicate a higher activation for the high-load, contra-lateral trials. For details, see Robitaille et al., [2008].

Figure 2. For present purposes, it is sufficient to note that clearcut evidence was found for an SPCM (the magnetic equivalent of the SPCN) that increased in amplitude as memory set size increased, which confirmed that the experimental task engaged VSTM and reproduced expected event-related effects. This enabled us to focus on oscillatory activity that has never been examined in this paradigm, which was the objective of the present study.

Time-Frequency Analysis

Time-frequency maps for each subject showed activity between 3 and 30 Hz, but the most stable and powerful activity during the retention period was in the alpha band (8–15 Hz). In Figure 3, top left panel, the grand average time-frequency results (z-score of induced power, relative to baseline) is shown for a sensor over right parietal cortex, for trials in the load 2R condition (two items encoded from right visual field). The top right panel shows induced power for the load 4R condition for the same sensor. The bottom left panel shows the difference of the 4R and 2R maps. Finally, the bottom right panel shows the phase locking factor of the induced activity in the 4R condition at each time and frequency. The mean phase locking factor was equal to 0.0974 during the retention interval (t: 600–1,400 ms; f: 8–15 Hz) which is about five time smaller than the mean phase locking factor for the evoked-responses (t: 170, f: 8–15 Hz). This indicates that induced activity evident in the other three panels was not strongly timelocked with the stimulus. Despite this, one can sometimes see hints of residual oscillations at about 10 Hz in the event-related averages [Fig. 2, Vogel and Machizawa, 2004, Fig. 1].

Figure 3.

Top panels: Grand Average time-frequency results (z-score of induced power, relative to baseline) for a sensor over right parietal cortex. Left: the load 2R condition, right: the load 4R condition for the same sensor. The bottom left panel shows the difference of the 4R and 2R maps. Bottom right panel: phase locking factor of this activity at each time and frequency. X-axis: time in second. Y-axis: frequencies in Hertz.

The spatial distributions of induced activity were first analyzed by computing a grand average over all the subjects. The mean power, for each sensor and for each condition (2L, 2R, 4L, 4R), in a window of 600–1,400 ms after the onset of the memory array for the frequency band of 8–15 Hz was calculated subject by subject and averaged across subjects. Finally, these values were projected on a 2D surface of the MEG helmet (Fieldtrip software (<http://www.ru.nl/fcdonders/fieldtrip/>), F.C. Donders Centre, Radboud University Nijmegen, the Netherlands), as shown in Figure 4. For all the conditions (2L, 2R, 4L, 4R), stronger activity was visible for the sensors situated over the occipital and parietal regions, and with an extension over pre-frontal-lateral regions. The maps of the differences 2L-2R and 4L-4R (right column) showed a positive difference for

the left hemisphere (indicating more oscillatory power for the encode-left trials than for the encode-right trials) and a negative difference for the right hemisphere (indicating more oscillatory power for the encode-right trials than for the encode-left trials). In other words, a contralateral (relative to the encoded stimuli) parietal decrease was found in both encoding conditions (encode left, encode right). There was an absence of modulation by encoding side for the frontal areas for these maps. In contrast, the differences 4L-2L and 4R-2R (bottom row) showed complex modulations in both parietal and over anterior central lateral regions and especially in the left hemisphere.

To have a better understanding of the statistical robustness of the signal variations described above, several ANOVAs were performed. First, an ANOVA was

Figure 4.

