Surround Suppression effects on Working Memory performance in the general population and in people with schizophrenia: behavioural and ERPs evidence

Maria Cristina Filannino

A thesis submitted for the degree of PhD in Psychology

City, University of London
Department of Psychology
Cognitive Neuroscience Research Unit

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List of abbreviations

ANOVA	Analysis of Variance
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDA	Contralateral Delayed Activity
CM	Contrast Matching
CPZ	Chlorpromazine
df	Degrees of freedom
DLPFC	Dorsolateral pre-frontal cortex
EEG	Electroencelophagram
ERPs	Event Related potentials
GABA	Gamma-aminobutyric acid
LI	Lateral Inhibition
M	Mean
MANSA	The Manchester Short Assessment of Quality of Life
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
µV	Microvolts
mg	Milligrams
ms	Milliseconds
MOT	Motor Screening test
OD	Orientation Discrimination
PAL	Paired Associate Learning
$p\eta^2$	Partial Eta squared

PANSS	Positive and Negative Syndrome Scale
SD	Standard Deviation
SE	Standard Error
SS	Surround Suppression
SW	Slow Waves
SWM	Spatial Working Memory
SZ	Schizophrenia
WM	Working Memory
2IFCD	Two Interval Forced Choice Detection

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Declaration

I grant powers of discretion to the University Librarian to copy the whole, as well as sections, of this thesis without further reference to me. This covers only single copies for study and research purposes. The contents of this thesis are subject to standard conditions of acknowledgement. Last, I declare that the content of this thesis is my own work.

Abstract

Visual Working memory (WM) is a cognitive ability that allows to retain and manipulate information for a short period of time. WM is fundamental for mental functions and it supports several everyday activities such as learning, reasoning and language comprehension. In fact, impairments in WM, which are established in clinical conditions such as schizophrenia, have been related to poor quality of life factors, such as work/education status. Despite a large number of studies investigating WM, its underlying mechanisms are still a matter of debate both in the general population and in schizophrenia. A number of landmark studies have shown that early visual areas are active during the maintenance of information in WM, which emphasizes the importance of low-level visual processes in higher-level cognition. However, few studies have examined the basic visual processes underlying encoding into WM. For example, surround suppression (SS), in which the perception of a target is altered by the context in which it is embedded, is a largely known basic perceptual mechanism. However, it has not been explored whether SS can also impact WM representations. In three experiments, this project investigated how individual variations in the SS sensitivity affect WM in typical participants (Experiment 1), in patients with schizophrenia (Experiment 2) and in interaction with attention (Experiment 3). Stimuli that differentially triggered the strength of SS activity in early visual areas were used in a contrast matching (CM) task, an orientation discrimination (OD) task and in a WM task. In the WM task, participants viewed 1 to 3 sequentially presented gratings with different orientations surrounded by either orthogonal or parallel circular regions. They then judged whether the orientation of a subsequent probe (without a surround) matched any of the targets. ERPs signals were also measured during the WM task.

In Experiment 1, in the CM task, 18 participants confirmed that a central target grating appeared to have less contrast in the context of a co-oriented surround compared to an orthogonally-oriented surround. WM performance decreased with the increment of load. Moreover, it was also decreased in the parallel compared to the orthogonal surround but only for Load 1, but not throughout all WM loads. During WM encoding, posterior P2 amplitudes were significantly higher in the orthogonal compared to the parallel condition, suggesting that posterior P2 respond to SS mechanisms.

Experiment 2 tested 19 patients with schizophrenia and 20 matched controls. Confirming previous studies, patients contrast perception was not affected by the SS. In addition, the OD threshold was significantly higher in patients compared to controls and it negatively correlated with WM performance, suggesting that basic visual skills can relate to higher cognitive processing. Overall WM accuracy was lower in patients compared to controls. However, in contrast to controls, patients' WM accuracy was not affected by SS. During encoding, posterior P2 amplitudes were decreased with stronger SS only in controls but not in patients. However, both in Exp. 1 and Exp. 2, no direct correlations were found between P2 and WM performance.

Experiment 3 tested 20 participants on a modified version of the WM task in order to test whether LI interferes with attention. Here, a cue highlighted which item had to be memorised, over a list of three. Only behavioural data were collected. For hit rate, the position of the item to remember influenced performance only for the parallel, but not for the orthogonal surround. Overall, Experiment 3 seems to suggest that the focus of attention might be subjective to perceptual interference triggered by SS.

Overall, this project successfully confirmed SS effects on perceived contrast in typical participants and the lack of SS in patients with schizophrenia. In addition, the difference in surround conditions was reflected in P2 in typical participants (Exp 1) but not in patients (Exp 2), suggesting that encoding processes in schizophrenia might not occur in the same time window as controls. Moreover, these results showed that lower

basic perceptual skills (such as OD) in schizophrenia are associated with decreased WM performance.
However, in this project a direct relationship between stronger SS and WM was not found both in healthy and in schizophrenia populations. Future studies will need to clarify whether overall SS mechanisms (regardless of the strength of the effect) have an influence on WM performance compared to conditions in which SS is absent by the use, for example, of a “no surround” condition.

Chapter 1 – General Introduction

1. Working Memory

Working Memory (WM) is defined as a limited capacity system that allows to temporarily maintain and manipulate information not currently available to the senses but necessary to successfully achieve short-term behavioural goals (Purves et al., 2008). A wide range of everyday activities are supported by working memory, such as holding in mind a telephone number, mental calculation, constructing and understanding a sentence, composing a writing, thinking and reasoning. Thus, given its ubiquity in cognition, WM has been described as a representation of the functioning of the human mind (Baddeley, 2003; Baddeley & Hitch, 1974; D'Esposito & Postle, 2015; Goldman-Rakic, 1996).

Although several theories and models have been developed about the functioning of WM, they all describe WM with similar general features that distinguish it from short and long-term memory (Purves et al., 2008):

- WM provides the ability to maintain memory representations active until a specific behavioural goal is met;
- WM contents have a limited duration. The active maintenance can be very brief unless the traces are explicitly rehearsed;
- WM has a limited capacity. The number of items that WM can hold at the same time (WM load) varies between three and nine, which is in contrast with the much wider capacity of long-term memory (LTM);
- WM provides the ability to manipulate, organise and associate memory contents.

Some authors have described WM as a process that evolves in three consecutive stages. At first, memory items need to be perceived (encoding phase). Secondly, when visual items are no more physically present, memory representations have to be retained during a brief temporal delay (maintenance phase). Finally, memory internal representations are actively recollected in order to be matched with a probe item (retrieval phase) (Haenschel & Linden, 2011; Proskovec, Heinrichs-Graham, & Wilson, 2016).

In the next section, the main WM models will be described.

Working Memory models

The multicomponent model

In 1974 Baddeley and Hitch (Baddeley & Hitch, 1974) adopted the term WM in order to characterise a cognitive skill that was different from short-term memory. In those years, short-term memory (STM) was described as a unitary system heavily relying on long-term memory (LTM), and in charge of the short-term storage of information (Baddeley, 2003). Baddeley and Hitch (1974) described WM as a cognitive ability that could work independently from LTM and that not only stores but also actively processes information. In contrast to the dominant unitary model of short-term memory (STM), the authors proposed a multicomponent model for WM composed of a central executive system and two buffers, the phonological loop and the visuospatial sketchpad (Baddeley, 2003; Baddeley & Hitch, 1974). Both buffers are further divided into two subcomponents: a store, that hold information for a few seconds, and a rehearsal system which is used to refresh the memory traces and keep them active before they decay (Logie, 1995; Purves et al., 2008). Each of the two buffers interacts with a specific long-term memory representation: the phonological loop with sound and language knowledge; the visuospatial sketchpad with visual stimuli (Purves et al., 2008). Specifically, the visuospatial sketchpad is extremely limited in capacity, typically three/four items (Luck & Vogel, 1997), and it seems that objects and spatial information are held separately (Della Sala, Gray, Baddeley, Allamano, & Wilson, 1999).

The information contained in the phonological loop and in the visuospatial sketchpad is controlled by the central executive, a limited capacity attentional system which allocates its resources to each of the two buffers (Purves et al., 2008). In the original version of the multicomponent model, the central executive did not allow interactions between information stored in the phonological loop and in the visuospatial sketchpad. This created some inconsistencies in the model since it was not clear how information containing both semantic and visual features were managed by the central executive (Logie, Della Sala, Wynn, & Baddeley, 2000). Therefore, Baddeley proposed to overcome this issue by including a fourth component in the model, the episodic buffer (Baddeley, 2000).

The episodic buffer is a limited capacity system able to store multi-dimensional information. With this buffer, the information contained in the phonological loop and in the visuospatial sketchpad can be bind together, if needed. Moreover, instead of just reactivating old memories stored in LTM, the episodic buffer can also manipulate information in order to create new representations. Thus, the episodic buffer is regarded as a component of crucial importance for the view of WM as a flexible cognitive capacity, that is able to actively manipulate information (Baddeley, 2003).

To summarise, in the latest version of the multicomponent model of WM, the phonological loop and the visuo-spatial sketchpad store and process verbal and visuo-spatial information independently from LTM. The contents of the two loops are controlled by the central executive, which allocates specific attentional resources to them, and are bound and manipulated by the episodic buffer (Baddeley, 2003).

The Cowan model

An alternative model for WM has been proposed by Nelson Cowan (Cowan, 1988). In contrast to Baddeley's model, Cowan assumed that both WM and LTM rely on the same representations. Specifically, Cowan described WM processing as a two stages system. In the first stage, an unlimited number of rapidly decaying LTM representations are set in an active state. Unlike Baddeley's model, different kind of information (visual and phonological) are all held in the same LTM store. On the second level, a central executive system guides the allocation of attention only to a particular set of the previously activated representations, which can then be used for WM processing. However, the focus of attention of the central executive can only hold up to four items at the same time. Thus, in contrast to Baddeley's model, the capacity limitation of WM is attributed to the focus of attention that can allocate its resources to a limited number of items, and not to the representations activated in LTM that, instead, can be unlimited (Purves et al., 2008).

Current state of the art of WM models

For almost 40 years Baddeley's multicomponent model has been the main theoretical framework for WM. However, more recently another kind of models called "*state-based models*" have started to emerge in the literature. Echoing Cowan (1988), these models assume that an internal representation enters WM primarily if it has been

selected by the focus of attention (D'Esposito & Postle, 2015). According to D'Esposito and Postle (2015), the studies that support the state-based models can be included in two sub-categories depending on the type of stimuli used. The experiments that have focused on semantic stimuli (i.e. letter, words, digits) would belong to the category of *activated LTM models*, while research that have focused on how WM processes the perceptual features of the stimuli (such as colours, orientation, auditory pitches, etc.) belong to the *sensorimotor recruitment models* (D'Esposito & Postle, 2015). Specifically, the sensorimotor recruitment models introduced the concept that the systems and mechanisms that are active during the pure perception of items are also active during working memory processing of information (D'Esposito & Postle, 2015). Several studies have shown that very basic visual features such as spatial frequency, orientation, motion, can be easily retained with high specificity in WM (Pasternak & Greenlee, 2005). Moreover, evidence has suggested that the storage of sensory information, a function traditionally attributed to the prefrontal cortex activity (Fuster & Alexander, 1971; Goldman-Rakic, 1995b), is also supported by posterior sensory areas (Albers, Kok, Toni, Dijkerman, & De Lange, 2013; D'Esposito & Postle, 2015; Harrison & Tong, 2009; Magnussen, 2000; Magnussen & Greenlee, 1999; Pasternak & Greenlee, 2005; Zaksas, Bisley, & Pasternak, 2001).

This body of evidence has led to a revised interpretation of the contribution of both sensory areas and prefrontal cortex to WM processing.

The role of prefrontal cortex in WM

The studies of neural underpinnings of WM started in 1971 with monkeys studies. Fuster and Alexander (1971), measuring action potentials with single unit recordings, reported persistent activity in monkeys prefrontal cortex (PFC) during the delay period of a WM task in which a relevant item, that was no longer physically present, had to be retained. Twenty years later, with the advent of functional magnetic resonance imaging (fMRI), similar results were also demonstrated in humans. PFC was found to stay active throughout all the delay period and its activity was also directly related to behaviour (Courtney, Ungerleider, Keil, & Haxby, 1997; Zarahn, Aguirre, & D'Esposito, 1997). Some authors have interpreted the persistent activity found in the PFC during the delay period of WM as representing a storage system that keeps sensory information active (Goldman-Rakic, 1995b). However, recent evidence has suggested

that the persistent activity of the PFC might instead reflect the ability to hold multiple task-related goals (Rigotti et al., 2013). For example, Lee and colleagues (2013) showed their participants common objects while recording brain activity through fMRI. In some trials, they asked them to remember a fine perceptual detail of the image, while in other trials participants had just to remember the general category the object belonged to. Data were analysed using a Multi-Variate Pattern Analysis (MVPA) that allows isolating highly selective neural representation of the item in a given brain region (D'Esposito & Postle, 2015; Kriegeskorte, Formisano, Sorger, & Goebel, 2007; Lewis-Peacock, Drysdale, Oberauer, & Postle, 2012). MVPA decoding revealed more selective activity in the occipitotemporal cortex only during the fine perceptual judgment trials, while PFC areas were more active during the general category judgment trials (Lee et al., 2013). This study suggested that the PFC would not simply reflect storage of information per se, but the maintenance of high-level information for behavioural goals. Since the PFC is able to operate at a very abstract level, the functional role of its persistent activity during WM delay might reflect conceptual computations, such as task rules or categorisation of stimuli, fundamental for a successful performance of the task (D'Esposito & Postle, 2015).

Moreover, other evidence failed to find persistent activity during the delay period, challenging the idea that sustained activity is necessary for short-term retention in WM (D'Esposito & Postle, 2015; Lewis-Peacock et al., 2012). In an fMRI study, Lewis-Peacock and colleagues (2012) have used a multistep delayed recognition task. After the presentation of two stimuli, a first cue, which indicated which of the two items was relevant for a subsequent recall, was presented. The first cue was followed by a first probe (first step). After the first probe, a second cue was presented, which indicated which of the two items encoded at the beginning had to be matched with the following probe (second step). With this paradigm then, the same encoded item could be relevant for one step but irrelevant for the second step. Only items that were relevant for the specific step of the task could be decoded by MVPA analysis, while signals for the irrelevant items dropped at baseline. However, when in the second step, the previously irrelevant item became relevant, the neural signals associated with it were restored. Thus, the authors did not find persistent activity for all the encoded items, but only for the items that were relevant for the specific step of the task. According to Lewis-Peacock and colleagues (2012), the same internal representation can acquire different functional states. Specifically, the items that are relevant for WM are the

ones that fall within the focus of attention. The items outside the focus of attention are not necessarily forgotten, but they can be processed by WM only if attention is shifted to them according to the goals of the task. Therefore, the sustained activity observed during the delay period might actually reflect the focus of attention rather than memory contents (Lewis-Peacock et al., 2012).

The importance of attention into WM processing seems to be so remarkable that several authors support the idea that these two mechanisms are so strictly interconnected that they might be considered as overlapping (Awh, Vogel, & Oh, 2006; Awh & Jonides, 2001; Chun, 2011; Cowan, 1988; Gazzaley & Nobre, 2012; Noonan et al., 2017; Postle, 2006). The authors believed that the focus of attention within WM is mainly driven by top-down activity, an ability that allows to ignore distractors and select the relevant information that needs to enter WM (Gazzaley & Nobre, 2012).

Attention and Top-down signalling

Attention is fundamental to WM success. Evidence has shown that failures of attention are related to WM limitations (Vogel, McCollough, & Machizawa, 2005). For example, attention has been associated with capacity, the number of information that can be successfully recalled (Cowan, 2001; Hartman, Steketee, Silva, Lanning, & McCann, 2002). Vogel and colleagues (2005) have proposed that attentional failures are at the basis of a low WM capacity in healthy individuals, as they prevent the filtering of irrelevant information (Vogel et al., 2005).

Capacity is considered one of the most challenging WM features to address. Although its underlying mechanisms are still not fully clear, attention seems to play a role in capacity limitations (D'Esposito & Postle, 2015). Luck and Vogel (2013) conducted a series of studies using a change detection paradigm in which an array of coloured squares are presented for a few milliseconds followed by a blank delay. After the delay, the same array of squares is presented but in half of the trials, one square has changed colour. Participants have to determine whether the array has changed or not (Luck & Vogel, 1997). They estimated a WM capacity of three/four items. According to the authors, this capacity does not change even when the stimulus is complex, i.e. if it incorporates more than one feature. They concluded that WM is organised in a specific number of slots, each one storing one WM item regardless of its complexity (Luck & Vogel, 2013b; Vogel, Woodman, & Luck, 2001).

However, this “slot” model has been challenged in several studies (Bays, Catalao, & Husain, 2009; Bays & Husain, 2008; Bays, Wu, & Husain, 2011; Schneegans & Bays, 2016). In contrast to Luck and Vogel’s slots model, Bays and Husain (2008) have proposed a continuous resource model which suggest that WM might not be organized in slots because there is a unique attentional resource that has to be distributed across all items. In support of this model, Bays & Husain (2008) have tested memory recall (instead of recognition). Specifically, based on the errors made at retrieval, they calculated precision as a measure of the quality of the internal representations (Bays et al., 2009; Bays & Husain, 2008; Pearson, Raskevicius, Bays, Husain, & Hospital, 2014). In their paradigms, they typically present to participants a set number of coloured arrows (or bars) pointing at different directions. At retrieval, participants are not asked to recognize an orientation previously presented, but they are asked to reproduce (i.e. recall) the orientation of the arrow presented at the same location, or with the same colour, during the encoding phase. They have demonstrated that errors in the recall are larger when participants have to remember more items simultaneously compared to when they have to remember just one (Bays & Husain, 2008; Pertzov, Bays, Joseph, & Husain, 2013). The authors explained that memory precision fails when the memory set is larger because attentional resources must be divided across a larger number of items. However, since attentional resources are limited, the quality of each memory content will be poorer (Luck & Vogel, 2013b). Thus, it is still an open debate whether WM capacity limitations are due to a restricted number of slots or to limited attentional resources that tend to deteriorate the representation of each item (Luck & Vogel, 2013b).

Nevertheless, evidence has shown that WM capacity, and eventually WM performance, benefits from the ability of attention to filter out irrelevant information (Vogel et al., 2005). One of the fundamental functions of attention is, in fact, to highlight the information that needs to enter WM while suppressing the distractors, an ability achieved through top-down mechanisms (Miller & Cohen, 2001). Top-down activity is exerted by signals sent from anterior areas (such as the PFC or parietal cortex) to posterior sensory regions (such as visual cortex) in order to drive the flow of brain activity related to sensory stimuli, and to select relevant items to maximize performance in a given task (Braver, Gray, & Burgess, 2012; Duncan, 2001; Fuster, 2008; Miller & Cohen, 2001; Shallice, 1982).

Gazzaley and colleagues (2005) have proposed that there are at least two kinds of top-down signals that drive WM behaviour: one system would enhance task-relevant information and the other would inhibit task-irrelevant information. To support this idea, the authors conducted an fMRI study in which they asked participants to attend either faces or scenes or to passively view the screen ignoring the stimuli. They found that during the active encoding of faces, the fusiform face area (FFA), an area in the visual cortex associated with face processing, was more active compared to the passive viewing, whereas FFA activity was suppressed when faces had to be ignored (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005). To demonstrate the ability of top-down signals to select specific items over the distractors, several studies have used cues, task signals appearing before or after the presentation of memory items with the aim of orienting the focus of attention on a particular stimulus or location. Indeed, the use of cues seems to be extremely beneficial for WM behaviour (Bollinger, Rubens, Zanto, & Gazzaley, 2010; Griffin & Nobre, 2003; Hawkins et al., 1990; Müller & Findlay, 1987; Palmer, 1990; Posner, 1980a). Griffin and Nobre (2003), for example, have used a delayed match to sample WM task in which four crosses of different colours were presented on the screen and, after a delay, participants had to judge whether a probe cross appearing in the middle of the screen was present or not in the encoded array. During the task, a cue consisting of an arrow indicating the position of the cross that was about to be probed (validly for 80% of trials and invalidly for the remaining trials) was presented either before (pre-cue) or after (retro-cue) the memory array. In a third control condition, a neutral cue (a square, instead of an arrow) did not highlight any location. Both for pre-cue and retro-cue, reaction times were faster in valid cue trials and accuracy decreased for invalid cue compared to the neutral cue condition. In a follow-up experiment, the authors replicated the same paradigm but they also collected Event Related Potentials (ERPs) data. ERPs are extracted from Electroencephalography (EEG) and they represent changes in voltages in the brain associated with perceptual and cognitive events (Luck, 2005). A detailed description of neural mechanisms and functions of the ERPs can be found later in the chapter. They found that N1 at posterior visual electrodes was elicited both for pre and retro-cue trials in the contralateral hemifield to the attended location, suggesting an attentional modulation of this visual component (Griffin & Nobre, 2003).

According to further evidence, this attentional modulation of visual areas exerted by top-down signals might reflect a preparatory activity arising after the appearance of

the pre-cue (Bollinger et al., 2010). Bollinger and colleagues (2010) used an object-delayed response WM task in which participants were asked to indicate whether either a probe face or scene matched or not a previously encoded stimulus. In half of the trials, a pre-cue indicated whether a face or a scene was about to appear, while in the other half a neutral cue was not informative about the following category of stimuli. The authors found in the time interval between the pre-cue for faces and stimulus appearance an increment in connectivity between fronto-parietal areas and the fusiform face area (FFA). This increment also predicted WM performance. The authors concluded that this preparatory top-down activity driven by expectations induced by the cue, increased WM accuracy (Bollinger et al., 2010).

Attention can drive WM behaviour not only in terms of expectations. The focus of attention can improve WM also by enhancing encoding mechanisms. Rutman and colleagues (2009) asked participants to selectively attend either faces of scenes that were shown overlapped. They found that P1 ERP component at lateral occipital electrodes was higher in trials in which participants had to attend the faces compared to the trials in which scenes had to be remembered. Moreover, this modulation also predicted WM performance, showing that visual cortex activity at encoding can be directly linked to WM behaviour. The authors concluded that visual signals, according to task goals, are able to prioritise specific WM contents over irrelevant items (Rutman et al., 2009).

