



Spatial working memory effects in early visual cortex

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ABSTRACT

The present study investigated how spatial working memory recruits early visual cortex. Participants were required to maintain a location in working memory while changes in blood oxygen level dependent (BOLD) signals were measured during the retention interval in which no visual stimulation was present. We show working memory effects during the retention period in early visual cortex which were retinotopically organized in the sense that evoked BOLD responses were specific to the position of the remembered location on an imaginary clock. We demonstrate that this activity is similar to activity observed in conditions in which participants have to direct spatial attention to the same location. We suggest that during the retention interval modulation of neurons coding the remembered location evoke a baseline shift, providing converging evidence for the notion that spatial working memory may use spatial attention as a rehearsal mechanism.

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1. Introduction

The ability to briefly maintain and interact with information held in memory is one of the pivotal qualities ascribed to “working memory”, and using this ability is functionally important for bridging the gap between perception and action. Over the years multiple models of working memory have been devised in an attempt to explain its many properties and functions (e.g. Baddeley, 1992; Baddeley & Hitch, 1974; Cowan, 1995). A widely accepted concept of working memory entails separate mechanisms for visuospatial and verbal storage of information, both of which have been studied extensively (for an overview see Jonides et al., 1996; Jonides, Lacey, & Nee, 2005). Spatial working memory refers to the ability to store and interact with location-specific information of stimuli presented in the visual field over a brief period of time (see Theeuwes, Belopolsky, and Olivers (2009), for a recent review). Usually this ability is tested with a delayed recognition task (Awh, Jonides, & Reuter-Lorenz, 1998; Postle, Awh, Jonides, Smith, & D’Esposito, 2004; Smith, Jonides, & Koeppel, 1996). In a typical spatial delayed recognition task, participants are instructed to remember the location of an item presented on a display. After a delay during which the item is no longer present, a new item is presented and participants have to indicate whether the new item is presented at the remembered or at a different location. Delayed recognition tasks are used to study the properties and constraints of spatial working memory at a behavioural level, but are also used to study its effects

at a neural level by looking at brain activity during the delay period. Due to the absence of visual stimulation during the delay period, observed neural activity is not confounded by sensory processes and therefore the observed neural activity is thought to reflect genuine working memory related processes.

Neural patterns during a working memory delay period are assumed to reflect memory-related maintenance processes, ensuring an active representation of spatial information. Studies investigating the neural correlates of spatial working memory have demonstrated numerous regions in the parietal and frontal cortex which seem to reflect these maintenance processes, such as the prefrontal cortex (PFC), the frontal eye fields (FEF) and the posterior parietal cortex (PPC) (Curtis, 2006; Naghavi & Nyberg, 2005). However, some studies have questioned the interpretation of delay-period activity as purely mnemonic in nature. For example, Lebedev, Messinger, Kralik, & Wise (2004) had two monkeys (Macaca) perform a task in which a saccade had to be made to either an attended or a remembered location. This study showed that neurons in prefrontal cortex of a monkey, that fired during a delay period, reflected maintenance processes only to a small extent, and that most cells in this region represented attended locations. They concluded that activity in prefrontal cortex observed during a delay period may exceed maintenance processes and that these processes may represent a broader scope of cognitive functions including spatial attention.

In line with Lebedev et al. (2004), spatial working memory is not the only source of activation in these areas in humans. Brain responses in the fronto-parietal network have also been observed in tasks involving spatial attention. Converging lines of research have suggested an intimate link between spatial working memory and spatial attention. Evidence for this suggested link comes from both

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behavioural and neuropsychological research. First, at a behavioural level it has been shown that processing visual information occurs more extensively at remembered locations compared to new locations, a finding similar to the observed enhanced processing of attended over unattended locations (Awh, Smith, & Jonides, 1995). Awh et al. showed that choice reaction times (RTs) to targets were faster when these targets were presented at a memorized location, compared to a non-memorized location, claiming that the speeded RTs were due to attentional enhancement of the processing of stimuli at the memorized location. In addition, when participants are unable to direct attention towards the remembered location, memory accuracy is attenuated (Awh et al., 1998; Smyth, 1996) indicating that spatial working memory utilizes spatial attention mechanisms. Second, at a neural level a large overlap is observed in the cortical circuitry active during spatial working memory and spatial attention tasks in the fronto-parietal network (Awh & Jonides, 1998, 2001; Corbetta, 1998; LaBar, Gitelman, Parrish, & Mesulam, 1999). Furthermore, Jha (2002) showed that ERPs (N1 and P1) evoked by non-relevant probe stimuli during a delay-period in a working memory task were of equal magnitude independent of whether the probe stimuli were presented early or late in the delay period, suggesting that attention is deployed during the entire delay period. Taken together, these observations entail that both constructs may be conceptually different, but that the underlying neural mechanisms may be much more intertwined than commonly thought.

If spatial working memory evokes neural responses similar to spatial attention, then this overlap may not only occur in the fronto-parietal network, but in additional brain regions as well. Recently, an increasing number of studies on spatial attention have focused on the effects of attention on early visual processing in regions of the occipital cortex such as striate and extrastriate cortex. These studies indicate that the neural response to a visual event can be modulated by focused attention in striate and extrastriate cortex in a retinotopic fashion (Brefczynski & DeYoe, 1999; Gandhi, Heeger, & Boynton, 1999; Martinez et al., 1999; Somers, Dale, Seiffert, & Tootell, 1999). Moreover, in the absence of visual stimulation an increase in baseline activity can be observed in early visual cortex prior to the presentation of an expected visual event. Baseline activity refers to the spontaneous firing rate of neurons in the cortex and an attention-induced increase in baseline activity can be observed in both extrastriate cortex (Corbetta et al., 2005; Hopfinger, Buonocore, & Mangun, 2000; Luck, Chelazzi, Hillyard, & Desimone, 1997) and striate cortex (Jack, Shulman, Snyder, McAvoy, & Corbetta, 2006; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Munneke, Heslenfeld, & Theeuwes, 2008; Ress, Backus, & Heeger, 2000). From these and other studies it has become apparent that visual cortex is involved in more than low-level processing of visual information.

If spatial working memory draws on the same neural circuitry as spatial attention, the question is whether visual cortex is also involved when remembering a location. In other words, does maintenance of spatial information in working memory elicit BOLD responses at retinotopic regions in early visual cortex? Previous research has shown some evidence that the visual cortex is modulated by remembering spatial information, but it is not always clear whether the observed activation pattern reflects working memory-related maintenance processes or sensory processes caused by the stimuli presented during the task (Awh et al., 1999). Moreover, the activation patterns observed were not retinotopic in nature, so the question as to what extent the observed effects are spatially specific to the target location remains (e.g. Courtney, Ungerleider, Keil, & Haxby, 1996). Postle, Awh, Jonides, Smith, and D'Esposito (2004) conducted a study which showed effects of spatial working memory in visual cortex; yet these effects did not reach statistical significance in primary visual cortex (V1)

during the retention interval, despite being of a similar magnitude compared to effects of spatial working memory observed in extrastriate cortex.