All the maps were constructed as follows: The mean power, for each sensor and for each condition (2L, 2R, 4L, 4R), in a window of 600–1400 ms after the onset of the memory array for the frequency band of 8–15 Hz was calculated subject by subject and grand averaged over subjects. Finally, these values were projected on a 2D surface of the MEG helmet. Other maps were calculated by taking means or differences of the maps of the four conditions (2L, 2R, 4L, 4R). The black dots on the 4L + 2L + 4R + 2R map show sensor locations selected by a thresholding at 40% of the maximum of the map. The black dots in the 2L-2R, 4L-4R, and 2L-2R + 4L-4R maps were selected in the 2L-2R + 4L-4R map (maximum intensity selection) to have 16 contiguous sensors in each hemisphere. The black dots in the 4L-2L, 4R-2R, and 4L-2L + 4R-2R maps were selected on the 4L-2L + 4R-2R map (maximum intensity selection) to have two pairs of seven sensors in each hemisphere, one more anterior and one more posterior.

performed on two sets (left and right hemisphere) of 57 contiguous sensors (see Fig. 4, top). The selection of the sensors was based on the 2D map of power distribution for the overall average (labeled 4L + 2L + 4R + 2R in Fig. 4). The sensors with a signal superior or equal to 40% of the maximum of the intensity were selected in both hemispheres. An ANOVA was computed over all the subjects on the mean oscillatory power signal (time window 600–1,400 ms after the onset of the memory array, frequency

band: 8–15 Hz) with the following factors: hemifield of the encoded stimulus (right or left), hemisphere of the sensor (right or left), and memory load (2 or 4). We found higher power when subjects were encoding stimuli from the right hemifield (Mean = $7.81\text{E-}25$ T^2 , Std Dev. $7.13\text{E-}25$) than when they were encoding from the left hemifield (Mean = $7.6415\text{E-}25$ T^2 , Std Dev. = $7.1052\text{E-}25$), $F_{(1,15)} = 5.85$, MSE = $9\text{E-}50$, $P < 0.0289$. Oscillatory power was larger over the left hemisphere (Mean = $9.18\text{E-}25$ T^2 , Std Dev. $8.51\text{E-}25$)

TABLE I. Mean and standard deviation of the oscillatory power for the factors “hemisphere of the sensors” (left/right) and “hemifield of encoding” (left/right)

Encoding hemifield	Hemisphere of the sensors	Mean	Std Dev.
L	L	9.24E-25	8.52E-25
L	R	6.04E-25	4.83E-25
R	L	9.12E-25	8.51E-25
R	R	6.51E-25	5.09E-25

Mean and standard deviation of the oscillatory power (in Tesla^2) during the retention period (600–1400 ms) for sensors having overall highest power (highlight in black on the top-most topographic map of Figure 4), for the factors “hemisphere of the sensors” (left/right) and “hemifield of encoding” (left/right).

than over the right hemisphere (Mean = $6.27\text{E-}25$ T^2 , Std Dev. $4.96\text{E-}25$), $F_{(1,15)} = 12.26$, $\text{MSE} = 1.2\text{E-}47$, $P < 0.0033$. Oscillatory power increased with increasing memory load (Mean = $7.52\text{E-}25$ T^2 , Std Dev. $6.94\text{E-}25$ for load 2; Mean = $7.93\text{E-}25$ T^2 , Std Dev. $7.28\text{E-}25$ for load 4), $F_{(1,15)} = 8.12$, $\text{MSE} = 3.7\text{E-}49$, $P < 0.0123$. There was a significant interaction between encoding hemifield and sensor hemisphere, $F_{(1,15)} = 5.85$, $\text{MSE} = 2.7\text{E-}49$, $P < 0.0289$, reflecting a decrease in power in the hemisphere contralateral to the encoding hemifield. There was also an interaction between memory load and hemisphere reflecting a larger effect of memory load over the left hemisphere (a larger increase in power from load 2 to load 4) than over the right hemisphere, $F_{(1,15)} = 5.47$, $\text{MSE} = 1.53\text{E-}49$, $P < 0.0337$. The relevant means can be found in Tables I and II. There was no interaction between encoding hemifield and memory load: $F_{(1,15)} = 0.65$, $\text{MSE} = 9.2\text{E-}49$, $P > 0.43$.