This concept has been more explicitly explored by Zokaei and colleagues (Zokaei, Manohar, Husain, & Feredoes, 2014) in a study aimed to test how selected WM items are retained in visual areas in a privileged state compared to non-target items. The authors applied Transcranial Magnetic Stimulation (TMS) over MT+, an area in the visual cortex associated with motion processing (Bisley & Pasternak, 2000; Pasternak & Greenlee, 2005). In the task, two groups of either green or red moving dots were presented above and below a fixation cross. During the retention delay, the fixation cross turned either green or red and the participant had to indicate whether the colour corresponded to the upper or lower group of moving dots previously encoded. The author named this phase as "incidental cueing" since it was aimed to facilitate the performance of the following task. After a further delay in which TMS pulses were applied (with an ineffective or effective intensity), either a red or green arrow appeared and participants were then asked to adjust the arrow to the motion direction of the dots with the same colour. Crucially, the colour of the probe arrow matched or

not the colour of the "incidental cue". The authors found that in the ineffective TMS condition participants remembered the congruent cued direction with greater precision compared to the incongruent cued direction, showing that specific WM contents have entered a privileged state over others. However, with effective high-intensity TMS, thus temporarily impairing visual cortex activity, this advantageous effect of the cue disappeared since the behavioural responses did not differ anymore between congruent and incongruent cue trials. Thus, when visual cortex activity was disrupted with TMS, the privileged state of the WM item associated with the congruent cue was impaired. The authors suggested that early visual areas contributed in maintaining specific WM items in a privileged state over other non-target items, providing evidence that the visual cortex, traditionally associated only with a perceptual function, is active during the retention of short-term visual information that is placed in a favourable state for WM recall (Zokaei et al., 2014).

Altogether, this evidence suggests that attention drives WM behaviour through top-down mechanisms that, by regulating activity in sensory areas, enhance relevant information and suppress the irrelevant ones. In addition, these studies seem to highlight that the visual cortex contributes to the retention of WM information (D'Esposito & Postle, 2015; Fallon, Zokaei, & Husain, 2016; Zokaei et al., 2014).

In light of this research, further studies have explored more closely the specific contribution of the sensory areas to WM performance.

The role of sensory areas in WM

A large number of studies have demonstrated the ability of WM to retain basic visual information (such as orientation, motion, spatial frequency) for several seconds and have tested to what extent the visual cortex is involved throughout the WM process (Pasternak & Greenlee, 2005).

Evidence has shown that the efficient encoding of WM information is a predictor of WM performance. Haenschel and colleagues (2007) carried out an ERPs study using a delayed matching to sample WM task with early onset schizophrenia patients and healthy controls. At encoding, they found that visual P1 increased with the increment of memory load in the healthy population. Moreover, P1 amplitudes correlated with better WM accuracy. These results suggest that visual ERP activity during the encoding phase directly influences WM performance (Haenschel et al., 2007).

The modulation of visual areas depending on memory load has also been found in fMRI studies. Emrich and colleagues (2013), tested how the number of items to encode affects visual cortex activity. In their fMRI experiment, three patches of coloured moving dots were presented in consecutive order. They manipulated memory load by varying the number of dots that moved in a coherent direction. After a delay, a coloured line appeared on the screen and participants had to adjust its orientation according to the direction of the colour-match moving dots. MVPA analysis revealed that visual cortex activity varied according to memory load. Specifically, in high load conditions, when the task was more demanding, they found decreased neural information in the patterns of activity in sensory areas, and this related to a decline in accuracy. Thus, the authors suggested that low-level sensory areas can play a critical role not only during encoding but also during the retention of memory items (Emrich, Riggall, LaRocque, & Postle, 2013). This has been demonstrated by further studies that have found activity in primary visual areas also during the maintenance phase. In fMRI studies with WM tasks testing orientation discrimination of simple gratings, BOLD signals in visual areas during the maintenance phase were found to be a predictor of which orientation was held in memory. More importantly, the BOLD signal in visual areas during maintenance resembled the one at encoding (Albers et al., 2013; Harrison & Tong, 2009).

Despite the importance of the maintenance phase as a reflection of the ability to keep memory traces active, studies have shown that early visual processes occurring during the encoding phase seem to be critical for the formation of the internal representations that will be eventually remembered in the later stage of retrieval (Haenschel et al., 2007; Peterson et al., 2014). Peterson and colleagues (2014) used a WM delayed matching to sample task while recording Steady-State Visual Evoked Potentials (SSVEP - EEG signals elicited by flickering items). During the task they showed bilaterally four items and, after a delay, one single item appeared in one of the four locations and participants had to decide whether the probe item was previously presented in that location or not. Comparing SSVEP of successfully remembered items with SSVEP of forgotten items, they found that SSVEP signals at encoding were larger when the items were successfully retrieved compared to when the items were forgotten. They concluded that effective encoding of memory representations, driven by attentional resources, has a direct influence on the

subsequent stages of WM. If an item is not successfully encoded, then it cannot be successfully maintained and retrieved (Peterson et al., 2014).

Moreover, visual cortex activity related to memory encoding seems to differ from the activity related to purely perceptual mechanisms. Sneve et al. (2012) carried out an fMRI experiment showing Gabor gratings. During retention, a tone was played either at the beginning or towards the end of the delay period. The tone played at the beginning of the delay period indicated to prepare for a memory task in which the orientation of the previously presented Gabor was relevant. The tone played at the end of the delay period indicated to prepare for an orientation discrimination task in which the previously presented Gabor was not relevant. Therefore, while the first tone condition was considered as a memory trial since the participants had to hold the memory information, the second tone condition served as a perceptual trial, since the participants could "drop" the memory trace. They found that specific areas in the visual cortex (dorsal V3a/b and ventral LO1/2) remained active even seconds after the stimulus had disappeared. More critically, across all visual areas, BOLD activity was increased when participants had to memorise the stimulus compared to when they just had to perceive it. Thus, since visual cortex activity seems to be increased during WM encoding compared to a simple perceptual task, the authors suggested that visual areas contribute to the active processing of WM contents (Sneve, Alnæs, Endestad, Greenlee, & Magnussen, 2012).

Furthermore, Serences et al (2009) have shown that activity in sensory regions during encoding can hold very specific information about the items that have to be memorised. In an fMRI study, they asked participants to remember either the colour or the orientation of two Gabor patches separated by 10 seconds of delay. MVPA decoding revealed that patterns of activity in the primary visual cortex (V1) differed depending on whether participants had to remember the colour or the orientation of the stimuli. Moreover, V1 activity observed during the delay period was similar to the one recorded during the encoding phase. The authors concluded that the visual cortex does not passively perceive memory information but that, already at encoding, it is actively tuned towards WM targets. V1 might be driven by top-down signals that select specific perceptual features relevant to the task, which can be retained also during the maintenance phase (Serences, Ester, Vogel, & Awh, 2009).

In sum, this evidence supporting the sensorimotor recruitment models demonstrates that visual cortex activity during the encoding phase can give a fundamental contribution to the overall WM process, since it can hold specific perceptual information about the items (Serences et al., 2009) and keep them active during the delay period (Albers et al., 2013; Harrison & Tong, 2009). Moreover, visual cortex activity is modulated by memory load (Emrich et al., 2013; Haenschel et al., 2007), it can directly influence the later stages of maintenance and retrieval along with behavioural performance (Haenschel et al., 2007; Peterson et al., 2014).

However, it is still not clear whether specific mechanisms that characterise visual perception can also affect the formation of memory representations and eventually influence WM performance. Visual perception involves complex mechanisms that are certainly triggered also during WM encoding. Therefore, it is important to understand more deeply how vision is computed and processed in the brain and the mechanisms underlying specific functions of visual perception.

2. Visual perception

General description of the visual system

The primary visual pathway of perception refers to the major route that begins in the retina of the eye and ends in the primary visual cortex (Purves et al., 2008).

Once the external light entrains the optical elements of the eye, it is transduced into a neural signal. This transduction process is computed in the retina by two types of specialized receptor cells: the rods, which activates in the presence of very low levels of light, and cones, which activates with high light intensities and are also responsible for the perception of details and colours. The information arising from both cells converges onto the retinal ganglion cells, whose axons leave the retina and are mainly connected to the lateral geniculate nucleus (LGN) in the thalamus. The LGN is structured in layers: two Magnocellular layers (containing larger neurons) and four Parvocellular layers (containing smaller neurons), which respectively have different functions (Purves et al., 2008). The Magnocellular pathway projects primarily to the middle temporal visual areas, inferior parietal cortex and other regions within the dorsal visual stream (areas that leads from the striate cortex and other visual areas into the parietal lobe) and it is more sensitive to low spatial frequency, low contrast, achromatic stimuli. The Parvocellular pathway projects predominantly to the lateral

occipital complex, inferior temporal and other ventral stream areas (areas that leads from the striate cortex to the inferior part of the temporal lobe) and it is tuned towards high spatial frequency, high contrast, chromatic stimuli (Butler et al., 2007; Derrington & Lennie, 1984; Lund, 1973; Merigan & Maunsell, 1993; Schechter et al., 2005; Schroeder, 1998; Tootell, Hamilton, & Switkes, 1988).

From the LGN, visual information is projected to the primary visual cortex (V1) (Purves et al., 2008). Although at a subcortical and a cortical level the magno and parvocellular systems are mostly separated, some evidence has suggested that they might converge in some layers of V1 and extra-striate cortex (Ferrera, Nealey, & Maunsell, 1992; Gegenfurtner, Kiper, & Fenstemaker, 1996; Levitt & Lund, 1994; Maunsell & Nealey, 1990; Vidyasagar, Kulikowski, Lipnicki, & Dreher, 2002; Yabuta, Sawatari, & Callaway, 2001). The convergence of the two pathways might have a functional relevance since it might work as a "frame and fill" mechanism in which the magnocellular pathway sends a template of very rapid but low resolution information to the ventral stream that then will be filled by the much slower, but more fine-grained, information arriving from the Parvocellular pathway (Chen et al., 2007; Javitt, 2009; Kveraga, Boshyan, & Bar, 2007). From V1 visual information is transferred to the extra-striate cortex, the occipital area surrounding V1 that is highly specialised in the processing of perceptual details such as colour or motion. At this level, top-down influences already occur in order to integrate and control the large flow of information coming from subcortical and primary sensory regions (Purves et al., 2008).

All the areas involved in visual processing communicate in a feedforward/feedback fashion (Purves et al., 2008). Specifically, information is feedforward from the subcortical level (the LGN) towards the striate and extra-striate cortex and then to the higher-level cortical areas. At the same time, higher level areas send feedbacks to lower level regions in order to gate the sensory information that is particularly relevant to achieve behavioural goals. Overall, this feedforward/feedback mechanism of communication between areas is modulated by lateral connectivity (Purves et al., 2008). Lateral connectivity refers to different types of neural interactions, specifically to the several ways in which neuronal activity can be influenced by their neighbouring cells. Lateral connectivity can be exerted in form of top-down feedback, lateral excitatory or lateral inhibitory activity (Butler, Silverstein, & Dakin, 2008). In particular, lateral inhibition in the early visual cortex can be very widespread (Sachdev, Krause, &

Mazer, 2012) and it would represent a fundamental feature of the functioning of sensory cortex (Blakemore & Tobin, 1972).

Lateral inhibition

In the early visual system, lateral inhibition (LI) seems to occur everywhere as it is seen as early as in the retina, at least in animals such as the limulus (Hartline, Wagner, & Ratliff, 1956), frog (Barlow, 1953) and cat (Kuffler, 1953).

LI refers to the suppressive activity of visual neurons towards the post-synaptic potentials of their neighbouring cells (Butler et al., 2008; Carandini & Heeger, 2012; Sachdev et al., 2012). LI activates when the responses of a neuron are inhibited by additional stimuli placed outside its classical receptive field (Blakemore & Tobin, 1972; Carandini & Heeger, 2012). The classical receptive field (CRF) in V1 is defined as the region where the onset (or offset) of a stimulus generates a firing rate. Non-classical receptive fields (nCRF), instead, refers to the region in which the onset (or offset) of a stimulus do not generate a firing rate. However, if nCRF is adjacent to a CRF, the responses of the nCRF can modulate the firing rate of the CRF (Angelucci & Sainsbury, 2006). In V1, CRF and nCRF are organised concentrically in a centre and surround fashion and have an opponent structure, so that stimulation of the surround suppresses the activity in the centre of the CRF (Sachdev et al., 2012). In extra-striate areas, receptive fields can cover a much larger fraction of the visual field (Purves et al., 2008). Nevertheless, they are still regulated by suppressive mechanisms (Zenger-Landolt & Heeger, 2003).

There is general agreement that lateral inhibitory mechanisms contribute to surround suppression (SS), the phenomenon by which contrast perception of a central target is altered by the presence of a high contrast surround (Chubb, Sperling, & Solomon, 1989; Dakin, Carlin, & Hemsley, 2005; Yoon et al., 2009).

Surround Suppression - Behavioural evidence

Although the surround suppression (SS) effect can vary significantly within participants (Cannon & Fullenkamp, 1993), it typically occurs when the perceived contrast of a central patch can be enhanced or suppressed if it is surrounded by a larger stimulus (Xing & Heeger, 2001).

Behaviourally, SS has been measured primarily with contrast matching tasks. For example, Xing & Heeger (2001) used a contrast matching task in which participants were asked to compare the contrast of a grating with the contrast of the same grating embedded in a larger surround. The paradigm was a two interval forced choice in which the isolated patch and the patch with the surround were presented in the first and second intervals in a randomised order throughout the trials. Participants pressed a button to indicate if the central patch with the highest contrast appeared in the first or second interval. In order to test different sizes of the effect, the authors varied the orientation and size of the surround, whereas the central gratings were always vertically oriented. In different conditions the surround could be either vertical (i.e. parallel to the central grating) with a 12-degree diameter; vertical with a seven-degree diameter; horizontal (i.e. orthogonal to the central grating) with a 12-degree diameter; horizontal with a seven-degree diameter (Figure 1.1). Moreover, while the contrast of the surround was kept constant, the contrast of the central patch was varied with a staircase procedure, in which the matching contrast was decreased or increased by one step in the following trial if the participant reported that the isolated patch had respectively a higher or a lower contrast than embedded patch (Xing & Heeger, 2001).

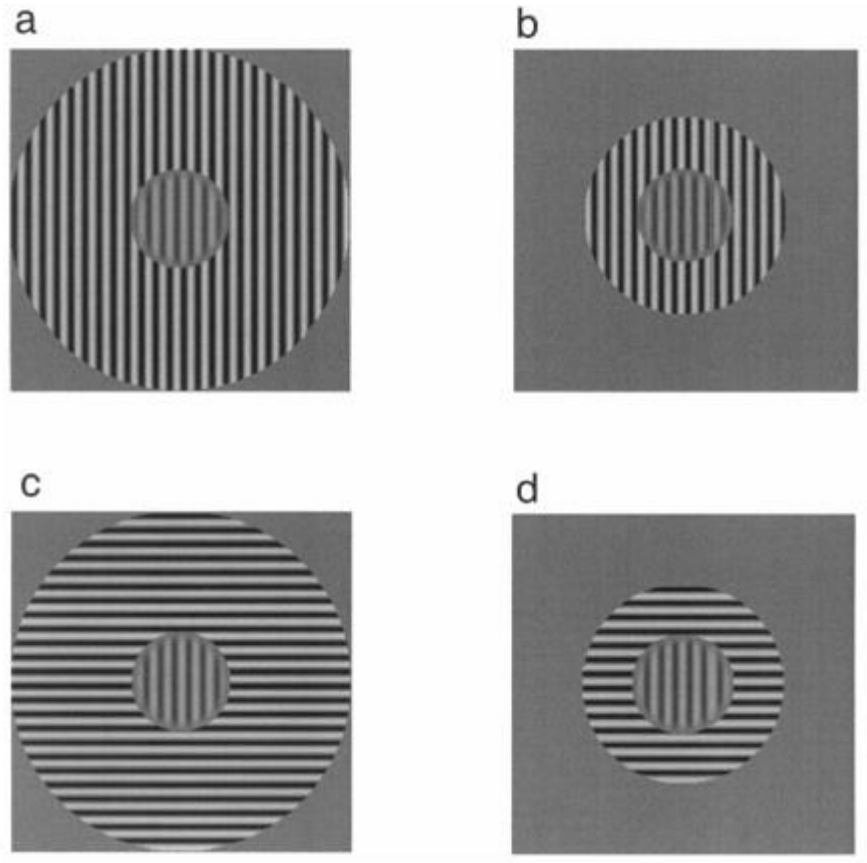


Figure 0.1. Stimuli used by Xing and Heeger (2001) in a contrast matching task. A central vertically oriented target was embedded in a parallel-wide surround (a), in a parallel-narrow surround (b), in a horizontal-wide surround (c) or in a horizontal-narrow surround (d). (b) and (d) conditions induced enhanced perceived contrast of the central target. (a) and (c) conditions induced decreased perceived contrast of the central target, which was stronger in the parallel surround condition (a).

Confirming previous results (Cannon & Fullenkamp, 1993), they found that the contrast of the central patch was perceived as decreased or enhanced depending on the contrast and size of the surround. Specifically, an enhancement was produced when the contrast of the surround was lower than the contrast of the central patch, and when the surround was reduced in size. Suppression was produced when the contrast of the surround was higher than the contrast of the central patch, and when the surround was bigger in size (Cannon & Fullenkamp, 1993; Xing & Heeger, 2001). As in previous studies, they also confirmed that the suppressive effect was highly orientation specific. The maximal suppression was induced by the parallel surrounds compared to the orthogonal, in which the suppression was greatly reduced (Solomon, Sperling, & Chubb, 1993; Xing & Heeger, 2001). This result is in line with physiological studies showing that inhibition is stronger when the centre and the surround have the

same orientation (DeAngelis, Freeman, & Ohzawa, 1994; Knierim & van Essen, 1992; Polat & Norcia, 1996).

In addition to contrast, SS can also alter the perceived orientation. The SS effect on perceived orientation is typically measured with orientation discrimination (OD) tasks in which a reference grating is presented sequentially to a test grating (shown either isolated or embedded in a larger surround) and participants have to judge whether the test grating is tilted clockwise or anticlockwise relative to the reference (Wilks, Rees, & Schwarzkopf, 2014). The perceived orientation is typically altered depending on the orientation difference between the target and the surround. Specifically, if the orientation difference between the target and the surround is between 10 and 20 degrees, the target will tend to be perceived as rotated towards the opposite direction of the surround, creating a "repulsive" effect. On the contrary, when the orientation difference between the target and the surround becomes larger, an "attraction" effect in produced, in which the orientation of the target will be perceived as rotated towards the same direction of the surround (Figure 1.2) (Schwartz, Sejnowski, & Dayan, 2009). However, the attractive effect can be quite small and not always measurable (Clifford, 2014). It has been consistently reported that this effect can vary substantially among individuals both at a behavioural and at a neural level (Song et al., 2013).

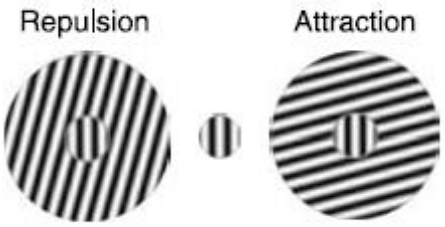


Figure 0.2. Adapted from Schwartz, Sejnowski, & Dayan, 2009. Repulsion and attraction in surround suppression on orientation discrimination. The central grating is vertical. However, the surround makes the grating appeared as rotated in the opposite (Repulsion) or in the same direction of the surround (Attraction).

For example, Song, Schwarzkopf, & Rees (2013a) compared orientation discrimination with SS effect on orientation discrimination. To measure the orientation discrimination threshold, they used an orientation discrimination task in which two circular gratings with different orientations appeared over two separate intervals. Participants had to judge whether the orientation of the second interval was rotated clockwise or

anticlockwise compared to the first interval. To measure the SS effect, the authors performed the same task but only in one of the intervals a larger surround was placed outside the central grating. Overall, they found a high inter-individual variability both for OD threshold and for the SS effects on orientation discrimination. Interestingly, they also found that OD threshold strongly correlated with the SS effect. Specifically, individuals that showed lower OD threshold also tended to be more immune from the SS effect. Thus this evidence shows a high inter-individual variability and that lower OD threshold is associated with a lower SS effect (Chen Song et al., 2013a).

In sum, the presence of a high contrast surround can alter the perceived contrast and orientation of a central target, creating a surround suppression effect.

Several studies have shown that this effect, which is driven by lateral inhibitory activity, can be measured also at a neural level. Specifically, the neural responses of neurons in the visual cortex appear suppressed when the stimuli are embedded in a larger surround (Blakemore & Tobin, 1972; Vanegas, Blangero, & Kelly, 2015; Zenger-Landolt & Heeger, 2003).

Surround Suppression - Neural evidence

One of the first physiological evidence of lateral inhibition was shown by Blakemore and Tobin in the cat visual cortex (1972). In their study, the authors measured single unit spike activity in Brodmann area 17 and 18 of cat's visual cortex. Then they presented a bar and made it oscillate in order to find the various receptive fields corresponding to the different orientations. After having identified a neuron's preferential orientation, they presented the bar along with a high contrast surround. In this condition, they found that the responses of that neuron were clearly inhibited (Blakemore & Tobin, 1972).

More recently, other studies aimed to show the same effect in humans. Zenger-Landolt & Heeger (2003) carried out a study in order to specifically link behavioural results with fMRI findings. They tested participants in an fMRI scanner and showed them a circular grating surrounded by a bigger surround region. Between the circular grating and the bigger surround, they build an annular target region divided into eight segments (see Figure 1.3, page 59). Participants, while fixating the middle of the screen, had to indicate whether one of the segments of the annulus had a lower contrast compared to the others, or whether all the eight segments had the same

contrast. In a passive viewing additional control task, each trial consisted of two stimulus intervals, with the first being task-relevant. The target stimulus always appeared in the first interval with pedestal contrast varying between 0% and 60%. A 100% contrast surround could appear together with the target either in the first interval (the task-relevant one) or in the second interval (task-irrelevant). In a third condition, no surround was shown in both intervals. At a behavioural level, the surround impaired contrast discrimination. The fMRI data matched this result since the responses to the target were lower when the surround was present. However, they found that the suppression effect was stronger in extra-striate areas (V2 and V3) compared to V1. The authors have advanced two different interpretations regarding the surround suppression effects in V1 and V2/V3. The authors have suggested that in V1 the surround might have induced suppression indirectly, through lateral inhibitory activity exerted by neighbouring neurons. The visual angle of the target annulus (3.3) was bigger than the usual classical receptive field size of V1 (from 0.5 to 1, (Cavanaugh, 2002; Smith, Singh, Williams, & Greenlee, 2001)). Thus, since the annulus was larger compared to V1 typical receptive fields, the neurons included in this area likely did not receive any direct input from the surround stimulus, but only indirect inputs (Zenger-Landolt & Heeger, 2003). In contrast, in V2/V3 a direct suppressive effect from the surround might have occurred since the receptive fields in these areas are larger compared to RF in V1. This study provides evidence for a continuity between behavioural and fMRI data suggesting that V1 is directly involved in the lateral inhibitory phenomena observed in behavioural performance (Zenger-Landolt & Heeger, 2003).