Furthermore, in a recent fMRI study by Serences, Ester, Vogel, and Awh (2009) multi-voxel pattern analyses (MVPA) showed that during the retention period of a working memory task, specific patterns of BOLD activation could be observed in V1 related to a to-be remembered feature of a stimulus (color or orientation). This result suggests that neural activation in early visual cortex may only reflect the coding of relevant features, but not the entire stimulus. A similar result was obtained by Harrison and Tong (2009) who were able to predict which of two gratings was held in working memory by the participant, based on classification of BOLD patterns. These studies show that early visual cortex is capable of maintaining to-be remembered information over a period of time during which the stimulus is no longer in view.

If visual cortex is capable of supporting working memory processes, this will add to the evidence linking the concepts of spatial working memory and spatial attention. A theoretical account of this overlap hypothesizes that maintaining location-specific information in spatial working memory is accomplished by shifts of spatial attention towards the memorized locations (Awh et al., 1998, 1999; Postle et al., 2004; Smyth, 1996). Rehearsal of the stored spatial representation by covert shifts of attention acts as a functional mechanism similar to verbal rehearsal as a mechanism for storing information in verbal working memory (e.g. Baddeley, 1998). In both types of working memory, maintenance of the active representation is established by rehearsal of the task-relevant features of the stimulus. The existence of an attentional rehearsal mechanism in spatial working memory would explain the observation that the performance level in such a task is dependent on the attentional constraints of that particular task. Attentional rehearsal as a means for storage of spatial representations again emphasizes the strong behavioural link between the two concepts. However, at a neural level, the two constructs have mostly been studied separately and many questions concerning the overlap and functionality of observed neural activation during those tasks remain.

Although Awh et al. (1999, 2001), and Postle et al. (2004) observed effects of spatial working memory in early visual cortex; the method used in these studies leaves open some questions concerning the spatial specificity of the observed effects. Awh et al. and Postle et al. used full stimulation of both hemifields in order to define regions of interest in the visual cortex which makes the specificity of the observed effects within a hemifield hard to determine. This leaves open the question of whether the reported effects are truly retinotopic in nature or whether they reflect more general processes such as hemispheric arousal or alerting. In the current study we aim to further specify the effects observed by Awh et al. and Postle et al. investigating the spatial specificity of the observed effects and the role primary visual cortex may play in attention and working memory. This is done by functionally defining the regions of interest (ROIs) in V1, V2 and V3 in a separate task based on target locations. Furthermore, ROIs based on nearby non-target locations were included in order to investigate whether the effects observed at target locations are spatially specific only for these locations or whether a larger part of the visual cortex is involved in spatial working memory.

2. Methods

2.1. Participants

Sixteen paid volunteers participated in an fMRI experiment. All participants were healthy and had normal or corrected-to-normal vision. Based on eye movement data, three participants were ex-

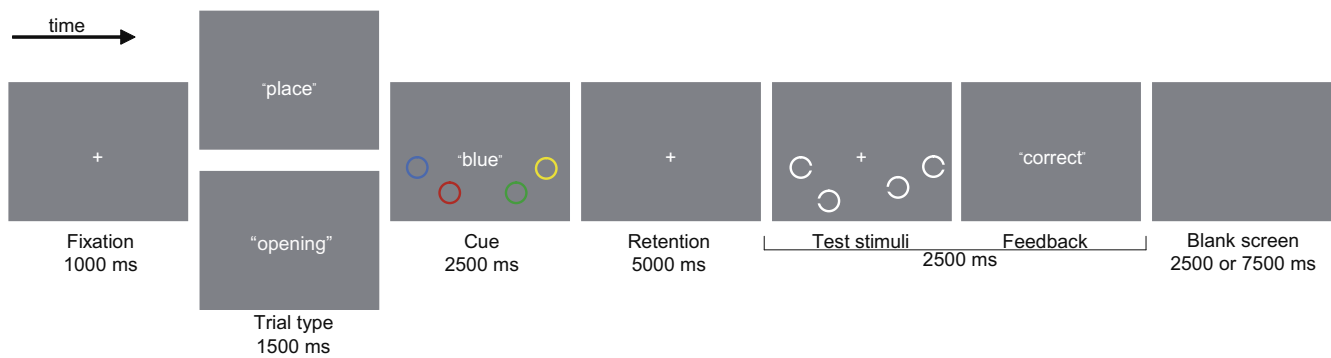


Fig. 1. Time course of a typical trial. Participants were instructed to either perform a spatial working memory (“place”) or a spatial attention (“opening”) trial. Based on this instruction, participants had to remember the exact location of a colored circle in the working memory condition, or use this stimulus as a cue for an upcoming target in the attention task. After a 5 s retention interval, four new white circles appeared. In the working memory task, participants had to indicate whether the relevant white circle was present at the memorized location, whereas in the attention task. Participants had to indicate which side of the white circle contained a gap.

cluded from further analyses, as systematic eye movements were observed during the task in the MRI scanner. Data from another subject was excluded from the analyses, because the behavioural results indicated that this subject was not able to perform the task in a proper fashion. All currently described analyses are based on data from the remaining 12 participants (1 male, mean age = 21.5 - years). The protocol was approved by the ethical committee of the VU University Medical Center, Amsterdam, The Netherlands.

2.2. Stimuli and task

Participants performed either a spatial working memory trial or a spatial attention trial. Trials were mixed within blocks. Fig. 1 shows a typical trial for either task. Participants performed 64 trials of each task divided over eight blocks. An additional practice block of 16 trials (eight trials of each task) preceded the test blocks. Participants were instructed to maintain fixation at the central fixation point during the critical part of the trial, which started at cue onset and lasted until the manual response.

2.2.1. Working memory trials

At trial onset, participants focused the fixation cross ($0.6^\circ \times 0.6^\circ$) for a duration of 1000 ms, after which the word “place” appeared for 1500 ms, indicating that it was a memory trial. Following this instruction, a color word appeared (“red”, “blue”, “green”, “yellow”),¹ which referred to one of four simultaneously presented colored circles (one *memory stimulus* and three distractor stimuli, in these colors). Participants had to remember the exact location of the circle indicated by the color word. For example, if the word “red” was presented, participants had to remember the location of the red circle. Following this display there was a 5 s retention period during which only the fixation point was present in the middle of the screen. Subsequently four white circles (the test stimuli) appeared, all containing a small gap on the right or the left side. The gap was irrelevant in the working memory trials, but had a function in the attention trials (see below). The white test circles could appear either at the exact location of the colored circles, or with a small offset. On each trial, two test stimuli were positioned at the exact location of the previously presented colored circles, whereas the remaining two were positioned a small distance away from the location of the colored circles. The relevant test stimulus presented at the memory location had a 50% chance of being in the same location as the memory stimulus. All circles (diameter = 1.4°) were presented in the lower half of the visual field, centered on the

positions of an imaginary clock at 4, 5, 7, and 8 h, resulting in one stimulus per octant of the visual field. The test circles were presented for a maximum period of 2500 ms, but disappeared when the participant responded with a button press. Importantly, in order to make sure that subjects were not verbally encoding the to-be-remembered location, the stimuli were not necessarily presented at the exact clock-positions, but could also be presented with a slight offset from this position, ensuring that participants had to store the actual location of the stimuli. Only the positions at 4 and 8 o'clock were used as memory locations, the remaining positions served as distractor locations.