The additivity of effects of load (a bilateral increase in alpha power) and the effect of encoding side (a contralateral decrease in alpha power) suggests a dissociation between these two phenomena. To have a better understanding of the effect of encoding side we identified a subset of two groups of 16 contiguous sensors selected where

TABLE II. Mean and standard deviation of the oscillatory power for the factors “hemisphere of the sensors” (left/right) and “load” (2/4)

Hemisphere of the sensors	Load	Mean	Std Dev.
L	2	8.87E-25	8.33E-25
L	4	9.49E-25	8.69E-25
R	2	6.18E-25	4.84E-25
R	4	6.37E-25	5.08E-25

Mean and standard deviation of the oscillatory power (in Tesla^2) during the retention period (600–1400 ms) for sensors having overall highest power (highlighted in black on the top-most topographic map of Fig. 4), for the factors “hemisphere of the sensors” (left/right) and “load” (2/4).

we found maximum signal strength in the 2D map for the condition 2L-2R + 4L-4R, see Figure 4. An ANOVA was computed over all the subjects on the mean oscillatory power signal with the following within-subjects factors: hemifield of encoding (right or left), hemisphere of the sensor (right or left), and memory load (2 or 4). The statistical test confirmed the statistical significance of the contralateral decrease of the signal relative to the hemifield of encoding in this sub groups of sensors (main effect hemifield of encoding: $F_{(1,15)} = 5.87$, $\text{MSE} = 5.65\text{E-}50$, $P < 0.0287$; hemisphere of the sensors: $F_{(1,15)} = 16.24$, $\text{MSE} = 5.41\text{E-}48$, $P < 0.012$; and the interaction between hemifield of encoding and hemisphere of the sensors: $F_{(1,15)} = 11.82$, $\text{MSE} = 1.2\text{E-}49$, $P < 0.0038$ (Table III). No load effect was found and there was no interaction between load and any other factor.

To have a better understanding of the memory load effect, groups of sensors were selected on the 2D map for the condition 4L-2L + 4R-2R, see Figure 4. As we said above, the load map showed complex modification in both parietal and anterior central lateral regions and especially in the left hemisphere. Four subsets (2 pairs) of 7 sensors were selected in both parietal (seven contiguous sensors, left and right) and temporo-frontal regions (seven contiguous sensors, left and right). An ANOVA was computed over all the subjects on the mean oscillatory power signal with the following factors: hemifield of encoding (right or left), hemisphere of the sensor (right or left), memory load (2 or 4), and position (anterior or posterior). Oscillatory power was lower at load 2 (Mean = $8.6325\text{E-}25$ T^2 Std Dev. = $7.5792\text{E-}25$) than at load 4 (Mean = $9.2496\text{E-}25$ T^2 Std Dev. = $8.2855\text{E-}25$), $F_{(1,15)} = 11.11$, $\text{MSE} = 1.5\text{E-}48$, $P < 0.0046$. The load effect was also modulated by the hemisphere of the sensors created by a larger signal in the left hemisphere than the right hemisphere, $F_{(1,15)} = 6.38$, $\text{MSE} = 7.25\text{E-}50$, $P < 0.0234$. The means can be found in Table IV. Oscillatory power was also higher when subjects

TABLE III. Mean and standard deviation of the oscillatory power for the factors “hemisphere of the sensors” (left/right) and “hemifield of encoding” (left/right)

Encoding hemifield	Hemisphere of the sensors	Mean	Std Dev.
L	L	1.11E-24	1.01E-24
L	R	6.37E-25	5.10E-25
R	L	1.08E-24	9.87E-25
R	R	7.17E-25	5.46E-25

Mean and standard deviation of the oscillatory power (in Tesla^2) during the retention period (600–1400 ms) for sensors having highest power in the encode-left minus encode-right maps (highlighted in black on the right column topographic maps of Fig. 4), for the factors “hemisphere of the sensors” (left/right) and “hemifield of encoding” (left/right).