Further studies have also provided electrophysiological measures of LI and SS. In a passive viewing experiment, Vanegas, Blangero, & Kelly (2015) measured the steady-state visual evoked potentials (SSVEP) of 21 healthy participants that, while fixating a small central fixation dot, were presented with either one or four vertically oriented circular grating that flickered at different frequencies, and embedded within a static (non-flickering) surround. Orientation specificity of SS was tested in two conditions in which the surround was either vertically or horizontally oriented to the flickering stimuli. In a separate experiment, they asked participants to perform a contrast matching task consisting in a two interval forced choice in which, at a random order, they presented the same stimuli either in isolation or embedded in the surround. Participants had to indicate whether the contrast of the stimuli was greater in the first

or in the second interval. They found large reductions in the SSVEP responses at all flickering frequencies depending on the surround orientation. Specifically, the SSVEP effect was greater when the target and the surround had the same orientation (vertical), with very little suppression seen with the orthogonal surround. Moreover, the magnitude of the suppression correlated with the contrast perceived in the contrast matching task (Vanegas et al., 2015).

Thus, both fMRI and EEG experiments have confirmed that the presence of a larger surround on a target stimulus induces reduced activity in primary visual cortex.

To summarise, LI refers to the suppressive activity exerted by neighbouring cells outside the classical receptive field of a neuron. LI activity seems to directly influence the surround suppression (SS) effect, in which the contrast perception of a central target is altered by the presence of a larger surround (Xing & Heeger, 2001). Moreover, SS is larger if the surround is vertically oriented to the target and it can be directly measured in the visual cortex with fMRI and EEG signals (Vanegas et al., 2015; Zenger-Landolt & Heeger, 2003).

The functional role of SS is still a matter of debate (Sachdev et al., 2012). One function attributed to SS is that it minimises the repetitive information in the visual scene, by activating the smallest number of neurons in response to a specific stimulus. This would decrease the high redundancy of natural scenes, making perception more efficient (Sachdev et al., 2012). Other interpretations have proposed that SS would enhance the precision of sensory representations by, for example, heightening the sensitivity to contrast edges, facilitating the perception of orientation discontinuity, texture, contours or by favouring the identifications of targets via pop-out mechanisms (Allman, Miezin, & McGuinness, 1985; Bakin, Nakayama, & Gilbert, 2000; Colin Blakemore & Tobin, 1972; Calford & Semple, 1995; Gilbert & Wiesel, 1990; Knierim & van Essen, 1992; Laskin & Spencer, 1979; Levitt & Lund, 1997; Mountcastle, 1975; Nelson & Frost, 1978; Sutter & Loftus, 2003; Von Békésy, 1967; Walker, Ohzawa, & Freeman, 1999).

It is reasonable to assume that LI and SS systems are active not only when an item has to be simply perceived but also when it needs to be memorised. If LI contributes to the precision of items perception, it might also potentially affect the formation of internal memory representations. However, to my knowledge, the effects of this perceptual phenomenon on memory contents stored in visual WM has not yet been explored.

In addition, a large body of evidence has found weakened LI mechanisms in psychiatric disorders, such as in schizophrenia. Several studies have found that contrast perception in people with schizophrenia is not affected if a target is presented embedded in a high contrast surround (Dakin et al., 2005; Yoon et al., 2009). However, it is still unclear whether these basic perceptual mechanisms altered in schizophrenia can also affect higher-order cognitive processing, such as working memory, also known to be impaired in this condition.

3. Schizophrenia

General description of the disease

Schizophrenia has been first described by Kraepelin (Kraepelin E., 1971) and Bleuler (Bleuler, 1950) which observed in their patients, symptoms such as difficulty in thinking straight, flattened affect, loss of goal-directed behaviour, retreat into an inner world that deteriorated in the long-term.

As today, schizophrenia (SZ) is placed among the world's top ten causes of disability and it is considered as the most impairing among the psychiatric illnesses (Mueser & Mcgurk, 2004). People with schizophrenia can be severely affected in many aspects of their everyday life such as in the ability to work, attend school, have close relationships and enjoy leisure time. The impaired functioning can be so severe that patients might need entitlement for disability and assistance in basic needs such as housing, self-care, food and clothing (Mueser & Mcgurk, 2004). Moreover, SZ is associated with high rates of mortality due to suicide, accidents, and cardiovascular and respiratory diseases (Brown, 1997).

Clinical description

SZ has a typical onset between the age of 16 and 30 years old, and more infrequently after the age of 45 (Almeida et al., 1995). SZ is characterised by three main symptoms: *Positive symptoms* such as psychosis (i.e. loss of contact with reality), false beliefs (persecutory, grandiose, and somatic delusions), abnormal perceptual experiences (visual, olfactory auditory hallucinations), bizarre behaviour; *Negative symptoms* such as blunted affect, anhedonia, apathy, alogia (reduced quantity of speech); and

Cognitive impairments including dysfunctions in attention and concentration, psychomotor speed, learning and memory, executive functions (such as abstract thinking, problem solving), perseveration or inhibition of irrelevant information, working memory (Barch & Ceaser, 2012; Keefe, 2008; Lee & Park, 2005; Mueser & Mcgurk, 2004; Nuechterlein et al., 2014). The onset of the disease can develop over a five years period and it typically starts with the emergence of negative symptoms followed by cognitive and social impairments and culminating several years later with the manifestation of psychotic symptoms (Häfner, Löffler, Maurer, Hambrecht, & Heiden, 1999; Häfner, Maurer, Löffler, & an der Heiden…, 2003). Once SZ has developed, the impairments are usually present throughout the whole life, although with different intensities. Specifically, whereas the presence and severity of positive symptoms tend to be episodic, negative symptoms and cognitive impairments seem to remain stable over time. In addition, pharmacological treatment (typical and atypical antipsychotics) broadly functions to reduce positive symptoms and prevent their relapse (Kane & Marder, 1993), but it seems to have low or no impact on negative and cognitive symptoms (Greden & Tandon, 1991; Mueser & Mcgurk, 2004).

For these reasons, it is believed that negative symptoms and cognitive deficits have the biggest impact on the difficulties that people affected by schizophrenia have to persistently face in their everyday life, even when they are under drug treatment and are not experiencing acute psychiatric symptoms (Green, Kern, Braff, & Mintz, 2000).

Working memory impairments in schizophrenia

Several studies have shown that cognitive deficits in patients can be a predictor of limitations of general everyday living such as employment status (Meitzer, Thompson, Lee, & Ranjan, 1996), residential status (Shamsi et al., 2011), social functioning (Green, 1996). Therefore, along with positive and negative symptoms, cognitive impairments are now considered as a core feature of the disease. Within the various cognitive dysfunctions, however, the ones related to working memory seem to represent a particularly crucial issue in schizophrenia, given that working memory supports many day-to-day activities, such as learning, reasoning and language comprehension, and it seems to be a predictor of quality of life factors, such as work/education status (Hubacher et al., 2013; Lee & Park, 2005; Shamsi et al., 2011). WM deficits are well established in SZ since they have been found in a variety of tasks with different kind of

stimuli (verbal, visual, spatial, etc.) (Lee & Park, 2005). Moreover since WM deficits have been found in biological relatives of SZ patients (Conklin, Curtis, Katsanis, & Iacono, 2000; Myles-Worsley & Park, 2002; Park, Holzman, & Goldman-Rakic, 1995) and healthy individuals with schizotypal traits (Park, Holzman, & Lenzenweger, 1995; Tallent & Gooding, 1999), Lee and Park (2005) suggested that WM could be a potential candidate for an endophenotypic marker for SZ. However, the sources of WM dysfunctions in SZ are still unclear (Lee & Park, 2005). Since deficits in manipulation (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Kim, Glahn, Nuechterlein, & Cannon, 2004), interference control (Fleming, Goldberg, Gold, & Weinberger, 1995; Goldberg, Patterson, Taqqu, & Wilder, 1998), and information updating (Ganzevles & Haenen, 1995; Goldberg et al., 2003; Perlstein, Dixit, Carter, Noll, & Cohen, 2003) have been repeatedly found, there has been general agreement that WM deficits in SZ are mostly related to storage, maintenance and retrieval abilities (Barch, 2006; Hartman et al., 2002; Lee & Park, 2005).

However, other evidence has shown that dysfunctions are already present in the encoding phase. In a meta-analysis, Lee and Park (2005) found that although WM impairments in schizophrenia are modality independent, the deficits found in visual working memory seem to be more consistent compared to verbal working memory. In particular, Lee and Park (2005) suggested that visual working memory impairments might be also attributed to inefficient encoding. This claim seems to be supported by several evidence (Bittner et al., 2015; Dias, Butler, Hoptman & Javitt, 2011; Haenschel et al., 2007; Hartman et al., 2002; Javitt, 2009; Tek, Gold, Blaxton, & Wilk, 2002).

Hartman and colleagues (2002) carried out a study aimed to demonstrate that WM deficits in SZ can be attributed to slowed encoding processing, rather than poor retention of information over time (Hartman et al., 2002). They tested participants with SZ and healthy controls on a delayed matching to sample task in which participants had to memorise three coloured rectangles. The subsequent delay period was designed in two different conditions: a 0-seconds delay condition, in which the probe rectangle was shown after 500ms of a blank screen delay, and a 6-seconds delay condition, in which the probe rectangle was shown after six seconds delay, filled with a verbal task used as a distractor. At retrieval, participants saw three rectangles and they had to identify the one that was present in the previously encoded set. To manipulate the encoding phase, the stimuli presentation times were subjectively adapted depending on the performance of a preliminary task. Specifically, participants

performed the same task described above in the 0-seconds delay condition, but the stimuli presentation times were varied (ranging from 67 to 3600 ms) until 80% of accuracy was reached. Then, this presentation time was used, per each participant, in the main WM task. The aim of this procedure was to equate all the participants to optimal encoding time needed to successfully perform the WM task. They found that in the preliminary task, patients needed a fivefold increment in presentation time in order to reach the same level of performance as controls. Moreover, in the subsequent WM task, after being equated to controls in terms of encoding times, patients did not show greater impairments compared to controls even in the hardest condition (with the 6-seconds delay). The authors proposed that encoding processing is sluggish in patients, probably because they are slower at creating a stable internal representation of working memory items. This is further demonstrated by the lack of difference in performance, compared to controls, when patients are given enough time to encode the memory items (Hartman et al., 2002).

However, it is still unclear whether the source of encoding deficits can be ascribed solely to a slowed processing of information since further evidence has shown contrasting results. For example, Tek, Gold, Blaxton, & Wilk (2002) also manipulated encoding in a working memory experiment with schizophrenia patients and healthy controls. They presented abstract polygon shapes and participants had to judge whether a probe shape matched the previously encoded stimulus either in terms of object (same object) or location (same location). Crucially, the researcher also performed a perceptual discrimination version of the same task in which the delay period was kept at a minimum, in order to minimize memory efforts, and in which the presentation times of the stimulus varied, in order to allow different levels of encoding duration. They found both WM performance and basic perceptual impairments in patients, which was greater in the object discrimination condition in which more detailed perceptual processing was needed, compared to location condition. Moreover, in contrast with Hartman et al., (2002), this impairment was independent of an increment in the exposure period of the stimulus, indicating that even after increasing the presentation time at encoding, the perceptual dysfunction was still present. The authors concluded that, more than slowed encoding, patients showed a pure encoding deficit, probably driven by perceptual impairments (Tek et al., 2002).

Traditionally, patients' behavioural results have been mainly explained with aberrant dorsolateral pre-frontal cortex (DLPFC) activity during the late phases of maintenance

and retrieval (Barch, 2006; Glahn et al., 2005; Goldman-Rakic, 1995a, 1996; Tan, Callicott, & Weinberger, 2007). However, evidence about prefrontal dysfunctions during working memory processing in schizophrenia is contrasting. Whereas some studies have shown decreased activation in the prefrontal cortex (Callicott et al., 1998, 2003; Mendrek et al., 2004; Mendrek et al., 2005; Meyer-Lindenberg et al., 2002; Meyer-Lindenberg et al., 2005; Quintana et al., 2003; Wykes et al., 2002), other studies have reported increased activation or no changes in DLPFC during WM tasks (Callicott, 2000; Callicott et al., 2003; Honey, Bullmore, & Sharma, 2002; Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004; Manoach et al., 2000; Sabri et al., 2003; Walter et al., 2003). For example, in an fMRI study, Ettinger and colleagues (2011) tested schizophrenia patients and healthy controls performing a spatial n-back task. In the task, participants saw coloured dots at the corners of a diamond shape. Participants had to judge whether a target dot was present in the current trial (0-back) or one (1-back) or two (2-back) trials backwards. Behavioural performance did not differ between patients and controls. Moreover, they found that BOLD activity in prefrontal areas increased with the increment of load similarly between patients and controls. However, in contrast with controls, patients showed increased BOLD activations in additional lateral prefrontal areas and in the left occipital cortex. The differences in activations compared to controls became higher with the increment of memory load. Since behavioural performance did not differ between patients and controls, the authors interpreted the BOLD results as reflecting additional compensatory mechanisms activated by patients. However, although these compensatory mechanisms lead to a successful WM performance, the authors suggested that the WM processing is still inefficient since it requires the recruitment of a significantly higher level of resources (Ettinger et al., 2011).

Recent evidence has reported PFC abnormal activations already at encoding. Bittner and colleagues (2015), in order to explore cortical activation and connectivity during encoding, analysed fMRI data from a cohort of early onset schizophrenia patients and healthy controls performing a delayed matching to sample WM task. They found hypo-activity in the prefrontal and visual cortex in patients compared to controls. Moreover, PFC and visual areas showed poor functional connectivity only in the patients' population. Furthermore, only controls exhibited a positive correlation between activity in the PFC and visual cortex and WM capacity. The authors concluded that impaired encoding is associated with poor communication between the prefrontal and

visual cortex. Moreover, since general lower activity was found also in visual areas, they suggested that visual activity at encoding, and presumably perceptual processing, might contribute to WM impairments in schizophrenia (Bittner et al., 2015).

In fact, an increasing number of studies is supporting the idea that WM deficits in schizophrenia need to be addressed not only to prefrontal areas but to a larger and distributed network, in which sensory regions play a major and active role (Javitt, 2009). For example, Haenschel and colleagues (2007) have demonstrated a relationship between visual ERPs elicited at encoding and WM performance in schizophrenia. They analysed ERP signals and compared WM performance of a population of adolescents with early onset schizophrenia with healthy control participants on a delayed matching to sample task. Up to three abstract shapes were presented and, after a brief delay, participants had to decide whether a probe shape matched or not with the previous test set. Patients showed lower accuracy and higher reaction times compared to control participants. More interestingly, within ERPs signals, visual P1 amplitudes were predictive of WM performance in healthy controls. However, in participants with schizophrenia, P1 was significantly reduced and it was not predictive of WM behaviour. Moreover, while for controls P1 amplitudes constantly increased with memory load, patients did not show the same modulation (Haenschel et al., 2007).

More recently, Dias and colleagues (2011) also found reduced ERPs signals in schizophrenia both at occipital and frontal electrodes. They measured EEG of participants with schizophrenia and healthy controls performing the AX Continuous Performance Task (AX-CPT). In this task, letters are displayed on the screen and a button has to be pressed when the letter A is followed by the letter X, while all the other conditions need to be ignored. Behaviourally, errors rate for patients was significantly higher compared to controls in all conditions. Furthermore, they found reduced early sensory components P1 and N1 at occipital electrodes. Specifically, P1 showed a larger impairment when stimuli were presented with a low (compared to high) spatial frequency, condition preferential for magnocellular pathway processing, suggesting a basic sensory dysfunction (Dias, Butler, Hoptman & Javitt, 2011). The authors also found that patients, compared to controls, exhibited reduced N2 and Slow wave activity (specifically, Contingent Negative Variations (CNV)) at fronto-central electrodes. However, while early sensory N1 positively correlated with WM performance in patients, indicating that higher visual N1 amplitudes were associated

with better performance, the later frontal component did not show the same trend. Thus, the authors concluded that although frontal ERPs were reduced in patients, they probably contribute to WM performance to a lesser extent compared to visual components (Dias, Butler, Hoptman & Javitt, 2011).

In sum, these studies suggest that WM deficits in SZ are present in the encoding phase and that visual neural activity is significantly involved in WM processing. However, it is still unclear how specific perceptual mechanisms can contribute to WM impairments. A considerable number of studies has shown that basic sensory mechanisms are abnormal in Schizophrenia. Therefore, it seems important to better understand basic visual impairments in SZ and whether they might interfere with WM processing (Silverstein & Keane, 2011b).

Visual dysfunctions in schizophrenia

Although auditory hallucinations are more common than visual hallucinations, a very high proportion of people with SZ report visual distortions (such as in the perception of brightness, motion, colours) in the prodromal phase, at first episode and also during the course of the illness (Bunney et al., 1999; Cutting & Dunne, 1986). These visual abnormalities seem to be clinically relevant. They have been related to suicidal ideation (Granö et al., 2015), impaired cognition (Calderone et al., 2013; Haenschel et al., 2007), social cognition (Butler et al., 2009; Green, Hellemann, Horan, Lee, & Wynn, 2012; Kim, Shim, Song, Im, & Lee, 2015; Kim et al., 2010), poor reading ability (Martínez et al., 2013), lower overall functioning (Green et al., 2012; Rassovsky, Horan, Lee, Sergi, & Green, 2011), and poorer treatment response (Silverstein et al., 2013; Silverstein, Schenkel, Valone, & Nuernberger, 1998).

Perceptual abnormalities in schizophrenia have been reported in various domains. Impairments have been found from the more global and integrating functions of vision, such as perceptual organization (Silverstein & Keane, 2011a), facial and emotion processing (Turetsky et al., 2007), visual illusions (Dima et al., 2009; Dima, Dietrich, Dillo, & Emrich, 2010; Horton & Silverstein, 2011; Joseph, Bae, & Silverstein, 2013); to the more basic visual processing skills, such as masking (Green, Lee, Wynn, & Mathis, 2011), motion processing (Chen, McBain, Norton, & Ongur, 2011; Lencer, Nagel,

Sprenger, Heide, & Binkofski, 2005), contour integration (Butler et al., 2013; Doniger et al., 2000) and spatial frequency processing (Shoshina & Shelepin, 2015).

Silverstein (2016) has proposed that most of these visual dysfunctions can be explained with an illness-related variability in contextual modulation, defined as the influences exerted from neighbouring neurons towards the normal receptive field of a cell (Silverstein, 2016). One form of contextual modulation is related to Lateral inhibition (LI) and Surround suppression (SS). As described earlier, lateral inhibition refers to the physiological phenomenon affecting most of the cells in the visual cortex in which the responses of a neuron are inhibited by the activity of the neighbouring cells (Colin Blakemore & Tobin, 1972; Butler et al., 2008; Carandini & Heeger, 2012). It is believed that LI contributes to the surround suppression effect in which, in healthy population, the perception of a central target is altered if it is surrounded by a larger stimulus (Chubb et al., 1989; Xing & Heeger, 2001; Zenger-Landolt & Heeger, 2003). However, several experiments have shown that in SZ patients the surrounding context does not attenuate responses to the target as much as it does with control participants. This phenomenon has been explained as a consequence of weak LI (Dakin et al., 2005; Tibber et al., 2013). Dakin and colleagues (2005) tested people with schizophrenia and healthy controls on a contrast matching task. A circular patch was presented either in isolation or embedded in a high contrast surround and participants had to indicate which patch had higher contrast. Surprisingly, compared to controls, patients were more accurate at judging the contrast of the central patch when embedded in the larger surround. Since contrast matching is supposed to test the earliest stages of visual perceptual processing (Chubb et al., 1989; Zenger-Landolt & Heeger, 2003), the authors concluded that the immunity from the SS effect showed by the patients can be attributed to a weakened lateral inhibitory system in schizophrenia, thus to a specific basic sensory failure independent from attentional or other cognitive interferences (Dakin et al., 2005).

Yoon and colleagues (2009) further demonstrated that LI and SS abnormalities in Schizophrenia are specific for orientation. Inspired by Zenger-Landolt & Heeger study (2003), they used a similar paradigm applied to a population of SZ patients and healthy controls. In their task, a circular annulus was divided into eight segments and participants had to judge whether or not one of the segments had decreased contrast compared to the others. The annulus was presented either in isolation or with a larger surround vertically oriented to the annulus (parallel condition) or with a larger

surround horizontally oriented to the annulus (orthogonal condition) (Figure 1.3). They found that in the parallel surround, contrast perception of the patients was less decreased compared to controls. In contrast, no differences between the two groups were found in the orthogonal condition. This indicates that only in healthy controls, but not in patients with SZ, the strength of surround suppression also depends on the orientation of the surround to the target (Yoon et al., 2009).

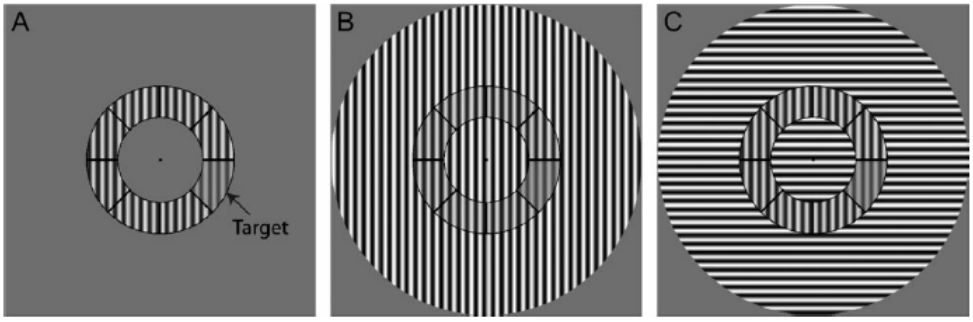


Figure 0.3. Stimuli used in a contrast matching task by Yoon et al., 2009. An annulus was divided into eight segments and presented either in isolation (A), embedded in a parallel surround (B) or embedded in an orthogonal surround (C). Participants had to judge whether one of the eight segments in the annulus had decreased contrast compared to the others.

The authors have proposed that this weakened LI mechanisms might be related to lower levels of ɣ-aminobutyric acid (GABA) interneurons, an inhibitory neurotransmitter that regulates activity in the cortical pyramidal neurons (Moghaddam & Javitt, 2012). In a follow-up study, the same group of researchers used the same experimental task but they also collected measures of GABA levels with high field magnetic resonance spectroscopy (MRS) from a group of schizophrenia patients and healthy controls (Yoon et al., 2010). They found reduced GABA levels in a voxel in the visual cortex in the patients' cohort compared to controls. Moreover, they also found that GABA levels in the visual cortex positively correlated with the magnitude of the surround suppression effect and that this correlation was stronger in the controls population (Yoon et al., 2010).