Following the onset of the test stimuli, participants had to indicate whether the relevant test stimulus was presented at the exact location of the previous memory stimulus or whether it was presented with a small offset from this location. Responses to the trial were unspeeded and at the end of the trial feedback concerning the correctness of the response was given. After the response, a blank screen was presented for 2500 or 7500 ms before a new trial was initiated.

2.2.2. Spatial attention task

Physically the attention task was identical to the working memory task. However instructions were different. If the word “opening” was presented at the beginning of the trial, instead of remembering the exact location of one of the colored circles, participants had to prepare for an upcoming target at that approximate location. Participants directed their attention covertly to the indicated colored circle which functioned as a location cue for the upcoming target. At the end of the trial, participants did not have to report the location of the test circle but had to report whether the opening of the test stimulus at the indicated location was on the left or the right side. Note that the cue itself was not indicative of the correct side of the target, but merely cued the location of the target stimulus. Other than the instruction word, properties and timing of stimuli were identical to the memory task. Again, only positions 4 and 8 were used as target positions, whereas position 5 and 7 were used as distractor locations.

Task difficulty for both tasks was adjusted online in order to maintain a steady performance level. For both tasks, a moving performance average was calculated over the four most recent trials for each task separately. A cut-off score of 75% correct responses was used and task difficulty was adjusted when participants scored higher (i.e. trials were made harder) or lower (i.e. trials were made easier) than the cut-off. Modulations in task difficulty for the memory trials were achieved by decreasing or increasing the distance between the location of the memory stimulus and the test stimulus by two pixels whenever participants performed above or below

¹ For interpretation of color in Figs. 1 and 2, the reader is referred to the web version of this article.

cut-off respectively. When the test stimulus was presented with an offset from the cued location, it was always presented on an imaginary line from fixation through the cued location, ensuring that no more than one stimulus per octant was presented. For the attention task, changes in difficulty were accomplished by decreasing or increasing the size of the gap in the test stimulus by one pixel whenever participants responded above or below cut-off respectively. For both tasks a performance level of 75% correct responses was aimed for. The initial difference in offset between target and test stimuli was 45 pixels (0.84°) and the initial gap size was six pixels (0.11°). Stimulus presentation and response collection were controlled using E-Prime 1.1 (Psychology Software Tools).

Even though the two tasks are perceptually similar and only differ in the instruction presented at the start of the trial, an important functional distinction underlying the tasks can be hypothesized. During a working memory trial, the exact stimulus location has to be memorized and carried over the delay period in order to make a comparison with the location of the newly presented target item. In other words, working memory trials contain a retrospective element in which a stimulus that is presented later in time has to be compared with a stimulus that has been presented at an earlier moment. In contrast, no such mechanism is required in the attention trials. As opposed to the retrospective nature of the working memory trials, attention trials contain only a prospective element, requiring preparation for an upcoming stimulus. Once the stimulus has been presented, no comparison has to be made with an item presented earlier in time, and a response can be given solely based on the presented target stimulus. Therefore, because of this functional distinction it may be argued that different neural processes may underlie the two tasks. However, if spatial attention is the means by which spatial working memory operates, both tasks may lead to very similar patterns of brain activity in visual cortex.

2.3. Scan acquisition

Scanning sessions took place at the VU Medical Center using a 1.5 Tesla Siemens Sonata MRI scanner (Siemens Medical Systems, Erlangen, Germany). An 8-channel phased-array coil was used to obtain functional and structural images of the brain. An EPI sequence was used to obtain functional data of the entire brain. Scanning parameters for the main task were: number of slices = 25, TR = 2500 ms, TE = 60 ms, flip angle = 90° , slice thickness = 4 mm, gap = 0.8 mm, acquisition matrix = 64×64 , in-plane resolution = 3.1×3.1 mm. To reduce the interfering effects of head

movements during scanning sessions, all volumes were online motion corrected.

To obtain a 3D anatomical scan a T1-weighted MP-Rage sequence was used at the end of the scanning session. Scanning parameters for the anatomical scan were: TR = 2730 ms, TE = 3.43, TI = 1000 ms, flip angle = 7° , sagittal slice thickness = 1 mm, acquisition matrix = 256×224 pixels, in-plane resolution = 1×1 mm.

During the scanning sessions horizontal electro-oculogram (EOG) was recorded by placing two carbon electrodes at the outer canthi of each eye. EOG was recorded (400 Hz) to ensure that participants did not make eye movements, as this would disrupt the patterns of functional activity obtained during the task. Analysis of these data showed that three participants were unable to maintain fixation during the critical scanning period (i.e. from cue onset, during the retention interval until target presentation). Data from these subjects were removed from further analyses. The remaining participants were able to maintain a steady gaze at the fixation point during the task.

2.4. Retinotopic mapping of visual areas

In order to map the borders between early visual areas (V1, V2, V3), the whole visual field was stimulated by presenting the participant with a slowly rotating checkerboard wedge. The wedge, with a width of 30° , completed one rotation in 24 TRs. In total, eight rotations were presented in a single run; checks were counterphased at 9 Hz.

In a second task, target and distractor locations were stimulated with 9 Hz counterphased circular checkerboard patterns, presented at clock positions 4, 5, 7 and 8 (diameter = 3.2°). Each stimulus was presented for 1 TR (2280 ms) and was randomly followed by the next after an interval of 2 or 3 TR. This task served to identify the exact visual field projections of the relevant locations in the experiment. Both tasks were combined (i.e. projections within the proper visual field borders) so that ROIs could be determined in striate and extrastriate cortex at the exact target location (see Fig. 2).

2.5. MRI data analysis

To analyze the MRI data Brainvoyager QX 1.10 (Brain Innovation, Maastricht, The Netherlands) was used. Because of differences in T1 saturation, the first two volumes of each run were removed. The remaining volumes were preprocessed, utilizing the following parameters: high-pass filtering (0.01 Hz), slice scan-time correc-

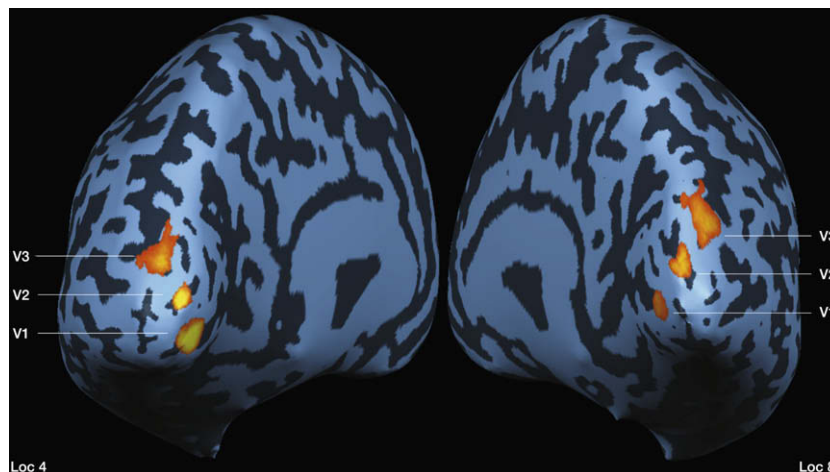


Fig. 2. Inflated left and right hemisphere from a typical participant. Patterns of activation show representations of the right and left target location (at clock position 4 and 8 h) in V1, V2 and V3.

tion and a very gentle spatial smoothing (3 mm FWHM). Temporal smoothing (3 s FWHM) was only applied to the data of the retinotopic mapping tasks and not to the data obtained in the main experimental task.