TABLE IV. Mean and standard deviation of the oscillatory power for the factor “hemisphere of the sensors” (left/right) and “load” (2/4)

Hemisphere of the sensors	Load	Mean	Std Dev.
L	2	1.05E-24	8.43E-25
L	4	1.15E-24	9.21E-25
R	2	6.75E-25	4.71E-25
R	4	7.04E-25	5.08E-25

Mean and standard deviation of the oscillatory power (in Tesla^2) during the retention period (600–1400 ms) for sensors having highest power in the load 4 minus load 2 maps (highlight in black on the bottom-most topomap of Figure 4), for the factor “hemisphere of the sensors” (left/right) and “load” (2/4).

encoded from the right hemifield (Mean = $9.0158\text{E-}25\ T^2$, Std Dev. = $7.91\text{E-}25$) relative to power when encoding from the left hemifield (Mean = $8.8663\text{E-}25\ T^2$, Std Dev. $7.98\text{E-}25$), $F_{(1,15)} = 4.66$, $\text{MSE} = 2.14\text{E-}50$, $P < .0476$. Power was, overall, higher over the left hemisphere (Mean = $1.0986\text{E-}24\ T^2$, Std Dev. $9.47\text{E-}25$) than over the right hemisphere (Mean = $6.8956\text{E-}25\ T^2$, Std Dev. = $5.31\text{E-}25$), $F_{(1,15)} = 15.61$, $\text{MSE} = 4.8\text{E-}48$, $P < 0.0014$. No other main effects nor interactions were found, and in particular for the position (anterior or posterior) variable (despite what might be suggested by the difference map in Fig. 4).

Overall, the statistical analyses demonstrated several things. First, we found consistent effects of memory load (increase in power with increase in load), of encoding side (a decrease in power over the hemisphere contralateral to the encoding side), and an overall left-hemisphere dominance (more power in left hemisphere, overall), during the retention interval. Importantly, effects of load and encoding side never entered into a significant interaction, suggesting that these two effects likely reflect different, dissociable, underlying mechanisms.

Distributed Source Localization of Oscillatory Activity

The data of the five subjects for whom we had an anatomical MRI scan were used to localize the sources that produced an increase in the oscillatory power in the retention period when we increased memory load from 2 to 4. ANOVAs like the ones described in the foregoing section (for the entire group of subjects) were performed on the data from this subgroup of five subjects. With some rare exceptions, the same patterns of results were found, suggesting that this subset of subjects was representative of the larger group.

We were particularly interested in the effects of memory load and the following analyses concentrated on localizing neural sources contributing to this effect. The analyses were executed in three steps. Firstly, the cortical surfaces

for each subject were extracted on the basis of the anatomical MRI scan. Secondly the IMF (induced magnetic field, using the procedure described previously, with a frequency band of 8–15 Hz and a time window of 600–1400 ms) was computed for each condition (2L, 4L, 2R, 4R). Thirdly the solutions to the inverse problem were computed using cortically-constrained source-localization method for each condition (2L, 4L, 2R, 4R)

An interesting property of the method we used to compute IMFs is that in addition to allowing us to localize induced oscillatory activity, it also revealed synchronized activity at distant sensor locations. Recall that, in order to remain in a linear signal space, a new event-related magnetic field was computed based on the time at which oscillations reached a maximum power for one particular sensor (which we called the event-alignment sensor). The signals from all other sensors were also realigned in time relative to the event-alignment sensor. We expected that sensors nearby the event-alignment sensor would show correlated (synchronized) activity, given that underlying brain activity would project to more than one sensor. Distant sensors, however, were not expected to show a net signal following the temporal realignment procedure, unless their activity is both in the same frequency range (or a harmonic component) and phase-locked with the event-alignment sensor. In four of five subjects we found strongly synchronized activity in the parietal area of the opposite hemisphere, and in all five subjects, we also found synchronized bilateral frontal activations. These patterns of results were found regardless of which sensor was used as the event-alignment sensor (over the parietal region), suggesting that the degree of synchrony (phase locking) was high, and that the results were not due to fortuitous choices at various steps in the analysis. To quantify the synchrony, we calculated phase synchrony maps for all the subject and all the conditions over the retention period (600–1400 ms) and for the frequencies between 8 and 15 Hz [Le Van Quyen et al. 2001; Nolte et al. 2004]. Synchrony maps were calculated for two seed sensors (MLP33, MRP33) situated over left and right parietal region, indicating the phase-coherence between these sensors and all other sensors.