With their inhibitory function, GABA interneurons activate to dampen excitation in the afferent pyramidal neurons (Moghaddam & Javitt, 2012). Hence, GABA interneurons control stabilises excitation in the pyramidal cells. This is fundamental for the coordination of cell assemblies since, without this GABA inhibitory control, excitatory activity on the pyramidal cells would increase in a never stopping rate (Buzsáki, Geisler, Henze, & Wang, 2004). As a consequence, if GABA levels are lower and have a reduced

inhibitory function on pyramidal cells, this would cause an unstable situation in which there is an excessive engagement of pyramidal neurons (Moghaddam & Javitt, 2012). Thus, an imbalance between GABA levels and the excessive activity of the pyramidal neurons might underlie the various perceptual dysfunctions observed in SZ, including a weakened lateral inhibitory system (Butler et al., 2008; Silverstein, 2016).

On a larger scale, these impaired mechanisms can seriously affect the processing of the flow of incoming sensory stimuli and the natural ability of the visual system to optimize responses from the external world and to integrate them into a unified image. In natural scenes, a weakened LI system might impair the ability to emphasise contours and to integrate different features of the visual scene (such as colours, luminance, contrast, etc.) into a unique and coherent interpretation, resulting in visual items not seen as an integrated whole, but more as an assembly of fragmented parts (Butler et al., 2008; Silverstein & Keane, 2011b; Yoon et al., 2009). Moreover, some researchers have proposed that these basic visual dysfunctions might also underlie higher cognitive processing (Javitt, 2009; Javitt & Freedman, 2014). Working Memory, for example, is one of the most studied cognitive skill in SZ, since its impairments can seriously affect the everyday life of patients. Yet, its underlying mechanisms are still not fully clear.

Although evidence suggests that visual cortex activity is linked to WM performance in Schizophrenia (Bittner et al., 2015; Haenschel et al., 2007), to my knowledge, the impact of an impaired LI system on visual WM has not yet been explored.

4. Event-related potentials

The neural origins of the ERPs

Electroencephalography (EEG) is a technique that allows measuring the electrical neural activity of the brain by placing electrodes over the scalp. Event-related potentials (ERPs) can be extracted from EEG and reflect the electrical activity of the cortex associated with a sensory, cognitive or motor event (Luck, 2005).

Electrical activity in the neurons gives rise to action potentials and postsynaptic potentials. Action potentials are voltages that travel up and down from the beginning of an axon to its terminal. Postsynaptic potentials (PSP) are generated on the membrane of the postsynaptic cells when, after neurotransmitters have been released

and bound together with the receptors, ion channels open (or close) causing an electrical potential (Luck, 2005). There is large agreement that most of the ERPs recorded from the scalp represent postsynaptic potentials, instead of action potentials, because of their duration and simultaneous firing (Luck, 2005). Specifically, when an action potential is generated, current starts to flow in and out of the axon until the action potential reaches a terminal. If two neurons send their action potentials in parallel to the axons, their action potentials will generate at the same time and the output voltage would be the summation of the two. However, this rarely happens as neurons tend to fire at different times and this creates a signal that is too small to be recorded from the electrodes. On the contrary, postsynaptic potentials can last for hundreds of milliseconds (ms) (instead of about 1ms for action potentials), they are confined in the dendrites or cell body and don't have to travel up and down in the axon. Moreover, when an excitatory neurotransmitter is released in the dendrites of a cell, current will flow both into the cell, creating a negativity in the outer part of the dendrite, and out of the cell body, creating a positivity in the outer part of the cell body (Figure 1.4). Together, the negativity outside the dendrites and the positivity outside the cell body will cause a tiny dipole (a pair of positive and negative electricity separated by a small distance). The dipole coming from a single neuron is too small to be visible in the EEG. However, often thousands of neurons will fire at the same time creating thousands of dipoles that will be positive and negative in the same directions (Figure 1.4C). This will make the current to summate and create a signal big enough to be captured by the EEG electrode (Figure 1.4A) (Luck, 2005). However, ERPs do not represent all the PSPs generated in the brain but only PSPs that meet certain conditions. Neurons must be spatially aligned and perpendicular to the electrode in order to be recorded (Figure 1.4B). If they are not aligned in the same direction, the positivity of one dipole might be proximate to the negativity of another dipole and this consequently cancels out the signal. On the cortex, the majority of neurons that are spatially aligned perpendicularly to the cortex are the pyramidal neurons (Luck, 2005). Thus, to summarise, it is widely accepted that ERPs recorded by the EEG electrodes represent PSPs of thousands of cortical pyramidal neurons firing at the same time (Kappenman & Luck, 2012b; Luck, 2005).

The typical ERP waveform appears as a series of positive and negative peaks that unfold over time. The positive or negative polarity observed in the ERP waveform might be due to several factors, for example, the orientation of the dipoles to the

electrodes. Therefore, it is not possible to associate the positivity or negativity of the ERP with a specific neural process (such as excitation or inhibition). Consequently, negative or positive polarities have no specific meaning (Luck, 2005). The entire waveform reflects the continuous activity of the brain, therefore, not only peaks but also the rest of the waveform can be relevant for cognitive processing (Luck, 2005).

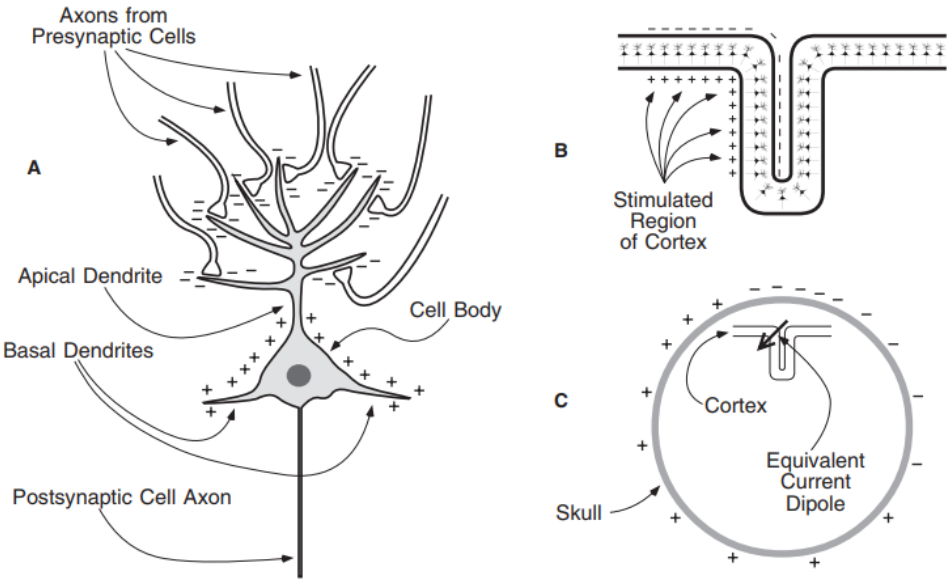


Figure 0.4. Adapted from Luck, 2005. (A) Schematic representation of a pyramidal cell. Positive ions ("+") flows in the cell body are caused after an excitatory neurotransmitter is released from the presynaptic terminal. As a consequence, negative ions ("-") arise in the outer parts of the neuron. Positive and negative ions create a small dipole. (B) Schematic representation of a sheet of cortex containing pyramidal cells. (C) Representation of summed dipoles. When all the dipoles created in the pyramidal cell summate, they become equivalent to a single dipole.

Advantages and limitations of the ERPs

The main advantage of the ERPs is their temporal resolution. The electrical potentials travel at extremely high speeds and can be measured by the EEG electrodes with no measurable delay. Thus, it is reasonable to assume that ERPs provide an instantaneous and milliseconds-resolution measure of brain electrical potentials (Kappenman & Luck, 2012a). For this property, ERPs can be extremely useful in neuroscience research. For example, while behavioural measures reflect the final output of a sensory or cognitive process, ERPs provides a continuous measure of brain signals, allowing to analyse with extreme temporal precision the brain processes taking place between the appearance

of the stimulus and the participant response. This allows to break down cognitive processes in different phases or to detect which stage is more influenced by specific experimental manipulation (Kappenman & Luck, 2012a).

The main limitation of the ERP technique is its poor spatial resolution. The brain is a conductive medium of current. Therefore, when current is generated in the neurons at a specific site it will spread throughout the cortex, following the least resistant path, until it reaches the surface (Luck, 2005). However, as the signal travels towards the scalp, it will tend to spread laterally since the highly resistant components of the head (such as the skull, skin or scalp) will oppose to a linear path. For this reason, it is usually very hard to determine with certainty in which area of the brain ERPs are generated, since the ERP recorded at a specific electrode might actually contain activity generated in different electrode sites (Luck, 2005). Another limitation of the ERPs technique is the "superposition problem". Kappenman & Luck (2012a) have distinguished between "peaks", that represent a maximal positive or negative deflection in the waveform, and "components" that instead represents a voltage change associated with a neural process. The same peak might reflect the summed activity of several components. Specifically, since PSPs associated with an ERP can last for hundreds of milliseconds, different mental processes associated with different components might overlap in the same ERP waveform. Thus, it can be difficult to isolate a specific component related to a mental process.

To summarise, ERPs represent neural activity arising from the PSPs of thousands of cortical pyramidal neurons simultaneously firing. With their high temporal resolution, ERPs allow to isolate and analyse in depth the different phases of a cognitive process. However, given their low spatial resolution, it is difficult to associate the neural process reflected by the ERP with a specific brain site (Kappenman & Luck, 2012a; Luck, 2005).

The ERP waveform and main components

The typical ERP waveform consists of a series of positive and negative peaks that arise over time. They are usually named with a "P", for positive voltage, or "N", for negative voltage, followed by a number which indicates the order or time of appearance in the waveform (Luck, 2005). Some of the main components associated with sensory and cognitive processing are briefly reviewed below.

C1

The first visual ERP arising from a typical waveform is the C1. It is largest at posterior electrodes and it peaks at 80-100ms after stimulus appearance (Luck, 2005).

Although it is typically elicited by stimuli built on very basic psychophysical parameters, such as Gabor patches, most of the times C1 is not visible as it merges with the following P1 (Clark, Fan, & Hillyard, 1994; Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002; Jeffreys & Axford, 1972). Moreover, it is believed that C1 is very likely generated in V1 (primary visual cortex) where the calcarine fissure unfold (Di Russo et al., 2002). In V1, the area that code the upper side of the visual field is on the lower bank on the fissure, while the lower part of the visual field is coded by the upper bank of the fissure. As a result, C1 voltage recorded on the lower part of the fissure will be negative, and the one recorded on the upper bank will be positive (Clark et al., 1994; Jeffreys & Axford, 1972). Thus, C1 is not labelled with P or N as its polarity depends on the part of the visual field on which the stimulus is displayed.

Hansen, Haun, Johnson, & Ellemberg (2016) conducted a study with the aim of clarifying the differences of C1 polarity when stimuli are presented in the fovea compared to the peripheral visual field. The authors presented to participants either achromatic checkerboards or achromatic sinusoidal gratings with six different spatial frequencies (from low to high). In both experiments, the stimuli were presented in random order either centrally (in the fovea) or in one of the four peripheral visual field quadrants. Participants were only required to keep fixation in the middle of the screen. The authors managed to clearly separate the peripheral C1 from the foveal C1 in terms of polarity, brain topography and responses to stimulus characteristics. Specifically, stimuli presented in the upper periphery elicited a negative polarity while stimuli presented in the lower periphery elicited a positive polarity. However, in line with previous findings (Ellemberg, Hammarrenger, Lepore, Roy, & Guillemot, 2001; Reed, Marx, & May, 1984), when the stimulus was presented in the fovea, C1 polarity was consistently negative. Moreover, peripheral and foveal C1 were modulated by the spatial frequency of the gratings in a different way. Specifically, while peripheral C1 showed the highest peak at 4 cycle/degree SF, foveal C1 had the highest peak with the highest SF used (12 cycle/degree). The author suggested that the dissimilarities found with C1 peaks might reflect that the distribution of selective neurons for the various SF is different between the fovea and the peripheral visual cortex. They also found different topographies and consequently different neural generators for peripheral

and foveal C1. Specifically, they found that both peripheral and foveal C1 seem to arise from the striate cortex, but foveal C1 seems to be generated on a more posterior location on the calcarine sulcus (Di Russo et al., 2002; Hansen et al., 2016; Whittingstall, Wilson, Schmidt, & Stroink, 2008).

Another controversial feature of C1 is that it seems not to be modulated by attention (Di Russo, Martinez, & Hillyard, 2003; Gonzalez, Clark, Fan, Luck, & Hillyard, 1994; Mangun, Hillyard, & Luck, 1993). Di Russo, Martinez, & Hillyard (2003) showed to participants a circular checkerboard displayed in four different locations, randomly selected per each trial, while recording EEG. Participants were instructed to orient their attention to one particular location indicated by an arrow placed in the central fixation dot. Participants were asked to detect infrequent stimuli in the cued location. Interestingly, C1 amplitudes for the attended location did not differ from the amplitudes for the unattended location, suggesting that C1 seems not to be affected by attentional processing (Di Russo et al., 2003).

In sum, these studies show the high variability of C1 depending on stimulus characteristics and location. However, it seems that foveal C1 has a negative polarity and it is likely generated at the more posterior visual electrodes (Hansen et al., 2016). Moreover, C1 seems to be a purely perceptual component, not modulated by attention (Di Russo et al., 2003).

C1 in Schizophrenia

C1 have been used to show parvocellular (P) and magnocellular (M) impairments in SZ. In a passive viewing EEG experiment, Schechter and colleagues (2005) showed participants with SZ and healthy volunteers simple checkerboards at high achromatic contrast (in order to target both magnocellular and parvocellular pathways), at low achromatic contrast (only magnocellular) and at high chromatic contrast (only parvocellular). Moreover, all participants were assessed for visual acuity with Early Treatment Diabetic Retinopathy Study (ETDRS) charts. C1 amplitudes were significantly lower in patients compared to controls. However, after controlling for visual acuity (which was significantly lower for patients) this result disappeared, suggesting a link between lower visual acuity and lower C1 amplitudes. In a similar passive viewing EEG experiment, Butler and colleagues (2007) tested a population of patients with SZ and schizoaffective disorder and a population of healthy controls.

They presented a 8x8 matrixes of isolated checks with five different contrasts (from low, to target the M pathway, to high, to target the P pathway) or black and white horizontal gratings at different spatial frequencies (from low, to target the M pathway, to high, to target the P pathway). They also tested participants for visual acuity and found that patients had a lower visual acuity compared to controls. After controlling for visual acuity, the authors still found all early visual ERP reduced in schizophrenia. However, the effect was stronger when participants were seeing stimuli that targeted the magnocellular pathway, whereas for the parvocellular pathway the ERPs components were relatively intact (Butler et al., 2007). Specifically, C1 amplitudes were reduced only in the low SF condition, suggesting dysfunction in the magnocellular pathway. In both studies, there were no relationships between ERPs amplitudes and medication effects (Butler et al., 2007; Schechter et al., 2005).

In sum, C1 amplitudes seem to be reduced in SZ, particularly when the magnocellular pathway is targeted. C1 amplitudes seem not to be influenced by medication intake. However, evidence seems to suggest a link between lower amplitudes and reduced visual acuity (Schechter et al., 2005).

P1

P1 wave is largest at lateral occipital electrodes and it usually peaks at around 100-130ms. Its latency can vary depending on stimulus contrast (Luck, 2005). Few studies have tried to localize P1 and have suggested that it might originate in the extra-striate cortex or in the fusiform gyrus (Di Russo et al., 2002).

Regarding its functions, P1 has been primarily associated with attention, since it seems to be driven by top-down mechanisms (Hillyard, Vogel, & Luck, 1998). In spatial attention paradigms, a typical finding is that P1 amplitudes appear larger for stimuli that have to be attended compared to stimuli that can be ignored. For example, in the Posner cueing paradigm, in each trial, a cue indicates to which side of the screen participants have to orient their attention. Typically, in "valid" trials the target appears in the attended location, whereas in "invalid" trials the target appears in the uncued location. On every trial, participants have to indicate where the target appears (Kappenman & Luck, 2012b; Posner, 1980a). In the Posner paradigm, P1 is typically

larger for attended compared to unattended stimuli and the result is maximal at lateral occipital electrodes (Eimer, 1994a, 1994b; Hopfinger & Mangun, 1998; Luck et al., 1994; Mangun & Hillyard, 1991).

However, it has also been shown that attentional responses of P1 are elicited also for non-spatial attentional paradigms. Valdes-Sosa, Bobes, Rodriguez, & Pinilla (1998) asked their participants to view a cluster of red and green dots presented simultaneously and moving in opposite directions. Participants were instructed to attend either to the red or to the green dots. Participants were asked to detect a random deviation of motion in the target colour group. They found that P1 was larger when the deviation occurred in the target attended colour, suggesting that it is modulated by top-down attention (Valdes-Sosa et al., 1998). More recently, Zhang & Luck (2009) used a variation of Valdes-Sosa et al. (1998) paradigm to show that P1 amplitudes are modulated by stimulus relevance also in the unattended location. They still showed participants clusters of red and green dots presented simultaneously but only on one side of the screen. In the unattended location, a group of dots were randomly flashed either in the target or not target colour. They found that P1 was larger for target colour, compared to non-target, even in the unattended location (Zhang & Luck, 2009).

Recently, P1 has also been studied within WM research. Haenschel and colleagues (2007) in a delayed matching to sample WM task have demonstrated that in healthy participants, P1 amplitudes at occipital electrodes increased with memory load increment. Moreover, P1 positively correlated with performance.

In summary, in healthy participants, visual P1 seems to be mainly related to attentional processing but also to WM load. Moreover, P1 amplitudes have been associated with WM performance.

P1 in Schizophrenia

P1 has also been associated with WM deficits in SZ. Haenschel et al. (2007) found that P1 amplitudes during the early encoding phase were significantly attenuated in early-onset SZ patients compared to controls and they were not modulated by memory load. Additionally, differently from healthy controls, P1 amplitudes did not predict WM performance in SZ population. The authors suggested that the WM deficits in SZ might

be influenced by early sensory impairments during WM encoding (Haenschel et al., 2007).

Early sensory deficits in SZ have also been found in terms of P1 reduced amplitudes related to magnocellular dysfunctions. In a passive viewing EEG experiment, Schechter and colleagues (2005) found that P1 was decreased in patients compared to controls when simple checkerboards at high achromatic contrast (which targeted both magnocellular and parvocellular pathways) and at low achromatic contrast (only magnocellular) were shown. In contrast, P1 amplitudes did not differ between the two groups when simple checkerboards at high chromatic contrast (targeting only parvocellular pathway) were displayed. In a similar passive viewing EEG experiment, Butler and colleagues (2007) found that P1 was decreased in SZ patients, compared to controls, only in conditions in which isolated checks with low contrast or low SF stimuli were shown. P1 seemed to be relatively intact when high SF isolated checks were displayed. Both these results suggest more severe P1 impairments in SZ relative to the magnocellular compared to the parvocellular pathway (Butler et al., 2007; Schechter et al., 2005). In all the studies, no links between P1 amplitudes and medication intake were found (Butler et al., 2007; Haenschel et al., 2007; Schechter et al., 2005).

Thus, P1 amplitudes in SZ have been found to be decreased and have been related to perceptual dysfunctions in the magnocellular pathway. Moreover, P1 has also been associated with WM deficits.

N1

Visual N1 can be divided into different subcomponents. The earliest N1 seems to arise at anterior electrodes and peaks at around 100-150ms. Two posterior N1 typically peak at 150-200ms post-stimulus appearance both at parietal and lateral occipital electrodes (Luck, 2005).

N1 has been mainly associated with attention processing (Griffin & Nobre, 2003; Hillyard, Vogel, & Luck, 1998; Mangun, 1995). For example, in WM experiment Griffin and Nobre (2003) used a delayed matching to sample task with a cueing paradigm in which an arrow, presented either before (pre-cue) or after (retro-cue) the memory set, indicated the location of the relevant stimulus to remember. They found that N1 at visual electrodes was larger in the hemifield opposite to the attended location both in

the pre-cue and retro-cue trials, suggesting that this component is modulated by the focus of attention (Griffin & Nobre, 2003).

However, further studies have suggested that N1 is not only modulated by attention but it is also involved in the discrimination of stimulus features (Ritter, Simson, Vaughan, & Macht, 1982; Vogel & Luck, 2000). Vogel & Luck (2000) conducted two EEG experiments to explore these functions of N1. In the first experiment, they showed participants a string of five differently coloured letters. In one condition, participants had to press a button as soon as they saw any array appearing (simple-RT condition). In the other condition, they had to press a button when a specific letter or colour was present or absent in the letter array (choice-RT condition). In this first experiment, they found that N1 was larger for the choice-RT condition compared to the simple-RT. However, there was no difference in the letter/colour condition, suggesting a general but not feature-specific discrimination effect. In the second experiment, they wanted to clarify whether the results obtained were not just attributable to task difficulty of the choice-RT condition over the simple-RT one. They showed participants the same stimuli but in an easy condition, participants had to search for a red target among a series of different colours. In the difficult condition, the target colour was perceptually very similar to the distractors (i.e. purple and pink). They found that N1 was elicited both in the easy and hard condition with no significant differences. The authors suggested that posterior N1 is related to some sort of visual discrimination processes that, however, are not stimulus specific (Vogel & Luck, 2000).

Visual N1 has also been related to specific perceptual processes, such as contour integration. Machilsen, Novitskiy, Vancleef, & Wagemans (2011) in a passive viewing experiment showed a Gabor matrix in which, in some trials, a contour shape appeared formed by a portion of the same gabors. The gabor matrix, which served as a background, could be either formed by gabors with the same orientation and parallel oriented with each other or by gabors all randomly oriented (Figure 1.5). They found that N1 was larger when the contour was embedded in the parallel oriented Gabor background compared to the randomly orientated Gabor background, suggesting that in the parallel and coherent background condition the contour might have been easier to perceive compared to the random-oriented background (Machilsen et al., 2011).