All preprocessed functional scans were coregistered to the individual anatomical scan and converted to Talairach space in order to obtain a 4D functional data set in Talairach space (Goebel, Muckli, Zanella, Singer, & Stoerig, 2001; Talairach & Tournoux, 1988). The 3D anatomical scan was converted to Talairach space and segmented, separating the various tissues of the brain. Based on the boundary between gray and white matter in the cortex, a reconstruction of the cortical surface was created and inflated. Data from the retinotopic mapping experiments were projected on the inflated mesh to determine the ROIs in each of the two hemispheres for V1, V2 and V3 (see Munneke et al., 2008).

The effects of spatial working memory and spatial attention in the visual cortex were investigated by determining the blood oxygen level dependent (BOLD) response by calculating event-related averages separately for each participant, task, and ROI. Event-related averaging provides a measure of BOLD signal change as a result of various events (i.e. cue onset, target onset) occurring in an experimental trial. In this analysis, the obtained time series were averaged across hemispheres for each ROI (i.e. V1, V2, V3). An advantage of the event-related average approach is that this type of analysis describes the BOLD response without any assumptions about amplitude or duration of this response, unlike a standard convolved GLM. In using this approach, the necessity to separate the different events in a trial can be circumvented when the duration between two events is sufficient. In the current study, cue and target presentation were separated by a delay period of 5 s, enabling a separation of cue and target related activity.

Effects of working memory and attention were investigated by comparing activity in ROIs evoked by cues indicating a relevant stimulus in the contralateral visual field compared to cues indicating a relevant stimulus in the ipsilateral visual field. This was done for both target and non-target locations. Because of the neural circuitry of the visual system, effects occurring in the retention period would lead to larger responses in the ROIs contralateral to the cued location.

3. Results

3.1. Behavioural data

Performance was calculated separately for both tasks. In the working memory task, average performance correct was 70%, whereas in the attention task it was 75%. All participants performed both tasks above chance level, which indicates that participants were performing the task as intended.

3.2. fMRI data

3.2.1. Targets

Hemodynamic brain responses evoked by the different events in each trial were determined from cue (color word) onset. The BOLD response was calculated using an event-related averaging procedure, reflecting percentages signal change in the BOLD response as a result of the different events in a trial.² Event-related averages were calculated independently for each subject, task and region-of-interest. Fig. 3 shows the averaged BOLD responses evoked during a trial for both tasks. At TR = 0, the cue is presented

which results in the BOLD response peaking 5 s later (TR = 2). A decrease in activity can be observed in the 5 s interval following this peak (TR = 3 and TR = 4), which reflects the retention period. The BOLD response to the test stimulus can be observed peaking at 12.5 s (TR = 5) and slowly dissipating afterwards.

In an initial, overall, within-subjects, ROI (V1, V2, V3) × task (memory vs. attention) × laterality (contralateral vs. ipsilateral) × TR (0–5) analysis,³ we found main effects of laterality ($F(1, 11) = 39.642, p < 0.001$), ROI ($F(2, 22) = 9.712, \epsilon = 0.921, p = 0.001$) and TR ($F(5, 55) = 16.561, \epsilon = 0.499, p < 0.001$) showing that cues indicating a contralateral target location (i.e. the memory location or attended location) resulted in a larger BOLD response compared to cues indicating an ipsilateral target location (i.e. a non-memory location or unattended location), and that these responses varied over time and region of interest. No main effect of task was observed, suggesting a similar overall BOLD response in memory and attention trials ($F < 1$). Significant three-way interactions between ROI × laterality × TR ($F(10, 110) = 4.835, \epsilon = 0.448, p = 0.002$) and task × laterality × TR ($F(5, 55) = 3.894, \epsilon = 0.699, p = 0.012$) were observed, suggesting that the difference between contra- and ipsilateral activity changed differentially over TR and ROI for each task. Significant interactions between laterality and ROI ($F(2, 22) = 12.584, \epsilon = 0.993, p < 0.001$) and laterality and TR ($F(5, 55) = 27.652, \epsilon = 0.424, p < 0.001$) indicated that the difference between contralateral and ipsilateral activity was not of equal magnitude for each ROI and TR. We therefore analyzed the effects of laterality and task independently for each ROI and TR. These follow-up analyses indicated significant differences between contralateral and ipsilateral activity in all ROIs, as indicated by main effects of laterality. In V1 this effect became significant 7500 ms (TR = 3) post-cue and remained significant during the retention period and BOLD response evoked by the target stimulus (V1: smallest $F(1, 11) = 11.476, p = 0.006$). Again, no main effects or interactions with task were observed. In V2 and V3, similar results were obtained, but the difference between contralateral and ipsilateral activity became significant 5000 ms (TR = 2) post-cue (V2: smallest $F(1, 11) = 9.620, p = 0.010$; V3: smallest $F(1, 11) = 22.207, p = 0.001$), showing modulation of the cue. Additionally, interactions between laterality and task were observed in V3 during the retention period (TR = 3: $F(1, 11) = 7.858, p = 0.017$; TR = 4: $F(1, 11) = 7.219, p = 0.021$), which were caused by larger differences in the memory trials.

3.2.2. Non-targets

In order to examine whether the observed BOLD responses were retinotopic in nature, the response at a non-target location in the same quadrant of the visual hemifield (contralateral) was compared to the non-target location in the opposite quadrant of the visual field (ipsilateral). The non-target locations corresponded to clock positions 5 and 7 and these locations were never used as target locations. Again, repeated-measures analyses were conducted separately for each ROI (V1, V2 and V3) and TR (2–5). Contrary to the findings regarding the target locations, no main effect of laterality was obtained in V1 and V2 at the non-target locations (V1: largest $F(1, 11) = 2.018, p = 0.183$; V2: largest $F(1, 11) = 3.749, p = 0.079$), nor were main effects of task or interactions between task and laterality observed. A different pattern of results was obtained for V3. Similar to the observed patterns of BOLD activity at the target locations, a main effect of laterality was observed for all TRs in V3 (smallest $F(1, 11) = 34.844, p < 0.001$). Furthermore, the analyses per TR and ROI showed significant interactions between task and laterality for certain TRs in V3. It was observed that during

² For confirmatory purposes all analyses were repeated using a deconvolution GLM. These analyses yielded results that were qualitatively identical to the event-related average analyses.

³ We used repeated-measures ANOVA, and Greenhouse–Geisser's ϵ to correct for violations of sphericity. Multivariate ANOVA yielded qualitatively identical results.