Figure 5 shows the average phase synchrony map between sensor MRP33 (right parietal) and all the sensors (top), and phase synchrony map between sensor MLP33 (left parietal) and all the sensors (bottom) (calculated at 10 Hz only, but the patterns were the same as for an average from 8 to 15 Hz). In the supplementary materials, Figure 2 shows the maps for each condition for each subject that were averaged to produce the maps in Figure 5. The constellation of peaks and troughs in the maps were very stable across subjects and condition and are well summarized in the average maps shown in Figure 5. The very high values of synchrony between the seed sensors and their respective neighbors were expected because neighboring sensors likely measure common underlying neural activity. The more interesting information was the extremum of

Figure 5.

Mean phase synchrony maps over the retention period (600–1400 ms), over the 16 subjects, over all the conditions and for the frequency 10 Hz. Phase synchrony map between the sensors MRP33 and all the sensors (top), and the phase synchrony map between the sensors MLP33 and all the sensors (bottom). The black dots referred to the positions of the sensors showing local the maxima of synchrony. For the MRP33 map these sensors were MLF53 and MLT25, and for the MLP33 maps these sensors were MRF52 and MRT24.

synchrony far away from the seed sensors suggesting a possible neural binding of two distinct regions generated by large-scale integration of neural activity (for review: Varela et al. [2001], Engel et al. [2001]). Two distinct regions are areas separated by one region with null or low synchrony. The two maps suggest synchronies between the parietal regions (left and right) and parietal regions and contralateral frontal regions. The black dots in Figure 5 indicate the positions of the sensors with local maxima of synchrony. For the MRP33 map, these sensors were MLF53 (Mean = 0.58, Std Dev. = 0.086) and MLT25 (Mean = 0.50, Std Dev. = 0.1576), and for the MLP33 map, these

sensors were MRF52 (Mean = 0.67, Std Dev. = 0.059) and MRT24 (Mean = 0.56, Std Dev. = 0.1204).

Group Image of Distributed Source Localization of Oscillatory Activity

For the group analysis we were particularly interested in the effects of memory load. To perform the calculation, the IMF for the conditions 4L, 4R, 2L, 2R was computed for all subjects (for whom we had a structural MRI scan). A parietal contralateral sensor relative to the stimuli (right parietal sensor for the 4L and 2L conditions, and the reverse for 4R and 2R conditions) was used as the event-alignment sensor. Each of these IMF was submitted to MEM source localization. And then we calculated the difference maps 4L-2L and 4R-2R. As expected following the absence of interaction between load and hemifield of encoding, these two maps showed similar patterns, so they were averaged prior to averaging across subjects. Figure 6 shows the results of the group analysis and the statistical group analysis projected onto a brain template (template: Collin's N27 brain, white matter surface, Montreal Neurological Institute) using SUMA and AFNI [Cox et al., 1996]. Table V summarizes the regions with an increase in power at load 4 relative to load 2 with a significance level of $P < 0.05$. The region number 14 (Right Superior Frontal Gyrus, BA 8/9, right DLPFC) appeared only at $P < 0.08$.

DISCUSSION

The goal of the present study was to characterize the oscillatory activity produced during retention of information in VSTM and to localize the brain regions that produced this activity. In time-frequency analyses of sensor data from whole-head high density MEG recordings of brain activity during the execution of a VSTM task, we found a significant increase in oscillatory power in the 8–15 Hz band, during the retention interval. Statistical analysis demonstrated that sensors over parietal and lateral prefrontal regions of the brain recorded a significant increase in α -band power when memory load increased. This increase in α -band power with increasing memory load suggests that the oscillations may reflect activity of neurons that are somehow involved in the neural circuitry that maintains active representations in VSTM. Interestingly, given the work on the SPCN in event-related work [e.g., Jolicœur et al., 2008], the load-related effect on α -band power did not interact with the effect of hemifield of encoding. More research will be required to clarify the relationship between load effects on oscillatory power and load effects in event-related measures. The presence of clear-cut laterality effects in event-related measures and their absence in induced oscillatory measures suggests possible dissociations of underlying mechanisms.