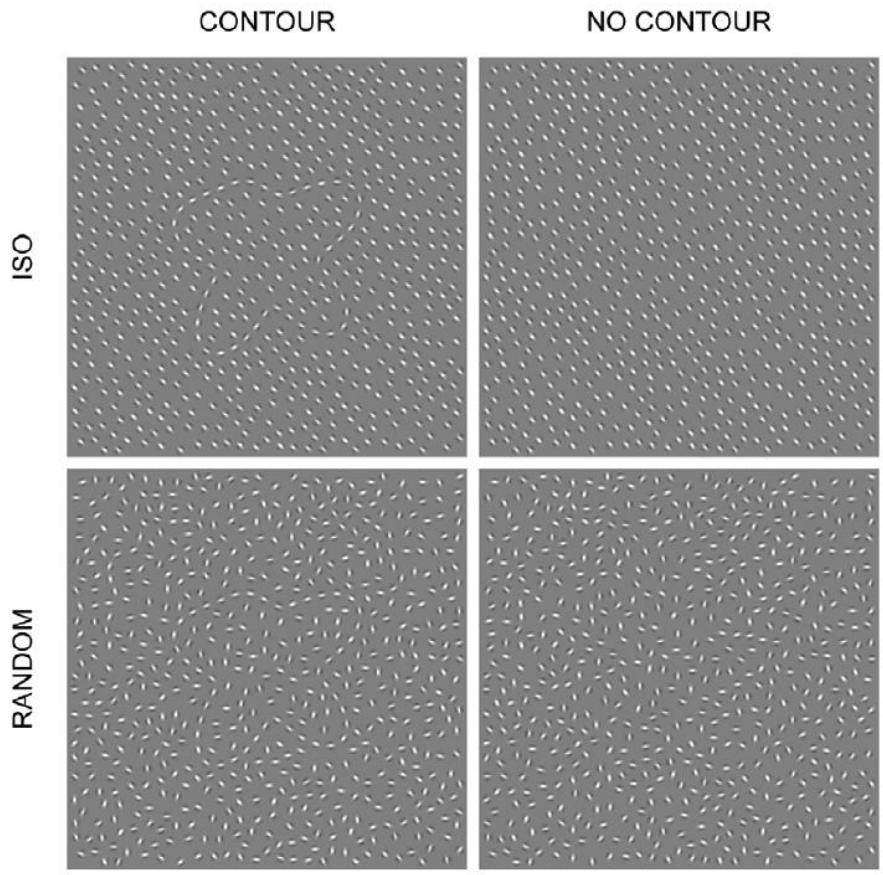


Figure 0.5. Stimuli used in a passive viewing experiment conducted by Machilsen et al., 2011. A contour shape formed by gabors differently oriented from the background could ("Contour") or could not appear ("No Contour") on the screen. The background was formed by gabors with the same orientation ("Iso") or randomly oriented ("Random").

In summary, the visual N1 has been related to attentional processing and filtering of relevant information (Griffin & Nobre, 2003), but also to more detailed perceptual processing such as stimulus discrimination and contour integration (Machilsen et al., 2011; Vogel & Luck, 2000).

N1 in Schizophrenia

N1 has been found to be decreased in schizophrenia (O'Donnell, Salisbury, Niznikiewicz, Brenner, & Vohs, 2012). It is still not clear whether N1 reductions in SZ are related to a deficit in the magnocellular or parvocellular pathway. In a passive viewing EEG experiment, Schechter and colleagues (2005) found that N1 was decreased in patients with SZ compared to controls only when simple checkerboards at high achromatic contrast (which targeted both magnocellular and parvocellular pathways) and at high chromatic contrast (targeting the parvocellular system) were

shown, suggesting a more pronounced N1 deficit related to parvocellular system in the patients. However, the researchers also found that group differences disappeared when acuity (significantly lower in the patients' cohort) was inserted as a covariate, leaving unclear whether N1 impairments were due to parvocellular dysfunctions or to lower visual acuity (Schechter et al., 2005). Moreover, Butler and colleagues (2007) reported contrasting results. In a passive viewing EEG experiment, participants saw black and white horizontal gratings at different spatial frequencies (from low, to target the M pathway, to high, to target the P pathway). They found decreased N1 in patients, compared to controls, in relation to low contrast or low SF isolated checks (targeting the M pathway), whereas amplitudes related to high SF stimuli (targeting the P pathway) were relatively intact in patients.

Thus, whereas Schechter et al., 2005 found N1 deficits with stimuli targeting the P systems (high contrast chromatic stimuli), Butler et al., (2007) found N1 impairments in the M pathway in SZ (low contrast, low spatial frequency stimuli). In both studies, N1 deficits have not been found to be associated with medication intake (Butler et al., 2007).

Thus, it seems unclear whether visual N1 impairments in SZ have a magnocellular or parvocellular (or mixed) origin. However, deficits found in the P pathway might be attributed to lower visual acuity (Schechter et al., 2005).

P2

P2 typically peaks between 180 and 300ms after stimulus onset and has been found both at frontal and at visual electrodes (Potts, 2004). At frontal electrodes, P2 appears larger for task-relevant stimuli (Potts, 2004). At posterior electrodes, P2 is difficult to isolate as it tends to overlap with N1 and N2. Therefore, not much is known about posterior P2 (Luck, 2005).

The evidence so far seems to suggest that visual P2 is associated with stimulus saliency and driven by top-down mechanisms. Straube & Fahle (2010) tested healthy participants on a figure detection task. Within a matrix of Gabor patches, a contour shape could appear. The contour was formed by the same Gabors that differed from the background in terms of orientation, spatial frequency (SF) or both. Participants had

to indicate whether the figure appeared on the left or on the right of the vertical midline of the monitor. Participants showed better behavioural performance in the condition in which the Gabors forming the contour differed the most from the Gabors forming the background in terms of orientation or SF. This likely suggests that when the contrast between the shape and its background is higher, the contour is easier to detect since it appears as more salient. Moreover, in this condition of high saliency, P2 amplitudes were lower compared to the condition in which the contour was less salient. Thus, P2 amplitudes decreased with higher stimulus saliency. The authors interpreted this result as a top-down attentional mechanism. They suggested that highly salient stimuli are more easily perceived as they pop out with more prominence. As a consequence, in this condition P2 amplitudes are lower as less attentional effort might be required. In contrast, with less salient stimuli there might be a larger attentional engagement in order to detect the contour, resulting in P2 amplitudes to increase (Straube & Fahle, 2010).

Similarly, Machilsen, Novitskiy, Vancleef, & Wagemans (2011) tested healthy participants on a passive viewing EEG task in which participants saw a matrix made by Gabors either parallel or randomly oriented. Only in some trials, a portion of these Gabors formed a contour. The authors found that P2 amplitudes were smaller for contour compared to no-contour stimuli, in both parallel and randomly oriented background conditions. The authors concluded that, in line with Straube and Fahle (2010), P2 seems to be related to perceptual saliency and may be driven by top-down mechanisms since the presence of the contour might have been involved a larger deploy of attention.

In sum, although there is still little evidence regarding posterior P2, it seems that this component is related to stimulus saliency and it is modulated by attention. Specifically, P2 amplitudes seem to be lower for highly salient stimuli.

P2 in Schizophrenia

In SZ P2 has been studied in relation to motion perception. Wang, Dobkins, Mcdowell, & Clementz (2012) tested a group of chronic SZ patients and a group of healthy controls on a speed discrimination EEG task in which two vertical sinusoidal gratings, showed over two intervals, moved away from fixation in a horizontal direction. The gratings could appear randomly either on the right or on the left of fixation at different

speeds. Participants had to indicate which of the two gratings was the fastest. Behaviourally, patients with SZ showed a higher speed discrimination threshold, indicating worse behavioural performance, compared to controls. Moreover, after the display of the second grating (therefore when the perceptual judgment should have occurred), only controls showed enhanced P2 amplitudes which also correlated with performance. In contrast, patients showed a reduced P2 but an enhanced later component (specifically, N2) which also correlated with their behavioural performance. Wang et al., (2012) suggested that while for controls the speed discrimination decision occurred more efficiently and earlier in time (as it is shown by the correlation with P2), for patients the perceptual consolidation is slower and sluggish, since they seem to have engaged in a delayed and unprecise compensatory mechanism (represented by the correlation between performance and the later component N2). Moreover, the authors found that these results were not driven by medication effects.

In summary, visual P2 component seems to be reduced in Schizophrenia in perceptual discrimination processing.

Slow Waves

In the ERP waveform, continuous sustained activity (slow waves) is observed typically after the early peaks. Slow waves latency might vary depending on the task (Brunia, van Boxtel, & Böcker, 2012).

Slow waves typically appear when participants are asked to prepare a movement or when they are waiting for a stimulus to appear in the following few seconds. Researchers distinguish among three types of anticipatory slow waves: *Bereitschaftspotential* (BP), also called *readiness potential*, which are negative slow waves recorded prior to the execution of a voluntary movement; the contingent negative variation (CNV), which is elicited in correspondence to a warning item indicating that a target stimulus is about to appear; the stimulus-preceding negativity (SPN), which, similarly to the CNV, is evoked when participants are aware that a stimulus with significant information will be presented shortly after (Brunia et al., 2012).

In the context of WM research, slow waves have been studied in the form of contralateral delayed activity (CDA). CDA is a negative slow wave typically measured with paradigms in which stimuli are displayed either on the left or on the right of the screen. In fact, CDA is calculated as the difference between the contralateral and ipsilateral side of fixation, in order to eliminate from the wave the local noise from ipsilateral activity (Luria, Balaban, Awh, & Vogel, 2016). Several experiments have shown that during the WM maintenance phase, CDA tends to increase depending on the number of objects that have to be retained. For this reason, CDA activity has been interpreted as reflecting individual variability in WM capacity (Luria et al., 2016; Vogel et al., 2005).

In sum, evidence shows that slow waves reflect motor preparation but also capacity limitation during WM processing (Brunia et al., 2012; Luria, Sessa, Gotler, Jolicoeur, & Dell'Acqua, 2010).

Slow Waves in schizophrenia

In SZ, slow waves activity during WM processing has been found to be lower compared to controls. Zhao and colleagues (2011) tested patients with SZ and healthy controls on a WM task in which, at encoding, sets of five digits were presented and after a delay, a single digit was showed. Participants had to indicate whether the digit was previously presented or not. During the maintenance phase, the authors found that slow waves were significantly more negative in patients compared to controls, specifically at fronto-central electrodes. The authors interpreted this result as reflecting impairments in memory rehearsal skills, probably driven by poor sustained attention (Bergman, O'Brien, Osgood, & Cornblatt, 1995; Zhao et al., 2011).

Slow waves deficits in schizophrenia have been also reported in relation to the CDA. Leonard et al. (2013) conducted an EEG study using a change detection WM paradigm in which two groups of coloured shapes appeared both on the right and on the left side of the screen. Participants were required to memorise the colours of the objects only one of the two sides. After a delay, the shapes re-appeared on the screen and participants had to detect whether a change in one of the colours had occurred in the target side. They found that CDA was larger in controls compared to patients at high memory loads (when more than three objects had to be remembered). However,

patients showed a larger CDA compared to controls when only one item had to be retained, whereas CDA tended to decrease at higher memory loads. The authors suggested that CDA activity, which reflects the maintenance of memory contents, is distributed differently in patients, compared to controls. Specifically, patients would be unable to distribute attention broadly, but they would hyperfocus only on a subset of memory content. This prevents them from retaining multiple information at the same time in high load conditions, leading to poorer behavioural performance (Leonard et al., 2013a). Moreover, it was found that CDA was not influenced by medication intake (Leonard et al., 2013a).

In sum, slow waves activity has been found to be lower in patients with SZ, compared to healthy controls, and distributed differently in relationship to memory load, reflecting poor sustained attention abilities.

In summary, ERPs represents the post-synaptic potentials activity of thousands of cortical pyramidal neurons simultaneously firing. Despite their poor spatial resolution, which prevents from exactly locating the source of the signal, ERPs provides an extremely high temporal resolution, allowing to measure brain processes on a millisecond per millisecond basis. The typical ERP waveform contains a series of positive and negative peaks, followed by a continuous slow wave activity, that has been related to several sensory and cognitive processes such as contour integration, attention and working memory. Moreover, early visual ERPs have been found to be reduced in SZ. Specifically, in SZ lower ERPs amplitudes in the ERPs have been associated with perceptual dysfunctions in the M or P pathway. Moreover, early visual ERPs and slow wave activity has been related to poor attentional mechanisms and to WM deficits in SZ.

5. Current project

Brief summary and aim of the project

In summary, WM is defined as the ability to temporarily hold memory information over a short period of time (Baddeley, 2003). WM impairments have been found consistently in clinical condition such as schizophrenia (Barch, 2006; Lee & Park, 2005).

Moreover, WM deficits seem also to have a negative impact on the quality of life of these patients (Shamsi et al., 2011).

Although several studies have shown that WM impairments in SZ are associated with maintenance and retrieval dysfunctions (Gold et al., 1997; Kim et al., 2004; Fleming et al., 1995; Goldberg et al., 1998; Ganzevles and Haenen, 1995; Goldberg et al., 2003; Perlstein et al., 2003; Courtney, Ungerleider, Keil, & Haxby, 1997; Zarahn, Aguirre, & D'Esposito, 1997), recent evidence has highlighted that mechanism occurring during the encoding phase can also have a significant impact on the overall WM performance (D'Esposito & Postle, 2015; Javitt, 2009; Javitt & Freedman, 2014; Lee & Park, 2005). This has been demonstrated in several studies conducted both in healthy populations (Albers et al., 2013; Emrich et al., 2013; Harrison & Tong, 2009; Peterson et al., 2014; Serences et al., 2009; Sneve et al., 2012) and in people with SZ (Dias, Butler, Hoptman & Javitt, 2011; Haenschel et al., 2007; Hartman et al., 2002; Tek et al., 2002). However, it is still not clear to what extent perceptual mechanisms affect WM performance.

Lateral inhibition (LI) refers to the inhibitory activity exerted from visual cortex neurons towards their neighbouring cells (Blakemore & Tobin, 1972; Butler et al., 2008; Carandini & Heeger, 2012; Xing & Heeger, 2001; Zenger-Landolt & Heeger, 2003). LI activity is directly related to the surround suppression effect (Sachdev et al., 2012). In the surround suppression (SS) effect, the perception of a central target depends on the context (Blakemore & Tobin, 1972; Silverstein, 2016; Chen Song, Schwarzkopf, & Rees, 2013b). Specifically, it has been shown that in healthy population the perception of a target can be altered by the presence of a larger surround (Vanegas et al., 2015; Xing & Heeger, 2001; Zenger-Landolt & Heeger, 2003). Moreover, evidence has demonstrated that the SS effect is abnormal in SZ. Patients performance of a central target seems not to be affected by the surround (Dakin et al., 2005; Yoon et al., 2009). This effect has been associated with abnormalities in the functioning of the GABA levels, which regulate inhibition in the brain (Butler et al., 2008; Yoon et al., 2010). Specifically, GABA levels have been found to be reduced in SZ during a contrast matching task (Yoon et al., 2010). Reduced GABA levels have been associated with reduced LI in SZ (Yoon et al., 2010).

However, it is not clear whether LI activity and the SS effect can affect WM performance both in healthy controls and in SZ patients.

In addition, it is believed that relevant WM content stored in sensory areas are selected by top-down attentional mechanisms (Gazzaley & Nobre, 2012; Noonan et

al., 2017). However, how LI interacts with attention during WM processing has not been explored yet.

Thus, in light of this research background, in the current project three experiments have been set out in order to explore to what extent LI activity affects WM performance in a healthy population (Experiment 1), in people with schizophrenia (Experiment 2), and whether LI can interfere with attentional mechanisms during WM processing (Experiment 3).

Throughout all the experiments LI and SS effects have been firstly measured on perceived contrast and orientation with a contrast matching and an orientation discrimination task (Experiments 1, 2 and 3). Then, LI effects on working memory have been measured with a delayed matching to sample WM task (Experiments 1 and 2). In order to specifically target attention, in Experiment 3 the WM task has been slightly modified by inserting a pre-cue at encoding.

Since the main aim of this project was to explore how LI influences working memory performance, a stimulus that could induce lateral inhibitory activity and that could also be encoded into working memory was needed. Sinusoidal gratings are particularly useful to study basic sensory perception and they have previously been used in working memory experiments (Albers et al., 2013; Harrison & Tong, 2009; Pasternak & Greenlee, 2005; Serences et al., 2009). Therefore, in order to trigger LI activity in the visual cortex during a WM task, throughout all the tasks of the experiments of this project circular gratings embedded in high contrast surrounds were used. Since the strength of the SS effect seems to be orientation specific (Yoon et al., 2009; Zenger-Landolt & Heeger, 2003), the surrounds were either parallel or orthogonally oriented to the central target.

In addition, EEG signals have been recorded in experiments 1 and 2 in order to extract Event-Related Potentials (ERPs). Given their high temporal resolution, ERPs have been used in order to explore the underlying mechanisms of WM encoding and retrieval.

Overall, this thesis is structured as follow:

- In Chapter 2, a complete description of the main methodology used in the studies is provided. Details about the stimulus, working memory and visual tasks, behavioural and EEG analysis are outlined in the chapter.
- In Chapter 3, the results of the EEG study that has tested the impact of LI activity on WM performance in a population of young adults (Experiment 1) are reported.
- In Chapter 4, the results of the EEG study that has tested whether a weakened LI system can affect WM performance in a population of people with Schizophrenia (Experiment 2) are reported.
- In Chapter 5, the results of the behavioural study that has tested whether LI can interfere with attentional top-down mechanisms during WM processing in a population of young adults (Experiment 3) are reported.
- In Chapter 6, it is provided a discussion of the overall findings of the project, the limitations of the studies and the potential future directions.

Chapter 2: Methods

This thesis includes three studies. Experiment 1 is an EEG study exploring the impact of lateral inhibitory (LI) mechanisms on working memory (WM) performance in a healthy population. Experiment 2 is an EEG study exploring the impact of LI mechanisms on WM performance in a population of people with schizophrenia and a population of healthy matched controls. Experiment 3 is a follow-up behavioural study from experiment 1, which analysed whether the LI effects on WM performance can be attributed to top-down attentional mechanisms.

In this chapter, each task will be described. Details about the characteristics of the sample, differences in the paradigm or additional measures are specified in the chapters dedicated to each experiment.

Ethics

Experiment 1 and 3 were approved by the ethics committee at City, University of London, whereas Experiment 2 received ethical approval from the NHS Research Ethics Committee. All participants signed an informed consent before participation. Testing for all the experiments was conducted in the Department of Psychology at City, University of London, London, UK.

Procedure

In all the three studies, participants sat in a dark and soundproof Faraday cage. Participants performed, in this order, a Two-Interval Forced Choice Detection task (2IFCD), a contrast matching task (CM), an orientation discrimination task (OD) and a Working Memory (WM) task. The same working memory task was used for Experiments 1 and 2. For Experiment 3, the task was slightly adapted (see Chapter 5 for description). For Experiments 1 and 2, EEG was recorded during the WM task, whereas for Experiment 3 only behavioural data were collected. In Experiment 2, additional measures for general cognitive performance, clinical symptoms and quality of life were collected. Description of these tasks is outlined in detail in chapter 4.

Stimuli and design

For all four tasks, circular grating items embedded in larger surrounds were generated using Matlab 9.0 (R2016a) software and Psychtoolbox 3.0.12 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) and presented centrally on a grey background NEC MultiSync CRT monitor (30 x 40 cm) with a gamma correction of 2.2. Viewing distance was 58cm. Stimuli consisted of a 4 cycles/degree circular grating (target) of 0.67° radius (adapted from Dakin et al., 2005). This circular grating was embedded within a larger 4 cycles/degree, one octave bandwidth bandpass filtered white noise circular region (surround) of 4° and sampled from orientations over a range of ±15°. Michelson contrast for the surround was always 100% throughout tasks and trials. The contrast of the target varied according to the tasks (see below for details). In the "parallel" condition the orientation of the surround relative to the centre was 0° and in the "orthogonal" condition the orientation relative to the centre was 90° (Figure 2.1). Participants were not informed about these two stimulus conditions. Trials were randomised among conditions and among participants in all the tasks.

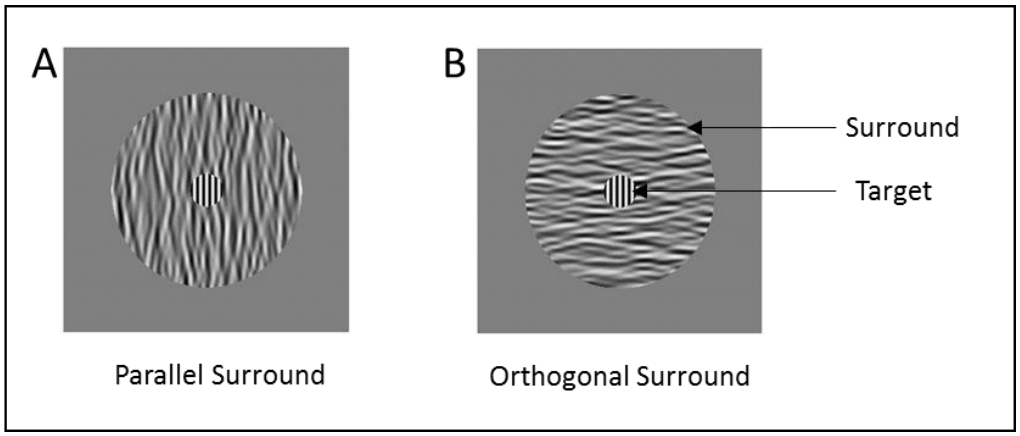


Figure 0.1. Stimuli used throughout the tasks: small circular gratings (target) embedded in bigger surrounds. In the Parallel Condition (A) the orientation of the surround was equal to the target, in the Orthogonal Condition (B) the orientation of the surround was rotated of 90° compared to the target. Participants were asked to focus on the target. The contrast of the stimuli has been heightened for presentation purposes.

Tasks

Orientation Discrimination (OD)

The Orientation Discrimination task allowed to determine the threshold at which participants were able to discriminate between two different orientations of the target when surrounded by a parallel or orthogonal annulus. The stimulus was presented over two consecutive intervals of 300ms each, with an inter-stimulus interval (ISI) of 300ms. The target was presented with the surround in both intervals. The contrast of the target was kept constant at 50% throughout the trials. Participants had to press the left or right arrow on a keyboard to indicate if the lines of the target in the second interval had tilted in an anti or clockwise direction compared to the first interval (Figure 2.2). Participants were provided with a visual feedback consisting of a dot turning green or red depending on whether the answer was correct or incorrect, respectively. No time limit was given to respond although participants were encouraged to respond promptly.

The task used a log-spaced one-up/three-down staircase method starting with a tilt orientation value of 20°. Orientation increased by 0.5 log units after one incorrect response and decreased by 0.5 log units after three consecutive correct responses. Participants performed four blocks comprising two randomly interleaved staircases of 15 trials each, one staircase for each parallel and orthogonal centre-surround conditions respectively, for a total of 120 trials.