TARGET LOCATIONS

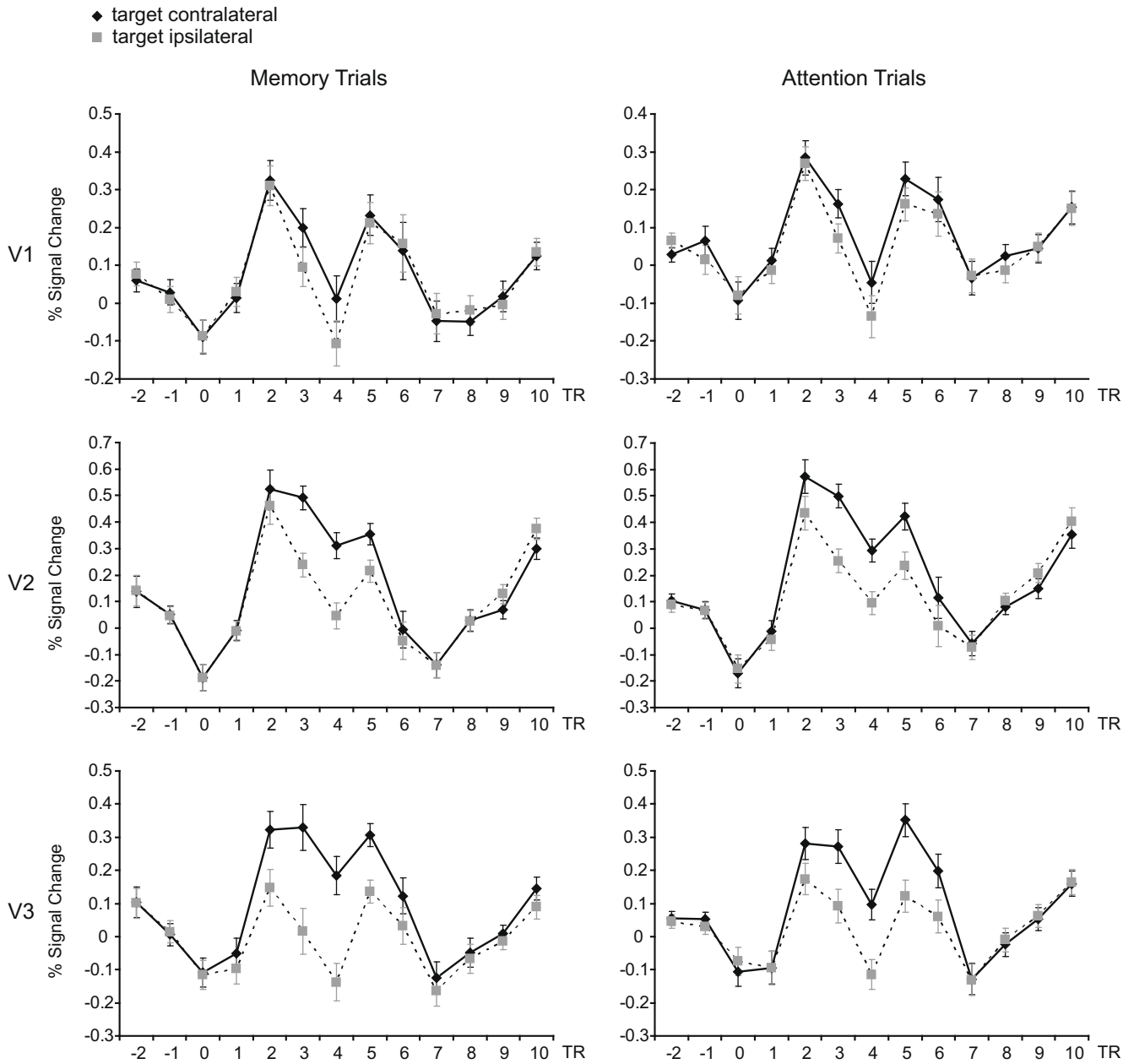


Fig. 3. BOLD responses to trials of working memory (left column) and attention (right column) separately for each ROI (V1, V2 and V3) at target locations. The continuous line represents the BOLD response contralateral to the target location, whereas the dotted line represents the BOLD response ipsilateral to the target location. In all ROIs both tasks elicited a larger BOLD response during the retention period contralateral to the target location. Error bars represent the standard error of the mean corrected for within-subjects designs.

the retention period a larger difference between contra- and ipsilateral activity was observed in the memory task compared to the attention task. For TR = 3, the differences in percentage signal change were: memory: 0.313% and attention 0.180% ($F(1, 11) = 9.642, p = 0.010$). For TR = 4 these differences were: memory 0.321% and attention 0.212% ($F(1, 11) = 6.752, p < 0.025$). In both cases the interaction between task and laterality was caused by a larger difference between contra- and ipsilateral BOLD responses in the memory condition (see Fig. 4).

3.2.3. Targets vs. non-targets

Additionally, the difference between target and non-target locations was further analyzed by comparing the effects of working

memory and attention at target vs. non-target locations in the same contralateral quadrant. For example, when clock position “4” was the indicated target location, a comparison between the ROIs reflecting location “4” and “5” was made. A repeated-measures ANOVA with location (target, non-target), ROI (V1, V2, V3), task (working memory, attention), and TR (0–5) showed a main effect of location, reflecting larger BOLD responses at target locations compared to non-target locations ($F(1, 11) = 7.200, p = 0.021$). Furthermore, significant interactions between location and ROI ($F(2, 22) = 14.282, \epsilon = 0.750, p = 0.001$), location and task ($F(1, 11) = 6.483, p = 0.027$), location and TR ($F(5, 55) = 4.344, \epsilon = 0.340, p = 0.033$) and location \times ROI \times TR ($F(10, 110) = 4.911, \epsilon = 0.407, p = 0.002$) were observed, indicating that the effects of location