Figure 6.

Shows the result of the group analysis projected onto a brain template (template: Collin's N27 brain, white matter, Montreal Neurological Institute) using SUMA and AFNI [Cox, 1996]. See Table V for the regions with an increase in power at load 4 relative to load 2 with a significance level of $P < 0.05$.

Using novel methods we were able to isolate the probable neural loci of the load-related oscillatory effects. The activations we found in inferior IPS and IOS are consistent with those previously reported by Todd and Marois [2004]. Using fMRI they found increases in BOLD signal strength with increasing memory load in IOS and IPS up to the capacity of VSTM. The convergence between our methods and MEG activations (time window 600–1400 ms after the onset of the memory array, frequency band: 8–15 Hz) and those found using fMRI provides an interesting point of convergence across rather different methodologies and suggests that further work designed to compare them would be fruitful.

We underline that the activations found in the parietal region (see Fig. 4; condition 4–2) are very close to those found by Portin and Hari (Fig. 2, 1999, see also Hari and Salmelin, 1997). Portin and Hari [1999], with a single source localization method, found sources in the parieto-occipital sulcus (POS). The authors argued that the human POS region corresponds to the macaque V6 complex, in which cells have receptive fields remaining anchored to the same absolute position in space. However, the authors also reported that the limits of the V6 complex in human are not well known. With a distributed source localization method we found activations in posterior IPS/IOS close to the POS. Maybe these activations are also in the V6 human complex and the activated cells are assumed to construct a head-centered cortical representation of visual space, which could be used to retain the spatial locations of the colored disks in our task.

In addition, activations in areas BA10/46 BA46/9 and BA9 BA8/9 were detected. Those areas are part of the DLPFC. This activity was synchronized with oscillations in

IOS/IPS. Todd and Marois [2004] did not detect the DLPFC in their fMRI study. These researchers used a multiple regression analysis in which they identified voxels with BOLD response profiles that varied across memory

TABLE V. Regions with an increase in power at load 4 relative to load 2 with a significance level of $P < 0.05$.

S. no	Regions	Talairach coordinates
1	Left inferior IPS	–34, –59, 52
2	Left middle occipital gyrus	–16, –84, 13
3	Right inferior IPS/IOS	25, –71, 26
4	Right posterior inferior temporal sulcus	47, –69, 5
5	Right Superior temporal sulcus, BA 21	42, –31, 4
6	Right middle temporal gyrus, Inferior temporal sulcus, BA21	56, –41, –2
7	Left post central gyrus	–47, –25, 53
8	Left superior frontal gyrus/sulcus, BA 8/9, DLPFC	–24, 37, 40
9	Left middle frontal gyrus, BA9/46, DLPFC	–42, 18, 32
10	Left middle frontal gyrus, BA10/46, DLPFC	–35, 41, 11
11	Left superior temporal sulcus, BA 21/38	–46, 12, –22
12	Left and right medial temporal gyrus, BA6	–6, –5, 67; 5, –5, 61
13	Right postcentral gyrus	39, –28, 59
14*	Right superior frontal gyrus, BA8/9, DLPFC	10, 40, 43

*Appeared only at $P < 0.08$ at the localization.

set size with the same function as the observed capacity of VSTM. This clever method allowed them to see portions of the memory network that were load-sensitive with a load-saturation level that followed memory capacity, while ignoring other brain regions that could participate in the network but without load saturation, as it could be the case for DLPFC. Given the range of loads used in the present work, we could not verify whether the regions we identified would saturate at the maximum capacity of VSTM, and this remains an important issue for future research.