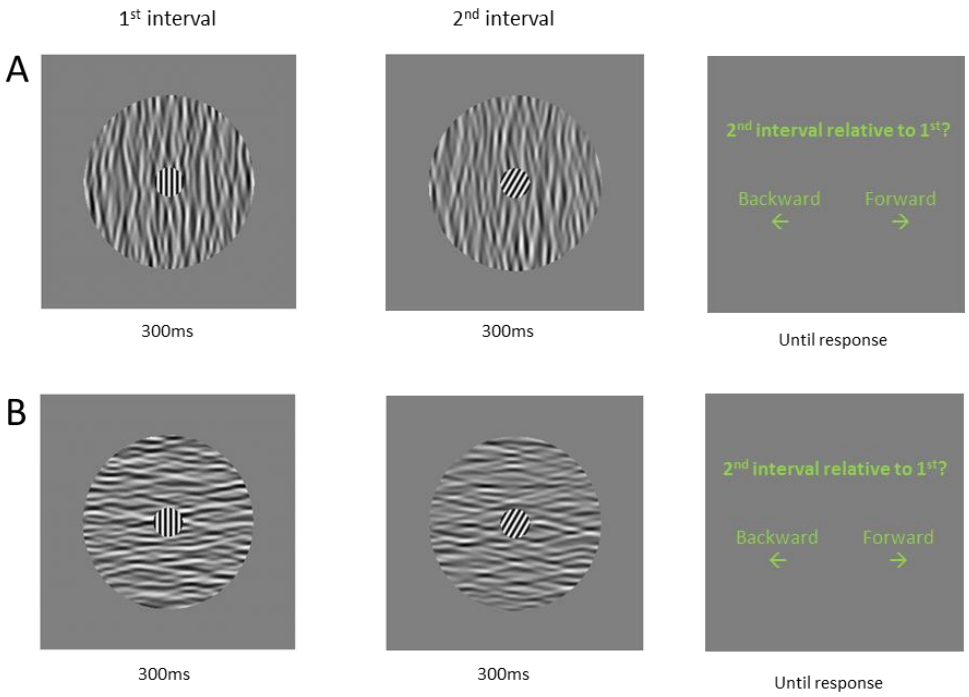


Figure 0.2. Orientation Discrimination task. Both in the first and second interval participants saw the target embedded wither in the parallel (A) or orthogonal (B) surround. After the second interval, participants had to indicate whether the orientation of the second target was rotated in a clockwise ("Forward") or anti-clockwise ("Backward") way compared to the first interval. The contrast of the items has been increased only for presentation purposes.

Contrast Matching (CM)

The Contrast Matching task was performed in order to determine the influence of the surround on the perception of the target's contrast. The task was based on Dakin, Carlin, & Hemsley (2005) that used a Two-Interval psychophysical procedure in which they showed, in the first interval, a target with or without a larger surround and a reference patch in the second interval. Participants were asked to report in which of the two intervals the grating had a higher contrast (Dakin et al., 2005).

As in Dakin et al., (2005), in this task the stimulus was presented over two consecutive intervals of 300ms each, with a 500ms ISI. A vertical target grating was clearly visible in both intervals. In the first interval, the target was always presented with the surround which could be either parallel or orthogonal to the target. In the second interval, the reference stimulus was displayed without the surround (Figure 2.3). Participants had to press the left or right arrow on a keyboard to indicate in which interval they perceived the target with a higher contrast. No time limit was given to respond although participants were encouraged to respond promptly.

The contrast of the target in the first interval was modulated using a staircase method based on a Modified Binary Search algorithm (MoBS) (Tyrrell & Owens, 1988) starting with a contrast value of 0.5. Contrast increased or decreased according to the MoBS algorithm varying proportionately to the difference between upper and lower estimates of matching contrast. The target of the second interval was used as a reference, therefore the contrast was kept constant in all the trials (Michelson contrast of 30%). Participants performed four blocks comprising two randomly interleaved staircases of 15 trials each, one staircase for each parallel and orthogonal centre-surround conditions respectively, for a total of 120 trials.

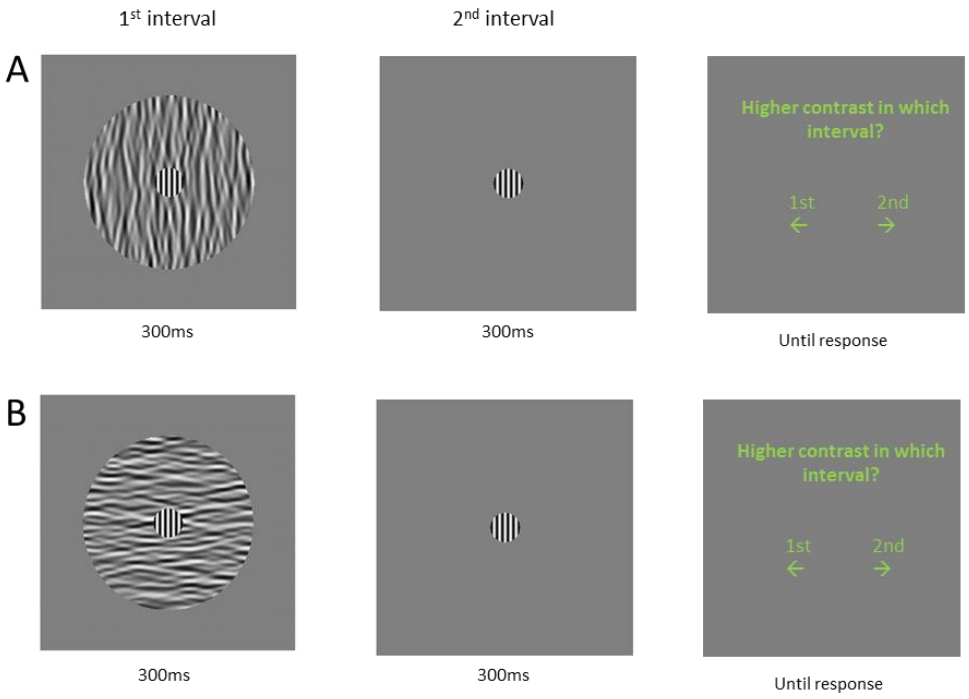


Figure 0.3. Contrast Matching task. In the first interval, participants saw the target grating embedded either in the parallel (A) or orthogonal (B) surround. In the second interval, the grating without the surround was displayed. Participants had to indicate in which of the two intervals the grating had a higher contrast. The contrast of the stimuli has been heightened for presentation purposes.

Two Interval Forced Choice Detection (2IFCD)

The aim of the 2IFCD task was to determine the contrast threshold for perceptibility of the target in the two surround conditions (Parallel and Orthogonal) for each participant. A multiple of the mean threshold value was then used to set individual supra-threshold contrast levels in the main WM match-to-sample task (details below).

The annulus (either parallel or orthogonal) was presented on two consecutive intervals of 100ms each, with an ISI of 500ms, whereas the target grating was only presented in one of the intervals. Participants had to press the left or right arrow on a keyboard to indicate if the target appeared in the first or second interval.

The contrast of the target was modulated by using a staircase method starting with a contrast value of 0.03. Contrast increased by 0.01 log units after one incorrect response and decreased by 0.01 log units after three consecutive correct responses. Participants performed four blocks comprising two randomly interleaved staircases of 15 trials each, one staircase for each parallel and orthogonal centre-surround conditions respectively, for a total of 120 trials. Thresholds for both conditions were calculated by computing the mean of the last five contrast values from each block.

Delayed Matching to Sample Working Memory task

The WM load was manipulated by presenting one, two or three gratings with the surround for 300 milliseconds each, with an ISI of 500 milliseconds (encoding phase). During the ISI a central black dot was presented. After this, a central white dot was presented on the screen for 1000ms, which indicated that the encoding phase was complete. Finally, a grating without the surround was presented for one second (retrieval phase). Participants had to press the left or right arrow on a keyboard to indicate if the orientation of the probe matched (or not) any of the orientations of the gratings presented during the encoding phase. No time limit was given to respond (Figure 2.4). Within one trial, stimuli were either parallel or orthogonal gratings. To avoid the possibility that the encoding of the target might be guided by the surround orientation, the orientation of the surround relative to the centre was also jittered randomly by ±7.5°. In order to manipulate lateral inhibition (LI) effects, the difference in orientation between the target and the surround was lower for the parallel surround condition (0 ± 15°) and higher for the orthogonal surround (90 ± 15°).

At the end of each trial, participants were provided with a visual feedback consisting of a dot turning green or red depending on whether the answer was correct or incorrect.

The task employed a 2x3 design with “surround" as the first within-participants factor with two levels (parallel and orthogonal) and “memory load" as the second within-participants factor with three levels (Load 1, 2 and 3).

The contrast of the target was calculated per each participant based on the performance of the 2IFCD task. Mean contrast values resulting from the 2IFCD task were averaged across conditions (orthogonal and parallel) and then the average was multiplied by 15 (in order to keep the target contrast during the WM task at around 40%. The value of 15 has been defined based on the results of a previous pilot study). This contrast level was kept constant throughout the trials. The session was preceded by one practice block in order to allow participants to familiarise with the task.

Participants performed 18 blocks of 24 trials each for a total of 72 trials per condition.

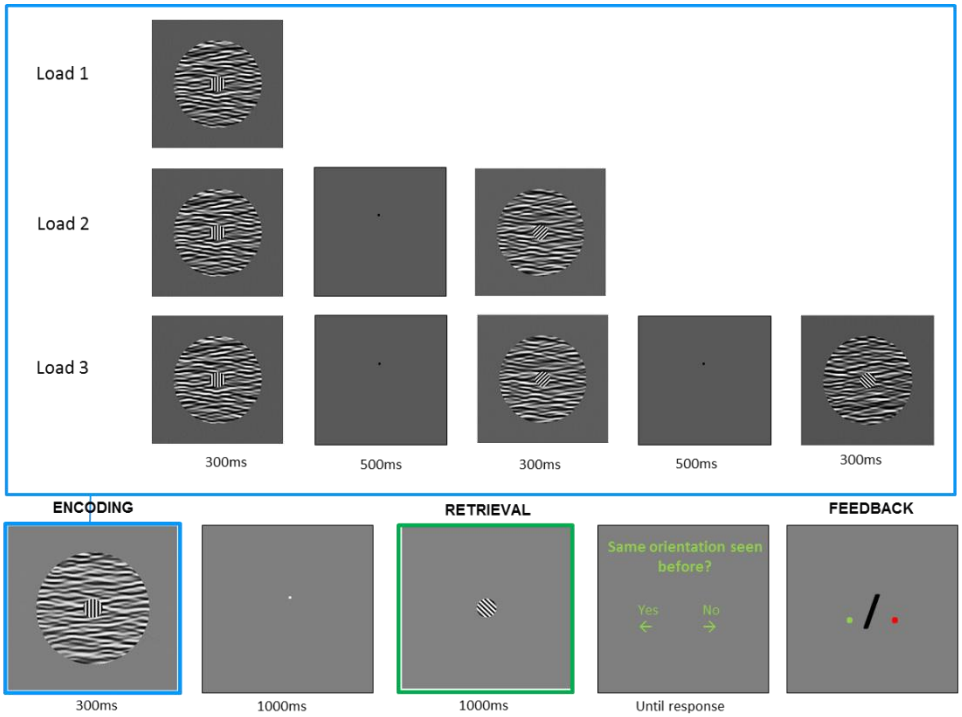


Figure 0.4 Delayed matching to sample WM task. Participants viewed one, two or three targets embedded in parallel or orthogonal surround throughout the trials (encoding). At each stimulus appearance, the target changed the orientation. After a retention interval of 1000ms in which a white dot was presented (maintenance), participants viewed a probe with no surround which either matches or did not match one of the orientations presented during the encoding phase (retrieval). Participants had to decide if the probe orientation was present or not in the previously encoded test set. The contrast of the items has been increased only for presentation purposes.

ERP Data acquisition, processing and analysis

During the WM task, a 64 electrode cap (actiCAP, Brain Products GmbH) based on the international 10-20 system (Jasper, 1958) was fitted on the participants' heads and

fixed with elastic bands attached to a strap placed over participants' chest. The ground electrode was placed at the middle anterior frontal electrode, the reference at the middle frontocentral electrode, and an additional vertical electrooculogram (VEOG) electrode below the left eye (electrode AF7). The EEG was recorded with BrainVision Recorder software (Brain Products, Munich, Germany) and it was amplified and digitalised continuously with a BrainAmp amplifier (Brain Products, Munich, Germany) at a sampling rate of 1000Hz. Electrodes were filled with EasyCap GmbH high viscosity electrolyte gel using syringes with blunt needles. Throughout the recording, impedance was kept below 20 kΩ.

EEG analysis during encoding and retrieval and ERPs extraction were performed with BrainVision Analyser software (Brain Products GmbH). Raw EEG data were first filtered with a low-frequency cut-off at 0.1Hz (12dB per octave) and a high-frequency cut-off at 30Hz (24dB per octave). Previous ERPs studies have used high pass filtering both in healthy (Griffin & Nobre, 2003; Rutman et al., 2009) and in schizophrenia populations (Kreither et al., 2017; Leonard et al., 2013b; Wang et al., 2012). High pass filtering has been recommended in clinical studies as it is useful to reduce head and body movements which can be more frequent in clinical populations (Liljander, Holm, Keski-Säntti, & Partanen, 2016; Luck, 2005).

After filtering, ocular correction for eye blinks was applied using an automatic Independent Component Analysis (ICA) over the VEOG channel. After filtering and ICA, data were re-referenced to the averaged electrodes activity (Haenschel et al., 2007; Rutman et al., 2009). Continuous EEG data for correct trials were segmented into intervals between 200ms before and 1000ms after stimulus onset and then baseline corrected from -200ms to stimulus onset. Automatic artefact rejection with an individual channel approach was applied to segmented data. Epochs that exceeded a threshold of ±50μV per ms were automatically excluded from the analysis (McDowell, Jeka, Schöner, & Hatfield, 2002; Proverbio & Orlandi, 2016). After artefact rejections, segments were averaged over trials.

To assess encoding, the final grating stimulus in each WM load condition was analysed (i.e., the first stimulus for a load of one, the second stimulus for a load of two, and the third for a load of three). This approach ensured an equal number of stimuli for each condition and, more importantly, maximized the effect of prior processing in the WM load conditions (Haenschel et al., 2007). At retrieval, segments related to the probe

arsing after Load 1, Load 2 and Load 3 separately, for correct trials, were included. Moreover, at retrieval correct trials in which the probe orientation matched one of the orientations in the previous test set were analysed as “match” trials, whereas correct trials in which the probe orientation did not match one of the orientations in the previous test set were analysed as “mismatch” trials.

Statistical analysis

Contrast Matching task

Matching contrast was assessed by calculating the mean of the last five contrast values from each block. For experiment 1 and 3, paired sample t-tests were used to assess differences in contrast matching between the parallel and orthogonal surround, and also between contrast matching for both surrounds and the reference contrast value (30% Michelson contrast). For experiment 2, 2x2 repeated measure ANOVA with “surround” as the two levels within-participants factor and “group” as the two levels between-participants factor was used to detect any differences between the two groups. Further paired sample t-tests were also applied.

Orientation discrimination task

Orientation discrimination thresholds were calculated by computing the mean of the last five orientation values in each block for each condition. Before computing the mean, trials that exceeded the value of seven were excluded from the analysis. The value of seven was chosen based on Song et al., 2013a which also used an orientation discrimination task and found that the OD threshold of their participants ranged until the value of seven. For experiment 1 and 3, paired sample t-tests were used to assess differences in orientation discrimination between the parallel and orthogonal surround. For experiment 2, 2x2 repeated measure ANOVA with “surround” as the two levels within-participants factor and “group” as the two levels between-participants factor was used to detect any differences between the two groups. Further paired sample t-tests were also applied.

Working Memory task

Working memory behavioural results were analysed in terms of accuracy, response times, dprime, hits and correct rejections. DPrime is a widely used measure of WM performance that takes into account a proportion of Hits and False alarms (FA) (Haatveit et al., 2010; Macmillan & Creelman, 2005; Macmillan & Creelman, 1990). In the context of this study, Hits were defined as trials in which participants correctly identified a probe that matched the orientation of one of the gratings of the encoded test set. Misses were defined as trials in which participants failed to identify a probe that matched the orientation of one of the gratings of the encoded test set. Correct rejections were trials in which participants correctly identified a probe that did not match the orientation of one of the gratings of the encoded test set. False alarms were trials in which participants failed to identify a probe that did not match the orientation of one of the gratings of the encoded test set.

To calculate d' we used the formula:

$$d' = z(\text{Hit rate}) - z(\text{FA rate})$$

where z represents the inverse of a normal distribution (z score) (Haatveit et al., 2010; Macmillan & Creelman, 1990).

Following Macmillan & Creelman (2005), Hit rate was calculated as:

$$N(\text{Hits})/(N(\text{Hits}) + N(\text{Misses}))$$

However, when misses were equal to zero, Hit rate was calculated as:

$$(N(\text{Hits})-0.5)/ (N(\text{hits}) + N(\text{Misses}))$$

FA rate was calculated as:

$$N(\text{FA})/(N(\text{FA}) + N(\text{Correct Rejections}))$$

However, when FAs were equal to zero, FA rate was calculated as:

$$0.5/(N(\text{FA}) + N(\text{Correct Rejections}))$$

Finally, to explore whether different types of correct answers might reflect distinct memory processes we also analysed Hits and Correct rejections separately.

A closer examination of the data highlighted that in some trials participants answered with a very short or a very long response time. Therefore, these trials were considered as a presumably unrealistic measure of WM behaviour and consequently excluded them from the analysis. Specifically, following Georgiadi, Liotti, Nixon, & Liddle (2011), response times that were below 200ms and one standard deviation above each condition's mean were excluded from the analysis. The same filter was applied for the measures of accuracy. Therefore, for accuracy, dprime, hits and correct rejection, trials in which response times were below 200ms and one standard deviation above each condition's mean were excluded from the analysis.

A 2x3 repeated measure ANOVA with "surround" as the within-participants factor with two levels (parallel and orthogonal) and "load" as the within-participants factor with three levels (load 1, 2 and 3) was performed to analyse the effects of surround and load on WM performance and response times. For experiment 2, the group was added as the between-participants factor with two levels (patients and controls). If sphericity was not assumed, Greenhouse-Geisser correction was applied. If main effects or interactions were significant, further pairwise comparisons were run with Bonferroni correction. Furthermore, bivariate correlations were run between WM results and contrast matching or orientation discrimination. Specifically, performance from the visual tasks for parallel and orthogonal surround was correlated with WM performance measures averaged within the load trials (for parallel and orthogonal surround), within the surrounds (for Load 1, 2 and 3) and within all conditions (overall performance).

ERPs

Time windows for ERPs analysis were chosen based on visual inspection of the Grand Averages for each experiment. For this reason, for the visual ERP peaks (C1, P1, P2 and N1), time windows were slightly adjusted depending on the Grand Averages of each cohort. Specific time windows will be reported in the methods section of chapter 3 (for Experiment 1) and chapter 4 (for Experiment 2). Electrodes to include in the analysis

were chosen based on visual inspection of topographic maps and based on electrodes used in previous studies.

Encoding

During encoding, peak latencies and amplitudes (detected as the highest voltage value in a given time window) were calculated for C1 at electrode Oz (central occipital electrode), P2 at electrodes O1, O2 and Oz (central occipital electrode), P1 at central (O1, O2, Oz) and lateral visual electrodes (PO7, PO8, PO9, PO10) and N1 at lateral visual electrodes (PO7, PO8, PO9, PO10). In addition, mean averaged Slow Wave activity was analysed in the time interval between 450 and 900ms at frontal (F1, F2, Fz) and lateral visual electrodes (PO7, PO8, PO9, PO10).

Retrieval

At retrieval, for both match and mismatch trials, peak amplitudes and latencies of P1 were extracted at central (Oz, O1, O2) occipital electrodes and N1 at lateral electrodes (PO7, PO8, PO9 and PO10).

At encoding a 3x2x3 (4x2x3 when four electrodes were loaded) (electrode, surround condition and WM load), whereas at retrieval a 2x3x2x3 (2x4x2x3 when four electrodes were loaded) (match/mismatch, electrode, surround condition and WM load) repeated-measures analysis of variance was used to test the effects within participants on all dependent measures. In experiment 2, the group was added as the between-participants factor with two levels (patients and controls). Main effects and interactions were reported only if significant. If sphericity was not assumed Greenhouse-Geisser correction was applied. If main effects or interactions were significant, further pairwise comparisons were run with Bonferroni correction. In the case of significant main effects or interactions, we also performed bivariate correlations between peak amplitude/latencies and WM, CM and OD performance. To perform the correlations, components latencies and amplitudes were averaged within the load trials (for parallel and orthogonal surround), within the surrounds (for Load 1, 2 and 3) and within all conditions (overall performance).

For both behavioural and ERPs results, measures of effect size were reported in terms of partial eta squared ($p\eta^2$) (Cohen, 1988; Cohen, 1973). According to Cohen (1973), $p\eta^2$ is calculated with the following formula:

$$p\eta^2 = \frac{df_A(F_A)}{df_A(F_A) + df_{Error}}$$

Where A is referred to the factor, df to the degrees of freedom and F to the F value of the ANOVA. As suggested by Cohen (1988), the magnitude of the effect size will be interpreted as small with $p\eta^2 = 0.01$ circa, medium with $p\eta^2 = 0.06$ circa and large with $p\eta^2 = 0.14$ circa (Cohen, 1988; Levine & Hullett, 2002; Norouzian & Plonsky, 2018).

Chapter 3 – Working Memory and lateral inhibition

Introduction

Working memory (WM) is the skill that allows the active and sustained storage of information in order to support ongoing cognition, complex behaviour and future planning (D'Esposito & Postle, 2015; de Vries, van Driel, & Olivers, 2017; Goldman-Rakic, 1995a; Luck & Vogel, 2013a; Morrison & Chein, 2011). The WM process is generally divided into three consecutive phases: encoding, when items are first perceived and turned into internal representations; maintenance, when the internal representations are sustained and isolated by interfering items; and retrieval, when the internal representations are actively recollected to respond to a specific cognitive demand (Haenschel & Linden, 2011; Proskovec et al., 2016). Traditionally, WM processing has been associated with PFC activity during the maintenance phase (Fuster & Alexander, 1971; Goldman-Rakic, 1995a). fMRI studies in humans have found sustained activity in the PFC when internal representations had to be held. Moreover, this activity was directly related to successful WM performance (Courtney et al., 1997; Goldman-Rakic, 1995a; Zarahn et al., 1997). The sustained PFC activity found during the retention interval has been interpreted as a storage system of sensory information, crucial for WM processing (D'Esposito & Postle, 2015; Fuster & Alexander, 1971; Goldman-Rakic, 1995a). However, recent evidence has proposed alternative interpretations of the PFC role during working memory processing. For example, in an fMRI experiment, Lee and colleagues (2013) asked participants to memorise either a specific detail of objects showed at encoding or the general category of the object. Multi-Variate Pattern Analysis (MVPA) revealed that, during maintenance, PFC was more active during the general category judgement. However, in the detailed perceptual judgment trials, more selective activity was found in the occipito-temporal cortex. The authors suggested that the PFC activity might be related to the retention of highly complex information, such as task instructions or categorisation of stimuli, which are fundamental to perform working memory. Thus, PFC activity might be associated with processes that go beyond the simple maintenance of information (Lee et al., 2013).