NON-TARGET LOCATIONS

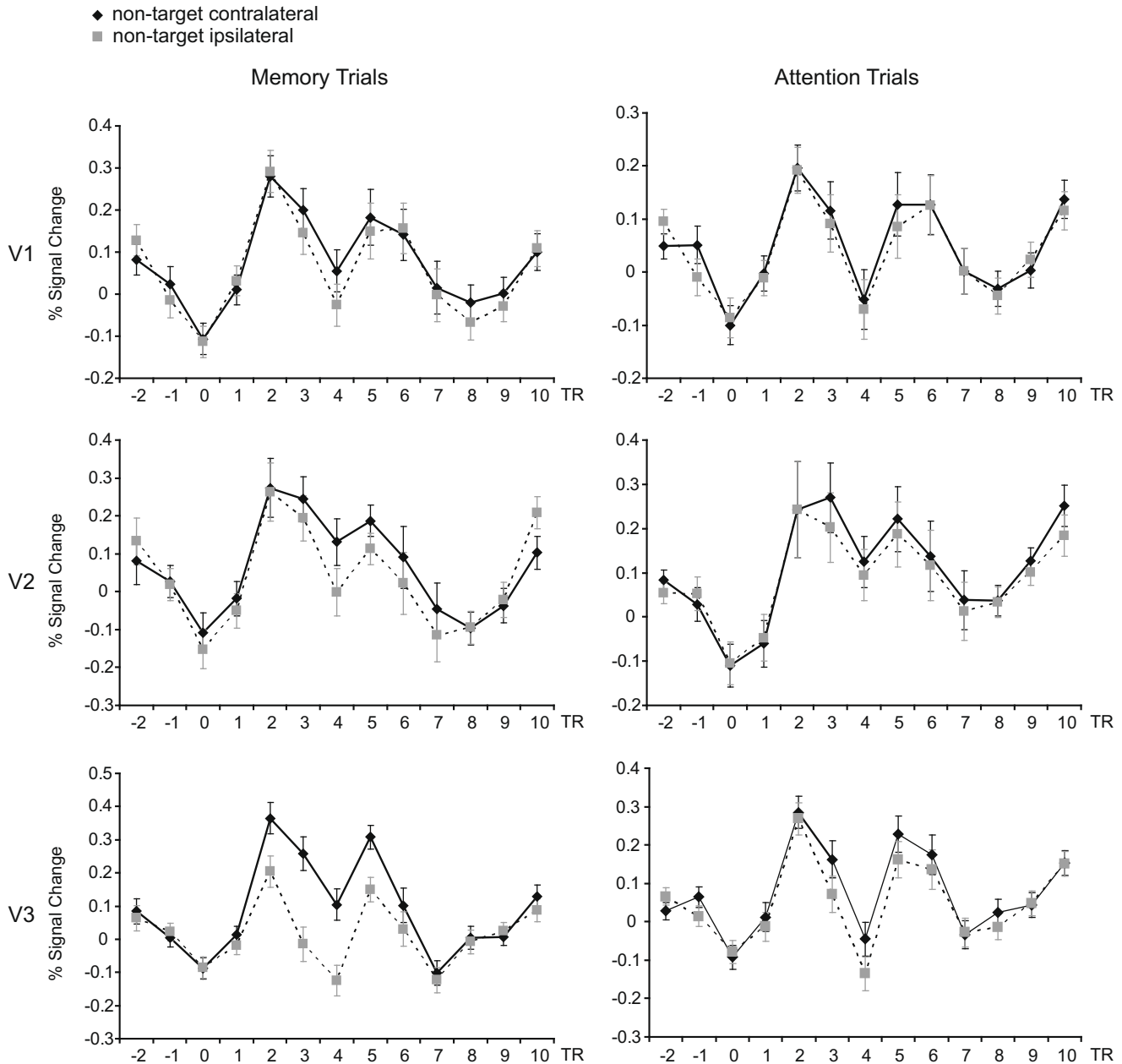


Fig. 4. BOLD responses to trials of working memory (left column) and attention (right column) separately for each ROI (V1, V2 and V3) at non-target locations. The continuous line represents the BOLD response contralateral to the target side, whereas the dotted line represents the BOLD response ipsilateral to the target side. No difference between BOLD responses evoked at the non-target locations were observed for V1 and V2. Only in V3 did the difference between contra- and ipsilateral non-target locations reach statistical significance.

were not the same for each ROI, task and TR. Post-hoc analyses per ROI and TR showed that the difference between the target and non-target locations during the critical period (TR 2–5) is strongest in V2 showing a larger BOLD response at the target location for all TRs (smallest $F(1, 11) = 7.172$, $p = 0.021$). In V3 a small difference was found only at TR = 4 ($F(1, 11) = 5.450$, $p = 0.04$). In V1 differences between target and non-target locations did not reach significance in the contralateral hemisphere during this period. Similar analyses for ipsilateral target and non-target locations showed a significant difference in BOLD amplitude between the target and non-target location in V1 for TR = 4 ($F(1, 11) = 6.570$, $p = 0.026$). In V1 a larger BOLD response was observed at the non-target location compared to the target location ipsilateral to the cued side.

Similar effects were not observed in V2 and V3 indicating that primary visual cortex was the only region in visual cortex showing decreased activation at the irrelevant target location compared to the non-target location.

4. Discussion

The present study aims to clarify and elaborate on previous work that shows that spatial working memory and spatial attention are mediated by early visual cortex. Looking only at target locations, it is shown that keeping a location in working memory results in an increased BOLD response in early visual areas V1,

V2 and V3 at contralateral target locations, compared to ipsilateral target locations. More importantly, this response is retinotopically organized in the sense that responses were specific to the position of the remembered location on an imaginary clock. The increased activity was observed during the retention interval when no visual stimuli were present on the screen. These findings suggest that the act of keeping a location active in working memory utilizes neural structures in early visual cortex.

An important feature of the present study is that we included two locations that contained a stimulus during cue and target presentation but which never needed to be kept in memory. For these non-target locations no difference was observed between the BOLD responses contralateral to the cued location compared to ipsilateral to the cued location in V1 and V2, suggesting that the modulation as a result of the spatial working memory instruction is retinotopic in primary visual cortex. In V3 a significant difference between contra- and ipsilateral non-target locations was observed. Even though this result may appear unexpected, it can be explained by the fact that the size of the receptive fields is relatively large in V3 (e.g. Smith, Singh, Williams, & Greenlee, 2001). When moving up the visual processing stream, receptive fields increase in size and in V3 they may be large enough to encompass both the target and non-target location, which makes it possible that target location effects are also present at nearby non-target location representations.

Importantly, when comparing BOLD responses at target and non-target locations within the quadrant contralateral to the cued side, qualitatively different results were obtained for V1, V2 and V3. Overall, a larger BOLD response was obtained for target locations than for non-target locations. This effect was most pronounced in V2, showing a larger BOLD response at target locations compared to non-target locations at all TRs. In V3 a larger BOLD response was observed at contralateral target locations. Unlike the effect in V2, this effect was only observed at one TR during the retention interval. The lack of an effect in V3 of equal magnitude and duration compared to V2 is most likely caused by overlapping receptive fields, encompassing both target and non-target location which may drown out the larger part of the effect.

No difference between contralateral target and non-target locations was observed in the primary visual cortex, suggesting that the previously reported effects in V1 between contra- and ipsilateral activity for target locations may be dependent on the ROIs ipsilateral to the cued side. Looking at the difference in BOLD amplitude between ROIs coding for target and non-target locations ipsilateral to the cued side, smaller responses were observed at the target location, compared to the non-target location. This deactivation at the uncued target location explains the initial difference between contra- and ipsilateral target locations.

Differences in BOLD amplitude contralateral to the uncued location, as is currently observed in primary visual cortex, have been observed in other studies. For example, Ruff and Driver (2006) showed in an fMRI study that foreknowledge about distractor presence resulted in BOLD effects only in visual cortex contralateral to the distractor location (i.e. ipsilateral to the target location), but did not influence target processing itself. This is in line with the current findings suggesting that the effects in V1 may be caused by a suppression mechanism attenuating the effects of the distractors in the ipsilateral visual field. Due to using only one location in the ipsilateral hemifield as a possible target location, it may be argued that this location gets suppressed more than the non-target location, resulting in less neural activation at the ipsilateral target location.

The cortical specificity of our findings, whether contra- or ipsilateral, rules out other possible explanations, such as alerting or other sources of arousal, as these would have resulted in a general increase of activity in ROIs coding for target and non-target loca-

tions in V1 and V2. We found spatially non-specific effects only in V3 suggesting that a non-target location next to a location held in memory leads to a larger BOLD response than a non-target location next to a target location not held in memory.