A widely accepted theory regarding the function of the prefrontal cortex is that it serves as a store of short-term memory representations [Baddeley, 1986; Baker et al., 1996] and that the DLPFC comprises a plausible anatomical substrate for central executive systems. Cohen et al. [1997], and Courtney et al. [1997] have also shown implication of the DLPFC in short-term memory. In a study to dissociate the role of the DLPFC and anterior cingulate cortex in cognitive control, McDonald et al. [2000] concluded that cognitive control is a dynamic process implemented in the brain by a distributed network that involves closely interacting, but nevertheless anatomically dissociable, components: the DLPFC would implement control and the anterior cingulate would monitor performance and signal when adjustments in control are needed. Several studies that have shown the recruitment of the DLPFC by several complex tasks, supported the hypothesis that the DLPFC serve as a central executive system: DLPFC activity has been linked to spatial short-term memory [Mottaghy et al., 2002; Nyffeler et al., 2002, 2004], to VSTM [Mottaghy et al., 2002], to verbal short-term memory [Mottaghy et al., 2003; Mull and Seyal, 2001], but also to a random selection task that did not require working memory [Hadland et al., 2001] and even to long-term episodic memory [Epstein et al., 2002; Rami et al., 2003].

In our study, DLPFC may be a part of a distributed network that involves also parieto-occipital regions. All these regions are likely closely interacting with each other in a dynamic process implemented in the brain for the maintenance of objects in VSTM. The parietal regions, that have activity levels that increase with memory load and saturate once memory span has been reached could be the actual loci of storage of memory representations (or of pointers to such representations), and the DLPFC could implement control structures required to maintain information in an active state and enable comparisons between memory and probe stimuli. This interpretation is reinforced by the synchronization we found for the α -band between posterior and anterior sensors.

We also found activations in the left middle occipital gyrus, right posterior inferior temporal sulcus and middle temporal gyrus. These ROIs are involved in the ventral visual stream with V4 and V5. These areas have the fundamental role to allow conscious perception, the recognition and the identification of the objects by treating their intrinsic visual properties like their form, their color, and so on

[for review: Grill-Spector and Malach, 2004; Op de Beeck et al., 2008].

Activations were found in left and right medial temporal gyrus, BA6, and left/right post central gyrus. Medial temporal gyrus, BA6, is a medial division of the premotor cortex that participates in the planning and execution of voluntary movements and is often activated during choice tasks with overt motor responses [Talati and Hirsch, 2005; Kaladjian et al., 2007; Picton et al., 2006]. In our experiment, however, these activations were observed during the retention interval and they could not reflect the selection of a specific response because a response could not be selected before the presentation of the probe disk. Nonetheless, it is possible that subjects anticipated the presentation of the probe disk and could initiate a general form of preparation (preparing for a finger press, without knowing which finger would ultimately produce the response), giving rise to the observed activations in these supplementary motor areas.

Activations were also found in the superior temporal gyrus. This area receives both visual input [from V1 and V2, Ungerleider and Desimone, 2004], and auditory input [Noesselt et al., 2007]. The role of this multisensory region in VSTM is unclear and worthy of future study.

Statistical analysis also demonstrated that sensors over lateral parietal parts of the brain decreased in oscillatory α -band power over the hemisphere contralateral to the attended side. Alpha suppression (local desynchronization) is probably one of the best-known time-frequency phenomena [Foxe et al., 1998; see Pfurtscheller and Lopes da Silva, 1998, for a review; Ahveninen et al., 2007]. Thut et al. [2006] in an EEG study of a visuospatial attention paradigm also reported a contralateral suppression of alpha power in the parietal regions. The suppression was contralateral relative to a lateralised auditory signal that cued the laterality of a subsequent stimulus. Wyart and Tallon Baudry [2008] also reported a significant decrease of the alpha band activity over bilateral posterior sensor at about 300–600 ms after a spatial cue. These various results suggest that α -band activity decreases in the hemisphere contralateral to the locus of spatial attention.