In addition to a revised interpretation of the PFC role during WM, recent models of WM have suggested that also sensory areas significantly contribute to WM functioning (D'Esposito & Postle, 2015; Javitt, 2009). Specifically, recent evidence has suggested that mechanisms taking place during the encoding phase can crucially influence WM performance (D'Esposito & Postle, 2015; Fallon et al., 2016; Pasternak & Greenlee, 2005). For example, Haenschel and colleagues (2007), using Event-Related potentials (ERPs), tested a population of early-onset schizophrenia patients and healthy matched controls in a delayed matching to sample WM task. They found that, only in healthy population, early visual P1 increased with an increment of memory load. Furthermore, P1 amplitudes during encoding predicted WM performance. The authors concluded that early visual ERPs respond to an increased working memory demand. Moreover, early sensory processing can directly influence working memory performance (Haenschel et al., 2007).

The ability of visual areas to support the maintenance of information in visual working memory has been highlighted by fMRI studies (Emrich et al., 2013). Emrich and colleagues (2013) showed participants three patches of coloured moving dots. In different trials, the number of the moving dots could increase or decrease. After a delay, a coloured line appeared on the screen and participants had to adjust its orientation according to the direction of the colour-match moving dots. In this study, it was found that when the number of the moving dots was higher (high memory load) visual cortex activity decreased. The authors interpreted the decrement of visual cortex activity associated with the increment of load as a reflection of resources that become limited when more information needs to be retained. Moreover, this decrement of activity correlated with a lower WM precision, calculated as the variability of recall of target and non-target responses. Thus, the authors suggested that memory precision can be directly limited by perceptual encoding processes related to sensory areas (Emrich et al., 2013).

The encoding and maintenance of WM contents might not only depend on the number of items but also on the complexity of the stimuli. Independently from memory load, the storage of perceptually complex items might be more effortful than the storage of simple features (Bays & Husain, 2008). For example, in an EEG study, Kursawe & Zimmer (2015) used a change detection task in which participants saw up to four abstract objects. After the retention interval, only one object was presented in one specific location and participants had to judge whether the object had the same colour

(simple features), the same shape or the same colour and shape (complex features) compared to the object of the previous test array. They found that N1 amplitudes increased depending on the number of objects to memorise in both simple and complex feature conditions. However, both posterior P2 amplitudes and posterior slow waves increased with the increment of load only in the complex, but not in the simple features condition. The result was mirrored by the behavioural performance. Independently from the memory load, accuracy was lower in the complex compared to the simple features condition. The authors suggested that the encoding and maintenance of perceptually complex stimuli might require more cognitive effort compared to more simple perceptual features (Kursawe & Zimmer, 2015). Further studies have also demonstrated that the neural correlates associated with individual items at encoding, can be a predictor of WM performance. Peterson and colleagues (2014) measured Steady-State Visual Evoked Potentials (SSVEP - EEG signals elicited by flickering items) during a delayed matching to sample WM task in which participants had to indicate whether the location in which a probe item appeared, matched or not the location previously encoded. They compared correct with incorrect trials and found that, in correct trials, SSVEP signals at encoding were larger compared to the incorrect trials. They concluded that effective encoding of memory representations has a direct influence on the subsequent stages of WM and, eventually, on WM performance (Peterson et al., 2014).

The active role of visual areas during WM encoding is further demonstrated by studies that have tested how visual memory encoding activity differs from visual non-memory processing. In an fMRI experiment, Sneve and colleagues (2012) used a WM task in which, within the delay period, a tone played either at the beginning or towards the end, could indicate whether the previously encoded item was relevant for a subsequent WM task or whether it could be ignored. This type of design allowed the authors to separate visual active encoding (needed for the subsequent WM task) from a passive viewing condition. They found that, across all visual areas, BOLD activity was increased when participants had to memorise the stimulus compared to the passive viewing trials. The authors suggested that visual areas activity can change according to WM goals since visual cortex activity seems to be increased when items need to be actively memorised compared to when they have to be solely perceived (Sneve et al., 2012). Furthermore, visual areas actively contribute to the maintenance of specific information about WM contents. In an fMRI study, Serences and colleagues (2009)

found visual cortex activity to be different depending on whether participants had to remember the colour or the orientation of Gabors patches during a working memory task (Serences et al., 2009). The authors concluded that the visual cortex is able to actively encode and maintain specific information in the service of WM goals (Serences et al., 2009).

These findings emphasise the importance of visual encoding for successful WM performance. However, it is still not clear how basic perceptual mechanisms triggered during the encoding phase influence WM. One of the most fundamental visual processes is lateral inhibition. Lateral inhibition (LI) affects most of the cells in the visual cortex and refers to the suppressive activity of visual neurons towards their neighbouring cells (Blakemore & Tobin, 1972; Butler et al., 2008; Carandini & Heeger, 2012; Watson & Solomon, 1997). LI is active when a high contrast surround is placed outside the classical receptive field of a neuron. This creates a surround suppression (SS) effect in which the perceived contrast of the target can be altered by its surround, compared to when it is seen in isolation (Dakin, Carlin, & Hemsley, 2005). Hence, while LI is the physiological phenomenon that affects cells in the visual cortex, SS can be considered as a method to behaviourally measure LI (Butler et al., 2008; Dakin et al., 2005). For example, Xing and Heeger (2001) used a contrast matching task in which participants were asked to judge whether the contrast of a grating was higher (or lower) compared with the contrast of the same grating embedded in a larger surround. They found that the contrast of the grating was perceived as decreased when it was embedded in a large, high contrast surround. Moreover, the SS effect seems to be larger when the surround and the target have similar perceptual characteristics. Specifically, Xing and Heeger (2001) also found that contrast perception of the central grating was more decreased when the surround was vertically (compared to orthogonally) oriented to the central grating. In addition, evidence has shown that activity in visual areas seems to be reduced when stimuli are embedded in a surround compared to when they are seen in isolation (Blakemore & Tobin, 1972; Vanegas et al., 2015; Zenger-Landolt & Heeger, 2003).

The presence of a larger surround can also affect the perceived orientation of a target. It has been demonstrated that when the orientation difference between the surround and the target is low (approximately 15 degrees), the orientation of the target is perceived as tilted in the opposite direction (Bosten & Mollon, 2010; Smith & Wenderoth, 1999; Wilks et al., 2014). However, this effect seems to be extremely

variable between participants (Clifford, 2014). Moreover, evidence has shown that participants that show higher orientation discrimination skills (i.e. lower orientation discrimination thresholds) also show a weaker surround suppression effect (Song et al., 2013b).

It has been proposed that, in natural vision, SS is recruited to efficiently encode images that present homogeneous characteristics (Coen-Cagli, Kohn, & Schwartz, 2015). Coen-Cagli and colleagues (2015) recorded single unit spike activity from three monkeys visual cortex during the display of natural images. They found stronger suppression in V1 for homogeneous compared to heterogeneous images. Thus, it is believed that SS is then needed to reduce the redundancy of the visual scene and to render the perception of visual images more efficient. Specifically, SS mechanisms facilitate the identification of the objects in relation to their background (Blakemore & Campbell, 1969; Blakemore & Tobin, 1972; Carandini & Heeger, 2012; Coen-Cagli et al., 2015; Li, 1999; Sachdev et al., 2012; Silverstein, 2016). However, it is still not clear whether LI can also influence the mental representations of memory contents. Specifically, whether the sensitivity to SS mechanisms might enhance (or hinder) the internal memory representations and, therefore, influence the overall WM performance has not yet been explored. To my knowledge, this is the first study that has examined the impact of LI on higher-order cognitive functions in humans.

Experiment 1: aims and predictions

The aim of Experiment 1 was to examine whether lateral inhibitory mechanisms have an effect on WM performance.

Stimuli were designed with the aim of inducing either a stronger (parallel surround) or a weaker (orthogonal surround) lateral inhibition. The same stimuli were used in a contrast matching task, in order to measure the surround suppression effect on contrast perception, and in an orientation discrimination task, in order to test surround effects on orientation perception. Finally, the same stimuli were used during a delayed matching to sample WM task, in order to test LI and SS effects on working memory performance. During the WM task, event-related potentials (ERPs) were also measured, in order to explore the neural mechanisms underlying the different WM phases.

It was expected:

- The parallel surround to induce a stronger surround suppression compared to the orthogonal surround, in line with previous research.
- WM performance related to parallel surround condition to differ from performance related to the orthogonal surround throughout all the WM loads.
- Early visual ERPs to be modulated both by memory load and by LI.
- Slow wave activity at frontal electrodes to increase with the increment of memory load.

Methods

Participants

Twenty right-handed participants (14 females and 6 males, mean age = 25.4 years, SD = 6.7) took part in the study. All participants self-reported to have normal or corrected to normal vision and to be free from neurological and psychiatric disorders. The study was approved by the ethics committee at City, University of London and all participants signed an informed consent before participation.

Two outlier female participants were excluded from all the analysis (behavioural and ERPs). For one outlier, the behavioural performance in the orientation discrimination task exceeded more than two standard deviations from the mean. For the second outlier, accuracy in the WM task was below 50% correct. Therefore, the final sample included 18 participants.

Stimuli and design

For all four tasks, circular grating items embedded in larger surrounds were generated using Matlab software and Psychtoolbox 3.0.12 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) and presented centrally on a grey background CRT monitor with a gamma correction of 2.2 at a viewing distance of 58cm. Throughout all the tasks the circular gratings were presented either in isolation or embedded in a larger, 100% contrast surround. In the "parallel" condition the orientation of the surround relative to the centre was 0° degrees and in the "orthogonal" condition the orientation relative to the centre was 90° deg (see Figure 2.1 – Chapter 2). Participants were not informed about

the two stimulus conditions. Trials were randomised among conditions and among participants in all the tasks. A more detailed description about stimulus and parameters is outlined in Chapter 2.

Tasks

Participants sat in a dark and soundproof Faraday cage. Participants performed a 2 Intervals Forced Choice Detection (2IFCD), a contrast matching task (CM), an orientation discrimination task (OD) and a working memory task. In addition, EEG was recorded only during the Working Memory task.

A detailed description of each task and stimulus parameters is outlined in Chapter 2.

ERP Data acquisition, processing and analysis

During the WM task, a 64 electrode cap (actiCAP, Brain Products GmbH) based on the international 10-20 system (Jasper, 1958) was fitted on the participants' heads and fixed with elastic bands attached to a strap placed over participants' chest. The ground electrode was placed at the middle anterior frontal electrode, the reference electrode was placed at the middle frontocentral electrode, and an additional vertical electro-oculogram electrode below the left eye. EEG analysis during encoding and retrieval and ERPs extraction were performed with BrainVision Analyser software (Brain Products GmbH). Details about the pre-processing analysis can be found in chapter 2. Time windows for ERPs analysis were chosen based on visual inspection of the Grand Averages. Electrodes to include in the analysis were chosen based on visual inspection of topographic maps.

Encoding

During encoding, peak amplitudes and latencies of C1 at electrode Oz (central occipital electrode) were defined in the interval between 60ms and 120ms, P1 at lateral visual electrodes (PO7, PO8, PO9, PO10) between 70ms and 130ms, N1 at lateral visual electrodes (PO7, PO8, PO9, PO10) between 100 and 213ms, and P2 at electrodes O1, O2 and Oz (central occipital electrode) between 170ms and 270ms after stimulus onset. For Slow Waves, mean averaged activity was analysed at frontal (F1, F2, Fz) and lateral visual electrodes (PO7, PO8, PO9, PO10) in the time interval between 450 and 900ms after stimulus onset.

Retrieval

At retrieval, correct trials related to match and mismatch conditions were analysed. For both match and mismatch trials, peak amplitudes and latencies of P1 were extracted at central (Oz, O1, O2) occipital electrodes in the time interval between 110ms and 200ms, and N1 at lateral electrodes (PO7, PO8, PO9 and PO10) between 156ms and 225ms after probe onset.

Statistical analysis

Contrast Matching

Paired sample t-test was performed to assess differences in contrast matching between the parallel and orthogonal surround, and also between the reference contrast value (30% Michelson contrast) and contrast matching for parallel and orthogonal surround.

Orientation Discrimination

Paired sample t-test was performed to assess differences in orientation discrimination between the parallel and orthogonal surround.

Working Memory

A 2x3 repeated measure ANOVA with "surround" as a within-participants factor with two levels (parallel and orthogonal) and "load" as a within-participants factor with three levels (load 1, 2 and 3) was performed for WM accuracy, dPrime, hit rate, correct rejections rate and response times. Only significant main effects and interactions were reported. If sphericity was not assumed, Greenhouse-Geisser correction was applied. If main effects or interactions were significant, further pairwise comparisons were performed with Bonferroni correction. To perform bivariate correlations, WM accuracy was averaged within all conditions and within Load 1, 2 and 3 both for parallel and orthogonal surround. WM was also averaged within parallel and orthogonal surround respectively for Load 1, 2 and 3. Then, we performed bivariate correlations between WM averaged accuracy and CM and OD for parallel and orthogonal surrounds. In addition, a correlation between overall WM accuracy and overall OD performance (averaged between parallel and orthogonal surround) was also performed.

ERPs

At encoding a 3x2x3 (4x2x3 when four electrodes were loaded) (electrode, surround condition and WM load) repeated-measures analysis of variance was performed. At retrieval, a 2x3x2x3 (2x4x2x3 when four electrodes were loaded) (match/mismatch, electrode, surround condition and WM load) repeated-measures analysis of variance was performed. Main effects and interactions were reported only if significant. In the case of significant main effects or interactions, further follow-up ANOVAs were performed. Bivariate correlations were also performed between peak amplitudes CM, OD and averaged WM accuracy (as described above). To perform the correlations, components amplitudes were averaged within the load trials (respectively for parallel and orthogonal surround) and within all conditions (overall performance).

For both behavioural and ERPs results, measures of effect size are reported in terms of partial eta squared ($p\eta^2$) (Cohen, 1988; Cohen, 1973). The magnitude of the effect size will be interpreted as small with $p\eta^2 = 0.01$ circa, medium with $p\eta^2 = 0.06$ circa and large with $p\eta^2 = 0.14$ circa (Cohen, 1988; Levine & Hullett, 2002; Norouzian & Plonsky, 2018).

Results

Behavioural results

Orientation discrimination (OD)

Orientation discrimination threshold for parallel surround (M = 1.36, SD = 0.67) did not differ from orientation discrimination threshold for orthogonal surround (M = 1.64, SD = 0.73) ($t(17) = 1.5$, $p = 0.15$).

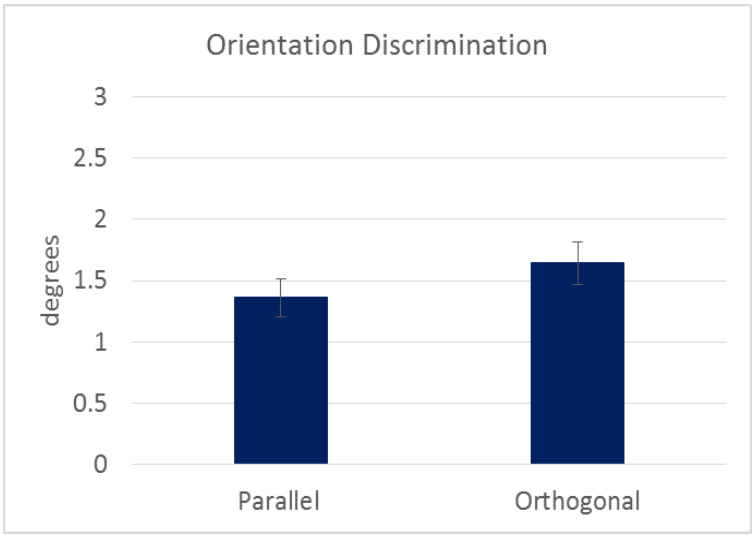


Figure 0.1. Orientation discrimination results for the parallel and orthogonal surround condition. The x-axis indicates parallel and orthogonal surround conditions. Values on the y-axis represent orientation discrimination thresholds expressed in degrees. Error bars indicate standard errors.

Contrast matching (CM)

Contrast matching for parallel surround (M = 0.33, SD = 0.04) was significantly higher than contrast matching for orthogonal surround (M = 0.31, SD = 0.04) ($t(17) = 2.9$, $p = 0.011$). Moreover, contrast matching for parallel surround differed from the reference ($t(17) = 2.9$, $p = 0.009$), whereas contrast matching for orthogonal surround did not differ from the reference ($t(17) = 1.3$, $p = 0.21$).

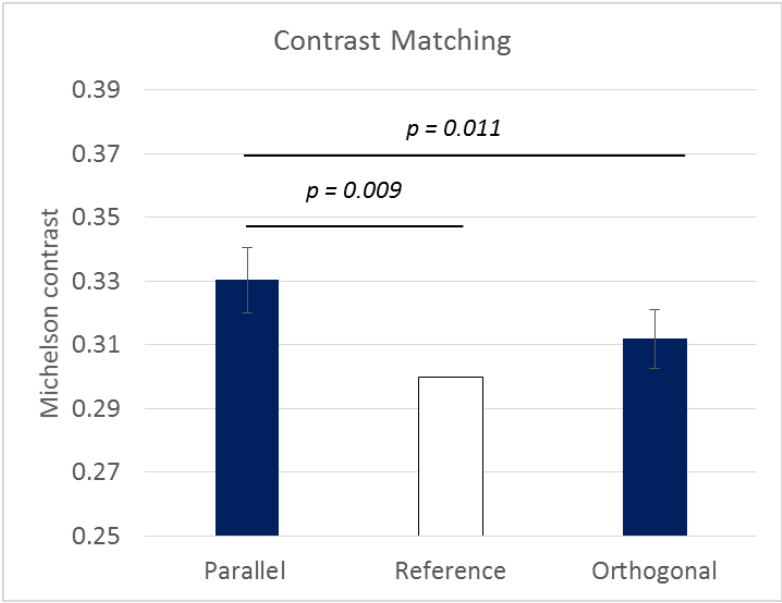


Figure 0.2. Contrast matching results for the parallel and orthogonal surround condition. The x-axis represents the parallel and orthogonal surround conditions. The white bar represents the reference contrast of the isolated patch which was constant throughout the task (30% Michelson contrast). Values on the y-axis represent contrast matching expressed in Michelson contrast. Horizontal black lines represent significant differences found between the parallel and orthogonal surround and between the parallel surround condition and the reference. Error bars indicate standard errors.

Working Memory

	Load 1 Parallel		Load 1 Orthogonal	Load 2 Parallel	Load 2 Orthogonal	Load 3 Parallel	Load 3 Orthogonal
Accuracy Mean *(SD)*	**0.92** ***(0.08)***	*	**0.95** ***(0.08)***	0.88 *(0.10)*	0.85 *(0.10)*	0.79 *(0.12)*	0.79 *(0.10)*
dPrime Mean *(SD)*	**3.03** ***(0.96)***	*	**3.41** ***(0.90)***	2.51 *(0.91)*	2.36 *(0.94)*	1.86 *(0.95)*	1.78 *(0.82)*
Hits Mean *(SD)*	0.91 *(0.10)*		0.94 *(0.10)*	0.88 *(0.12)*	0.86 *(0.13)*	0.79 *(0.16)*	0.80 *(0.11)*
Correct Rejections Mean *(SD)*	0.92 *(0.09)*		0.95 *(0.07)*	0.87 *(0.09)*	0.84 *(0.11)*	0.80 *(0.12)*	0.78 *(0.12)*
Response Times Mean (seconds) *(SD)*	0.40 *(0.09)*		0.40 *(0.08)*	0.39 *(0.08)*	0.39 *(0.09)*	0.40 *(0.10)*	0.38 *(0.06)*
* $p < 0.05$							

Table 0.1 Working Memory behavioural results for each condition. Mean and standard deviations (in brackets) are displayed for accuracy, dPrime, hits, correct rejections, and response times. For response times, means and standard deviations are expressed in seconds. Numbers in bold with asterisks represent conditions in which a significant difference (with $p < 0.05$) was found.

Mean and standard deviations for working memory behavioural results are reported in Table 3.1.

A main effect of load was found for accuracy ($F(2,34) = 52$, $p < 0.001$, $p\eta^2 = 0.76$), dPrime ($F(2,34) = 57$, $p < 0.001$, $p\eta^2 = 0.77$), Hits ($F(2,34) = 25$, $p < 0.001$, $p\eta^2 = 0.59$) and correct rejections ($F(2,34) = 35$, $p < 0.001$, $p\eta^2 = 0.67$). Correct answers decreased with the increment of load. Moreover, an interaction surround*load was found for accuracy ($F(2,34) = 3.6$, $p = 0.04$, $p\eta^2 = 0.18$) and dPrime ($F(2,34) = 6.2$, $p = 0.005$, $p\eta^2 = 0.27$). Responses for parallel surround were lower than orthogonal surround only in Load 1 condition both for accuracy ($t(17) = 2.5$, $p = 0.02$) and dPrime ($t(17) = 2.6$, $p = 0.02$). Response Times did not differ depending on load or surround.

Correlations

Orientation Discrimination and Contrast Matching

A negative correlation was found between CM and OD only for the parallel surround condition ($r = -0.53$, $p = 0.025$), but not for the orthogonal.

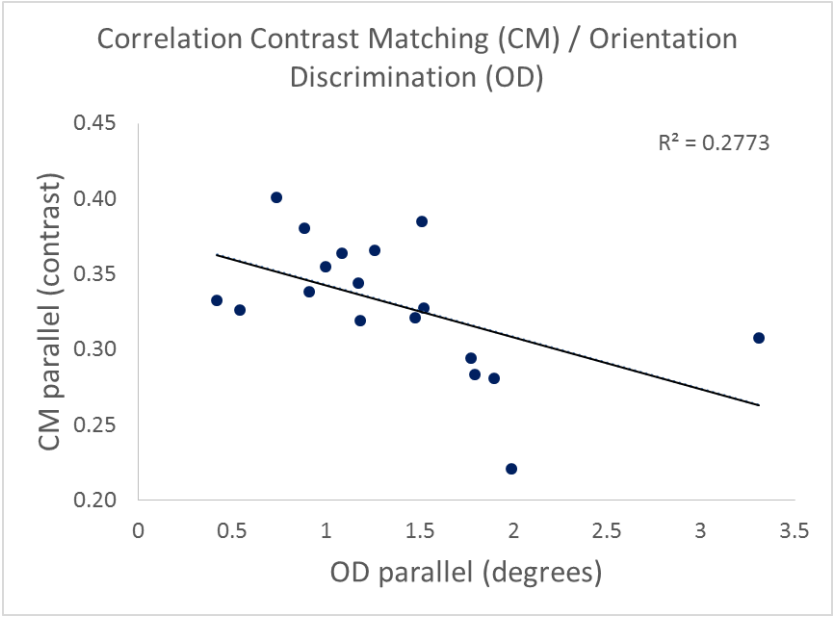


Figure 0.3. Correlation between orientation discrimination (x-axis) and contrast matching (y-axis) for the parallel surround condition. Lower OD threshold was associated with higher contrast matching in the parallel surround. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

Orientation Discrimination and Working Memory

OD in the orthogonal surround negatively correlated with accuracy in Load 3 (r = -0.50, p = 0.034). However, a negative correlation was also found between overall OD performance and accuracy for Load 3 (r = -0.51, p = 0.032).