The present study supports the hypothesis that attentional rehearsal is the mechanism by which information is kept in spatial working memory as no differences were observed between BOLD responses reflecting the two tasks (Awh et al., 1998, 1999; Postle et al., 2004). The current study shows a great resemblance between BOLD responses evoked by keeping a location in memory and BOLD responses elicited during a spatial attention task. Previous studies have shown that in both striate and extrastriate cortex, a neural response is elicited when spatial attention is allocated to a location of interest, showing sensory modulation of a stimulus (Brefczynski & DeYoe, 1999; Gandhi et al., 1999; Somers et al., 1999; Tootell et al., 1998) and preparatory effects for an upcoming stimulus (Corbetta et al., 2005; Hopfinger et al., 2000; Jack et al., 2006; Kastner et al., 1999; Luck et al., 1997; Martinez et al., 1999; Munneke et al., 2008; Ress et al., 2000; Silver, Ress, & Heeger, 2007). In the current study, similar effects during spatial working memory trials and spatial attention trials were obtained in V1 and V2, both tasks showing evoked BOLD responses of equal magnitude. This effect was observed in V3 for both tasks as well, but a difference in the size of the effect was observed between the two types of tasks, showing a larger effect in the spatial working memory task.

Previous studies have also provided evidence that spatial working memory recruits early visual areas. For example, Awh et al. (1999) showed that BOLD responses to a task-irrelevant flickering checkerboard, presented during the retention interval, were enhanced. Moreover, this effect was spatial in origin as there was more activity contralateral to the location kept in memory. Even though this study shows evidence for hemisphere-specific activity related to working memory, it should be realized that this is an effect in response to the test stimulus (i.e. the checkerboard). In other words, unlike what we show here, this study did not show an increase in activity in the absence of visual stimulation.

Postle et al. (2004) addressed the question whether neural activity in visual cortex would be present during the delay period in the absence of visual stimulation. Even in the absence of visual stimulation, Postle et al. observed an increased BOLD response evoked in extrastriate cortex as a result of keeping a location in memory. However, this baseline shift did not reach statistical significance in striate cortex during the delay period, leading to the conclusion that maintenance processes in spatial working memory are modulated in extrastriate cortex. Based on the quantitative effect observed in striate cortex, it could be hypothesized that a similar effect of spatial working memory might occur in striate cortex. Clearly, the current study shows that keeping a location in memory results in a modulation of activity in the absence of visual stimulation in both striate and extrastriate cortex.

Another possible cause for the larger modulation in primary visual cortex observed in the current study may be the role distractors play in attentional processing and, in line with the rehearsal theory, in spatial working memory maintenance processes. Serences, Yantis, Culbertson, and Awh (2004) showed that when a target is likely to be accompanied by distractors, excitatory patterns of activation related to attentional enhancement of the target location can be observed, accompanied by an additional inhibitory component which is thought to reflect suppression of distractor interference. Desimone and Duncan (1995) showed that in the face of competition, attentional effects become larger as the attentional system has to suppress irrelevant information. The presence of distractors adds competition to the visual display and may therefore result in a larger preparatory response which could lead to the effects observed in V1 in the current study. In the study by Postle et al. no distractors were present, minimizing the need for resolv-

ing competition in the visual display. Therefore, the absence of distractors may have resulted in a diminished preparatory effect due to which no effect in V1 was observed.

In a recent paper by Serences et al. (2009), it was hypothesized that maintenance during the delay period in a working memory task involved modulation of the sensory cortex coding the relevant feature of the stimulus (features were “color” and “orientation”). Multi-voxel pattern analysis (MVPA) showed that voxels in V1 coding color were significantly more active than voxels coding orientation during the retention period when color was the feature to-be-remembered. The reverse pattern was observed when orientation was the feature to-be-remembered. Even though no differences in BOLD amplitude between the response during the retention period and the response in a sensorily similar non-memory condition were observed, the MVPA showed that V1 plays a major role in maintenance of feature-specific information over a period in time. Our current findings add a spatial component to this data, indicating that voxels in V1 (and V2, V3) coding a to-be-remembered location show more activation than voxels coding a location not actively stored in working memory. Serences et al. conclude that the effects observed in V1 reflect actual maintenance processes and are not the result of attention-modulated sensory processes, encoding the to-be-remembered stimulus. A similar conclusion can be drawn from the current study. Based on the measured BOLD response in visual cortex, it is clear that during the retention period voxels coding the remembered location are significantly modulated at a time interval which does not coincide with sensory modulation. The BOLD response observed during the retention interval reflects an attentional baseline shift most likely indicating the manifestation of working memory-related maintenance processes.

In a study by Supèr, Spekreijse, and Lamme (2001), working memory related modulations in the primary visual cortex were investigated by having macaques make an eye movement towards a remembered stimulus. The Supèr et al. study showed that contextual modulation (i.e. the enhancement of the sensory response – in this case a task of figure-ground segregation) continues in V1 during a delay period, in the absence of the stimulus, but only when this information is needed at a later point in time. Nevertheless, the strength of the overall contextual modulation decreased over time, suggesting that the task required working memory processes. The results observed by Supèr et al. are not consistent with the current findings, as we did not observe this overall decline in working memory related processes over time. This discrepancy may be explained by the fact that fMRI may be less sensitive than single-cell recording and therefore may not be able to reveal a subtle decline as reported by Supèr et al. Moreover, one should be careful when comparing BOLD responses as measured with fMRI in humans with neuronal spike trains as measured with single-cell recording in a monkey brain. Even though the responses measured by both techniques are assumed to reflect underlying neural processes, the physical processes underlying these measurements are entirely different and may therefore yield different results under similar conditions.

A recent study by Offen, Schluppeck, and Heeger (2009) also investigated the overlap between visual short-term memory (a component of visual working memory) for features and visual attention. It was shown that early visual cortex, including V1, showed spatially specific sustained activity during a delay period in tasks with high attentional demand, but not in a perceptually similar task utilizing spatial working memory. This dissociation between visual attention and visual working memory seems inconsistent with the current results as well as the notion of attention-based rehearsal as the mechanism by which working memory operates. However, as Offen et al. point out themselves, it is known that there are distinct mechanisms for spatial working memory and working memory for object features. Because Offen

et al. used a feature-based working memory task, this may very well be the critical distinction between their study and the current study. This would indicate that the rehearsal mechanism only applies to location-based working memory processes as opposed to feature-based working memory processes.

The current findings suggest that the visual cortex, including V1, is actively involved in maintaining spatially specific properties of to-be-remembered information. These maintenance processes are most likely the result of a rehearsal mechanism in which covert shifts of top-down attention are made towards the memory location. The involvement of attentional processing explains why a spatial attention task resulted in similar patterns of activation in all ROIs. Therefore, it can be concluded that spatial working memory and spatial attention, even though conceptually different, are mediated by a similar functional neural network.