Medendorp et al., 2007, required subject to perform a delayed double-step saccade task involving the sequential presentation of two saccade targets. They found a contralateral (to the stimulus presentation) suppression of alpha power in the parietal regions in the MEG signals following the presentation of the first saccade target, during the retention interval between targets. Interestingly, they found a further suppression of alpha activity following the presentation of the second saccade target. According to the authors, this suppression could have resulted from an anticipation of the second target. The findings of Medendorp et al. [2007] could be viewed as conflicting with ours because they observed a further decrease in alpha power visual memory load increased from one to two, whereas we observed the opposite, namely an increase in alpha power as visual memory load increased (from two to four,

in our case). This discrepancy may be more apparent than real, however, because there were substantial differences between the procedures used in the two studies. In particular, the sequential presentation of the visual stimuli in the Medendorp et al. [2007] study likely required an explicit deployment of visual attention at the time of encoding of the second saccade target. This additional orienting response could have been accompanied by a further suppression of alpha power, which could have masked a simultaneous (smaller) increase in alpha power associated with the increase in visual memory load. In our procedure, all stimuli were presented simultaneously and briefly, likely requiring a single active shift of attention and encoding following the presentation of the memory array, which may have allowed us to observe both phenomena (the contralateral decrease in alpha related to attention and the bilateral increase in alpha related to memory load). Further research will be required to determine which of the numerous methodological differences between our study and the Medendorp et al. [2007] study can account for differences in results, and a good hypothesis would be that the mode of presentation (simultaneous vs. sequential) may be important.

We note that the increase in alpha power, with increasing memory load, was found mainly in the latter portion of the retention interval. Early after the presentation of the memory array, we found a decrease in alpha that was modulated by load (a greater decrease for 4 items than for 2 items, visible in the time-frequency maps shown in Fig. 2). At these latencies, however, modulations of α -band activity could reflect spatial attention or encoding operations. Activity measured during the latter portion of the retention interval is more likely to reflect neural activity required to maintain information in VSTM in an active state. Given that our goal was to study memory retention mechanisms, we focused on the latter portion of the retention interval (i.e., 600–1400 ms).

Several authors have found an increase (local synchronization) in alpha activity in memory tasks, during the retention interval, when subjects needed to keep in mind several items after encoding, and later responded to a probe [Busch and Herrmann, 2003; Cooper et al., 2003; Jensen et al., 2002; Klimesch et al. 1999; Sauseng et al., 2005; Schack and Klimesch, 2002; see Klimesch et al., 2007, for a review]. Increases in alpha power were found when the number of items to be remembered increased [Jensen et al., 2002; Klimesch et al., 1999; Schack and Klimesch, 2002]. We note, however, that these three previous studies used variants of the Sternberg STM task in which items are most likely represented in a verbal memory system. In contrast, our procedure was designed to ensure that representations remained in a visual format [Vogel et al., 2001], and thus our results most likely reflect activity specifically related to VSTM. Interestingly, we were able to demonstrate both a load-related increase in α -band power as well as the contralateral decrease in α -band power related to attention to the relevant side, at the same time during the

retention interval of a VSTM task. The fact that we could observe these two phenomena simultaneously allowed us to determine that the two effects were statistically independent, suggesting separable underlying mechanisms.

CONCLUSION

In the present study we combined the methods used by Vogel and Machizawa [2004] with time-frequency analysis techniques. We found activation during the retention period, in the 8–15 Hz band in parietal regions (inferior IPS, IOS) that increased as VSTM load increased. Activations in IPS and IOS provided converging evidence for a special role of this region for retention in VSTM [Todd and Marois, 2004]. The load effect on α -band power was not modulated by other factors, however (hemifield of stimulus encoding, hemisphere of the sensors). Importantly, we also found oscillatory activity in DLPFC that varied in amplitude with VSTM load. This activity was synchronized with the activity in inferior IPS/IOS, suggesting that DLPFC and inferior IPS/IOS may be important nodes in a network implementing VSTM functions in the human brain. We also found a decrease in power during the retention period, in the 8–15 Hz band in parietal regions, contralateral to the hemifield from which stimuli were encoded that was statistically independent from load-related effects, suggesting a possible dissociation between attentional control and VSTM.

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