References

- Awh, E., & Jonides, J. (1998). Spatial selective attention and spatial working memory. In R. Parasuraman (Ed.), *The attentive brain* (pp. 353–380). Cambridge, MA: MIT Press.
- Awh, E., & Jonides, J. (2001). Overlapping mechanisms of attention and spatial working memory. *Trends in Cognitive Sciences*, 5(3), 119–126.
- Awh, E., Jonides, J., & Reuter-Lorenz, P. A. (1998). Rehearsal in spatial working memory. *Journal of Experimental Psychology – Human Perception and Performance*, 24(3), 780–790.
- Awh, E., Jonides, J., Smith, E. E., Buxton, R. B., Frank, L. R., Love, T., et al. (1999). Rehearsal in spatial working memory: Evidence from neuroimaging. *Psychological Science*, 10(5), 433–437.
- Awh, E., Smith, E. E., & Jonides, J. (1995). Human rehearsal processes and the frontal lobes. Pet evidence. In J. Grafman, K. Holyoak, & F. Boller (Eds.), *Annals of the New York academy of sciences. Structure and functions of the human prefrontal cortex* (pp. 97–119). New York: New York Academy of Sciences.
- Baddeley, A. (1992). Working memory. *Science*, 255(5044), 556–559.
- Baddeley, A. (1998). Recent developments in working memory. *Current Opinion in Neurobiology*, 8(2), 234–238.
- Baddeley, A. D., & Hitch, G. J. (1974). In G. Bower (Ed.), *Working memory*. Hillsdale, NJ: Erlbaum.
- Brefczynski, J. A., & DeYoe, E. A. (1999). A physiological correlate of the ‘spotlight’ of visual attention. *Nature Neuroscience*, 2(4), 370–374.
- Corbetta, M. (1998). Frontoparietal cortical networks for directing attention and the eye to visual locations: Identical, independent, or overlapping neural systems? *Proceedings of the National Academy of Sciences of the United States of America*, 95(3), 831–838.
- Corbetta, M., Tansy, A. P., Stanley, C. M., Astafiev, S. V., Snyder, A. Z., & Shulman, G. L. (2005). A functional MRI study of preparatory signals for spatial location and objects. *Neuropsychologia*, 43(14), 2041–2056.
- Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex*, 6(1), 39–49.
- Cowan, N. (1995). *Attention and memory: An integrated framework*. New York: Oxford University Press.
- Curtis, C. E. (2006). Prefrontal and parietal contributions to spatial working memory. *Neuroscience*, 139(1), 173–180.
- Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual-attention. *Annual Review of Neuroscience*, 18, 193–222.
- Gandhi, S. P., Heeger, D. J., & Boynton, G. M. (1999). Spatial attention affects brain activity in human primary visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 96(13), 7610.
- Goebel, R., Muckli, L., Zanella, F. E., Singer, W., & Stoerig, P. (2001). Sustained extrastriate cortical activation without visual awareness revealed by fMRI studies of hemianopic patients. *Vision Research*, 41(10–11), 1459–1474.
- Harrison, S. A., & Tong, F. (2009). Decoding reveals the contents of visual working memory in early visual areas. *Nature*, 458, 632–635.
- Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nature Neuroscience*, 3(3), 284–291.
- Jack, A. I., Shulman, G. L., Snyder, A. Z., McAvoy, M., & Corbetta, M. (2006). Separate modulations of human V1 associated with spatial attention and task structure. *Neuron*, 51(1), 135–147.
- Jha, A. P. (2002). Tracking the time-course of attentional involvement in spatial working memory: An event-related potential investigation. *Cognitive Brain Research*, 15, 61–69.
- Jonides, J., Lacey, S. C., & Nee, D. E. (2005). Processes of working memory in mind and brain. *Current Directions in Psychological Science*, 14(1), 2–5.
- Jonides, J., Reuter-Lorenz, P. A., Smith, E. E., Awh, E., Barnes, L. L., Drain, M., et al. . In D. Medin (Ed.), *Verbal and spatial working memory in humans* (pp. 43–88). Orlando, FL: Academic Press.
- Kastner, S., Pinsk, M. A., De Weerd, P., Desimone, R., & Ungerleider, L. G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron*, 22(4), 751–761.

- LaBar, K. S., Gitelman, D. R., Parrish, T. B., & Mesulam, M. M. (1999). Neuroanatomic overlap of working memory and spatial attention networks: A functional MRI comparison within subjects. *Neuroimage*, *10*(6), 695–704.
- Lebedev, M. A., Messinger, A., Kralik, J. D., & Wise, S. P. (2004). Representation of attended versus remembered locations in prefrontal cortex. *PLoS Biology*, *2*(11), 1919–1935.
- Luck, S. J., Chelazzi, L., Hillyard, S. A., & Desimone, R. (1997). Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. *Journal of Neurophysiology*, *77*(1), 24–42.
- Martinez, A., Anillo-Vento, L., Sereno, M. I., Frank, L. R., Buxton, R. B., Dubowitz, D. J., et al. (1999). Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nature Neuroscience*, *2*(4), 364–369.
- Munneke, J., Heslenfeld, D. J., & Theeuwes, J. (2008). Directing attention to a location in space results in retinotopic activation in primary visual cortex. *Brain Research*, *1222*, 184–191.
- Naghavi, H. R., & Nyberg, L. (2005). Common fronto-parietal activity in attention, memory, and consciousness: Shared demands on integration? *Consciousness and Cognition*, *14*(2), 390–425.
- Offen, S., Schluppeck, D., & Heeger, D. J. (2009). The role of early visual cortex in visual short-term memory and visual attention. *Vision Research*, *49*, 1352–1362.
- Postle, B. R., Awh, E., Jonides, J., Smith, E. E., & D'Esposito, M. (2004). The where and how of attention-based rehearsal in spatial working memory. *Cognitive Brain Research*, *20*(2), 194–205.
- Ress, D., Backus, B. T., & Heeger, D. J. (2000). Activity in primary visual cortex predicts performance in a visual detection task. *Nature Neuroscience*, *3*(9), 940–945.
- Ruff, C. C., & Driver, J. (2006). Attentional preparation for a lateralized visual distractor: Behavioral and fMRI evidence. *Journal of Cognitive Neuroscience*, *18*(4), 522–538.
- Serences, J. T., Ester, E. F., Vogel, E. K., & Awh, E. (2009). Stimulus-specific delay activity in human primary visual cortex. *Psychological Science*, *20*(2), 207–214.
- Serences, J. T., Yantis, S., Culbertson, A., & Awh, E. (2004). Preparatory activity in visual cortex indexes distractor suppression during covert spatial orienting. *Journal of Neurophysiology*, *92*(6), 3538–3545.
- Silver, M. A., Ress, D., & Heeger, D. J. (2007). Neural correlates of sustained spatial attention in human early visual cortex. *Journal of Neurophysiology*, *97*(1), 229–237.
- Smith, E. E., Jonides, J., & Koeppel, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cerebral Cortex*, *6*(1), 11–20.
- Smith, A. T., Singh, K. D., Williams, A. L., & Greenlee, M. W. (2001). Estimating receptive field size from fMRI: Data in human striate and extrastriate visual cortex. *Cerebral Cortex*, *11*(12), 1182–1190.
- Smyth, M. M. (1996). Interference with rehearsal in spatial working memory in the absence of eye movements. *Quarterly Journal of Experimental Psychology Section A – Human Experimental Psychology*, *49*(4), 940–949.
- Somers, D. C., Dale, A. M., Seiffert, A. E., & Tootell, R. B. H. (1999). Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(4), 1663–1668.
- Supèr, H., Spekreijse, H., & Lamme, V. A. F. (2001). A neural correlate of working memory in the monkey primary visual cortex. *Science*, *293*, 120–124.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.
- Theeuwes, J., Belopolsky, A., & Olivers, C. N. L. (2009). Interactions between working memory, attention and eye movements. *Acta Psychologica*, *132*, 106–114.
- Tootell, R. B. H., Hadjikhani, N. K., Vanduffel, W., Liu, A. K., Mendola, J. D., Sereno, M. I., et al. (1998). Functional analysis of primary visual cortex (V1) in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(3), 811–817.