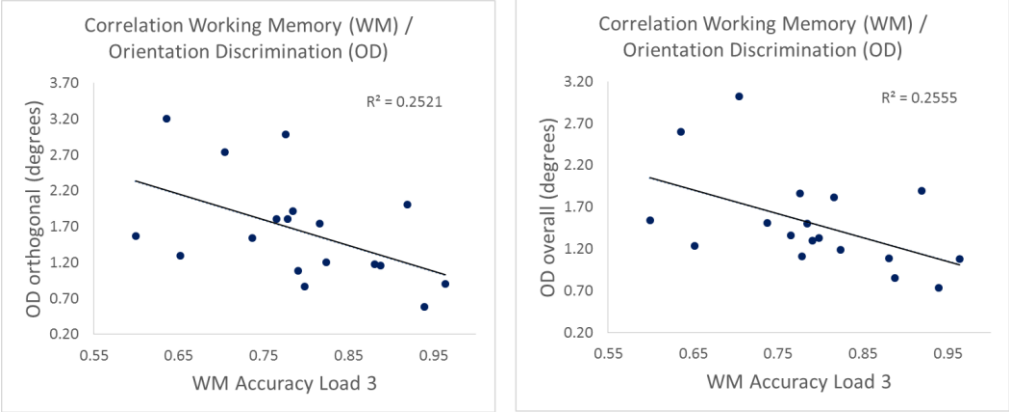


Figure 0.4. (Left) Negative correlation between WM accuracy for load 3 condition (x-axis) and orientation discrimination for the orthogonal surround (y-axis). (Right) Negative correlation between WM accuracy for load 3 condition (x-axis) and orientation discrimination averaged for parallel and orthogonal surround (y-axis). Lower OD threshold was associated with higher performance in load 3 condition. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

Contrast Matching and Working Memory

A positive correlation was found between CM and Correct Rejections for parallel surround (r = 0.46, p = 0.05).

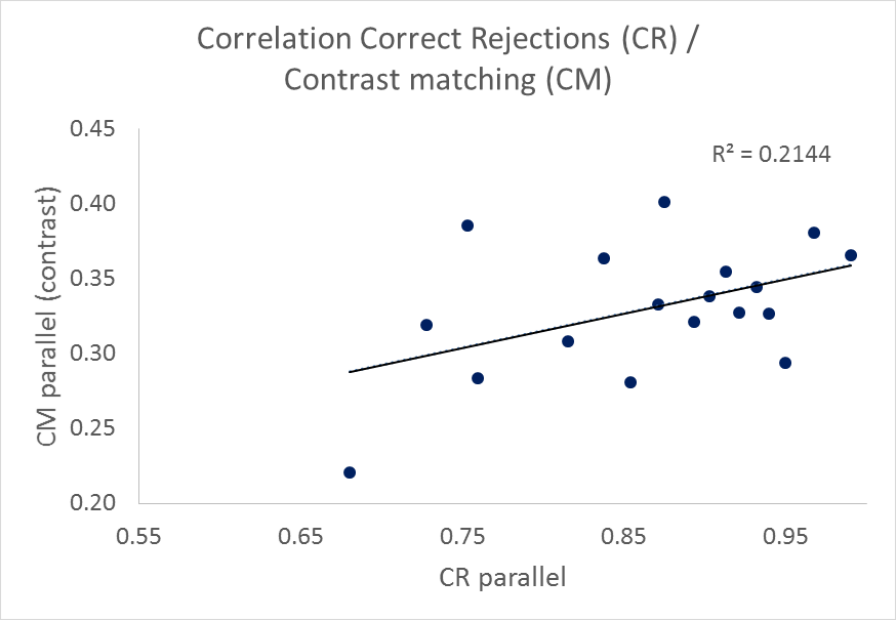


Figure 0.5. Positive correlation between WM correct rejection rate (x-axis) and contrast matching (y-axis) for the parallel surround condition. Higher contrast matching was associated with higher correct rejection rate in the parallel surround condition. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

ERPs results

Encoding

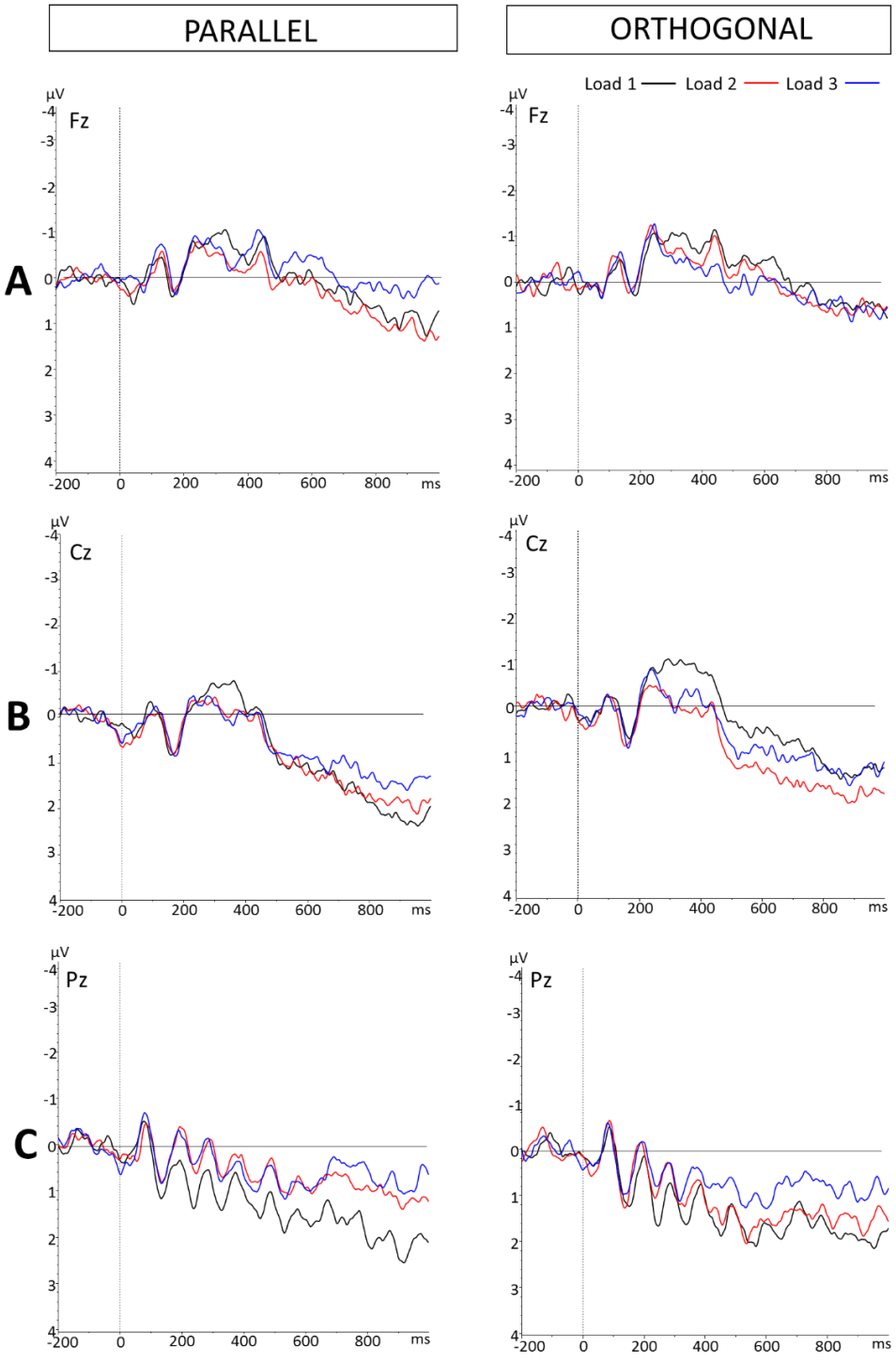


Figure 0.6 Grand Average ERPs of WM loads 1, 2, and 3 in response to the parallel (left) and orthogonal surround (right) gratings during encoding. The x-axis represents time in milliseconds (ms) where 0 is stimulus onset. The y-axis represents voltage in microvolts (µV). Slow wave activity was observed after stimulus offset (from 450ms onwards) at frontal (A), central (B) and parietal (C) electrodes. At parietal electrodes (C), activity from 0 to 400ms might reflect ongoing alpha. However, this activity was only observed at this electrode, and not at more occipital electrodes (see Figure 3.7). Moreover, we did not observe a similar activity in the same electrode at retrieval (see Figure 3.13).

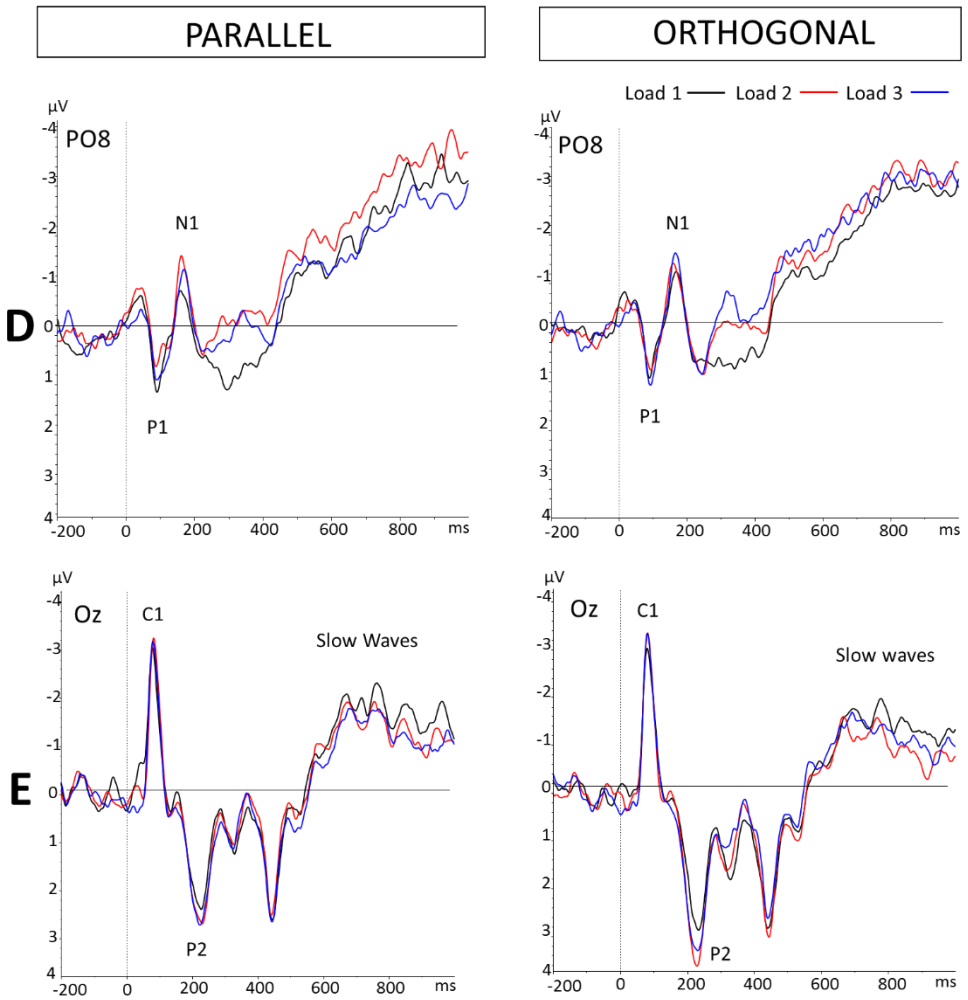


Figure 0.7 Grand Average ERPs of WM loads 1, 2, and 3 in response to the parallel (left) and orthogonal surround (right) gratings during encoding. The x-axis represents time in milliseconds (ms) where 0 is stimulus onset. The y-axis represents voltage in microvolts (µV). The grating with the surround elicited P1 and N1 at lateral occipital electrodes (D) and C1 and P2 at central occipital electrodes (E). Slow wave activity was observed after stimulus offset (from 450ms onwards) both at lateral (D) and central occipital electrodes (E). The positive peak arising after 400ms at central occipital electrodes (E) has been interpreted as related to stimulus offset (300ms) and therefore it was not analysed.

C1

The stimuli elicited a C1 with a negative polarity with a mean latency of 83 ms (SD = 11ms) at the central occipital electrode, Oz. (Figure 1B). However, neither C1 amplitudes nor latency were significantly modulated by load or surround.

P1

P1 component was observed at lateral occipital electrodes with a mean latency of 105ms (SD = 19). No significant results of load or surround were found neither for P1 latency nor for amplitudes.

N1

N1 component was observed at lateral occipital electrodes with a mean latency of 158ms (SD = 29). Analysis for N1 latency was not significant, whereas only an interaction electrode*load ($F(3.7,62.3)= 5.3$, $p = 0.001$, $p\eta^2 = 0.24$) was found for N1 amplitudes. However, the follow-up analysis was not significant.

P2

The P2 component was observed at visual electrodes (O1, Oz, O2) with a peak latency of 220ms (SD = 21ms).

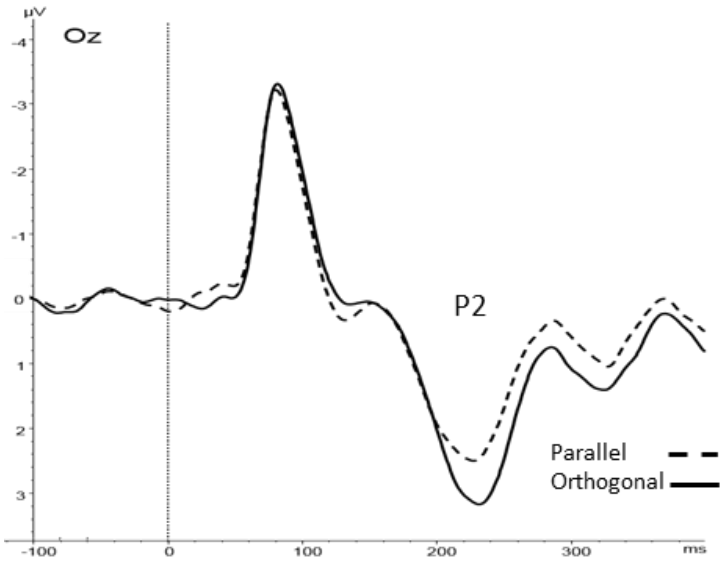


Figure 0.8. P2 component at Oz electrode elicited during encoding at 200ms after stimulus onset. The x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in µV. Amplitudes for the parallel surround were reduced compared to the orthogonal.

Latency

P2 latencies were shorter in response to the parallel compared to the orthogonal surround ($F(1,17)= 17$, $p = 0.001$, $p\eta^2 = 0.50$). No effect of load was found.

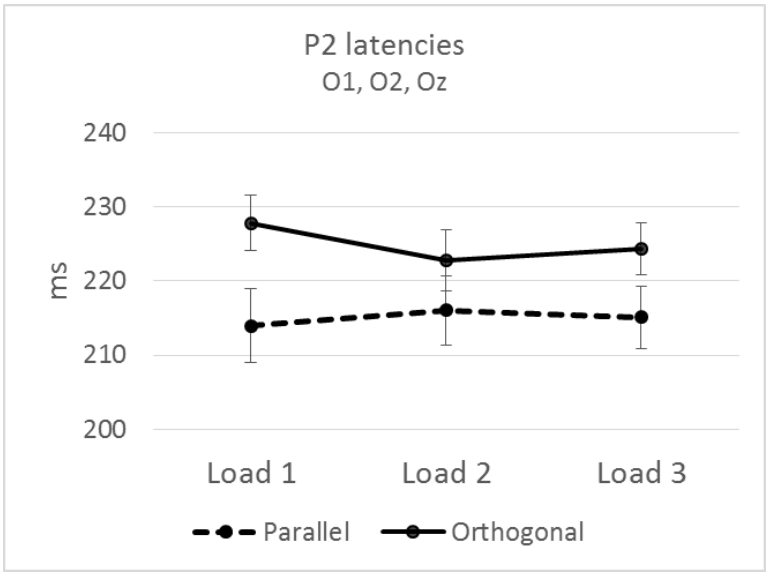


Figure 0.9. Main effect of surround for P2 latencies averaged for electrodes O1, O2 and Oz. The x-axis represents WM load conditions 1, 2 and 3. The y-axis represents time in ms. Error bars represent standard errors.

Amplitudes

A main effect of surround ($F(1,17)= 5.1$, $p = 0.04$, $p\eta^2 = 0.23$) was found. P2 amplitudes were significantly lower in response to the parallel compared to the orthogonal surround condition. There was no main effect of load, but a significant interaction electrode*load ($F(2.6, 44.4)= 3.9$, $p = 0.02$, $p\eta^2 = 0.19$). Further ANOVAs performed at each load revealed that parallel peaks were lower than orthogonal specifically for Load 3 (main effect of surround: ($F(1,17)= 7.1$, $p = 0.016$, $p\eta^2 = 0.30$) and marginally for Load 2 ($F(1,17)= 4$, $p = 0.06$, $p\eta^2 = 0.19$).

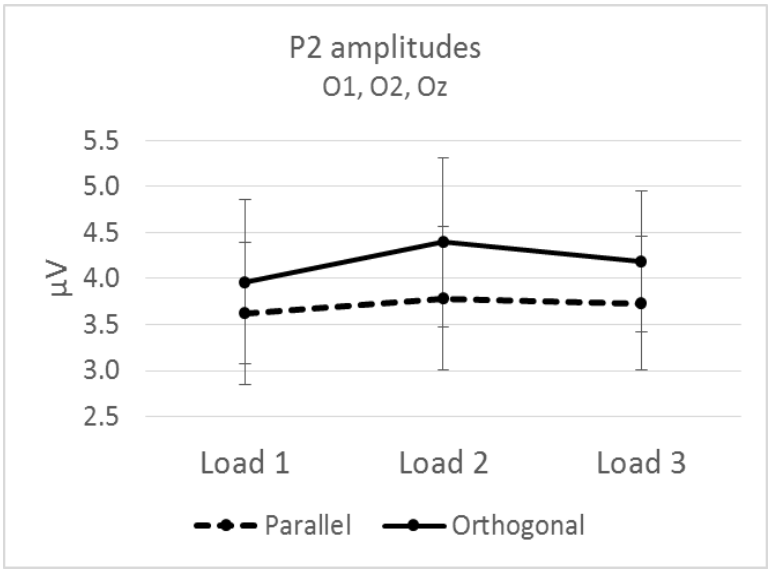


Figure 0.10. Main effect of surround for P2 amplitudes averaged for electrodes O1, O2 and Oz. The x-axis represents WM load conditions 1, 2 and 3. The y-axis represents voltage in µV. Error bars represent standard errors.

There were no correlations between P2 and WM behavioural measures. However, we found a positive correlation between CM for parallel condition and P2 amplitudes averaged for parallel condition (r = 0.48, p = 0.04).

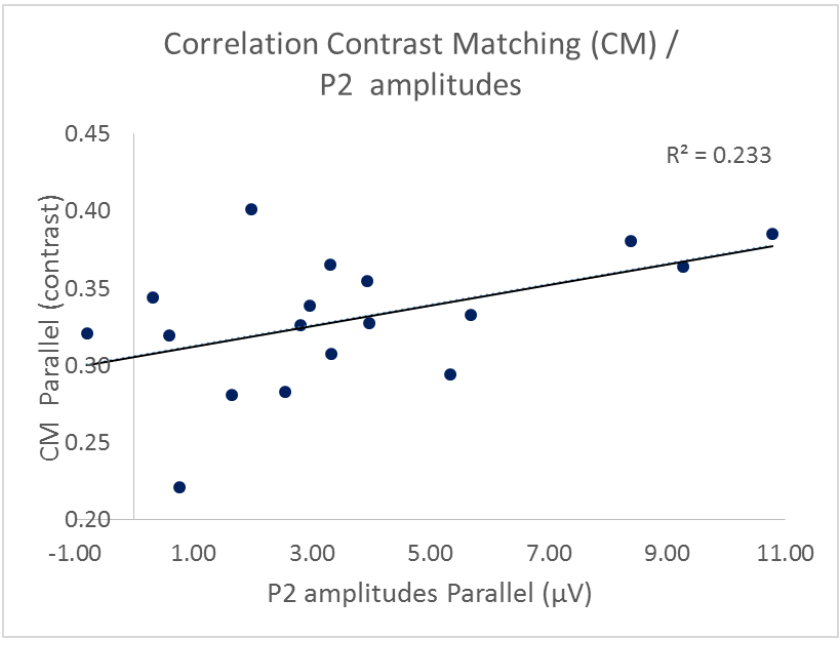


Figure 0.11. Positive correlation between P2 amplitudes (x-axis) and contrast matching (y-axis) for the parallel surround condition. Higher P2 amplitudes were associated with higher contrast matching in the parallel surround. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

Slow Waves (SW)

Slow wave activity was observed in the time window between 450 and 900 ms after stimulus onset and analysed at frontal and visual electrodes. However, significant results were found only at frontal, but not at visual electrodes.

Frontal electrodes

An interaction surround*load ($F(2,34) = 3.2$, $p = 0.05$, $p\eta^2 = 0.16$) was found. Further analysis only revealed a weak trend to a main effect of surround in Load 2 condition ($F(1,17) = 3.8$, $p = 0.07$, $p\eta^2 = 0.18$), in which SW activity for parallel was higher compared to orthogonal surround. No correlations were found with the visual or working memory tasks.

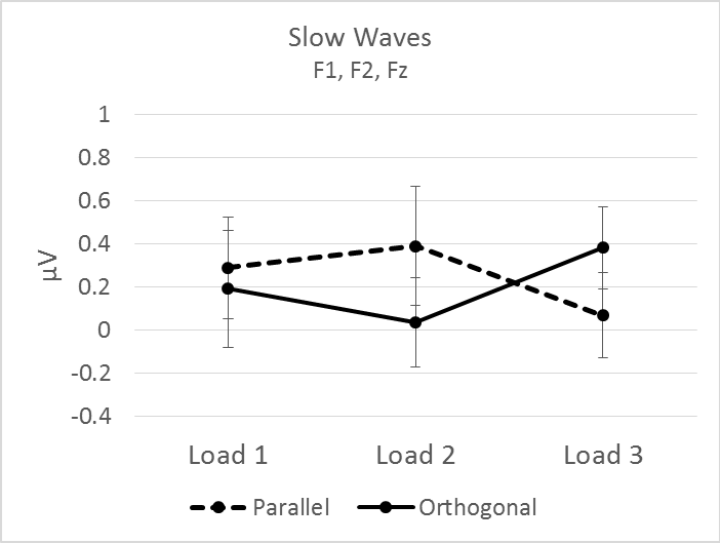


*Figure 0.12. Interaction surround*load for slow wave activity at frontal electrodes averaged for electrodes F1, F2 and Fz. The x-axis represents WM load conditions 1, 2 and 3. The y-axis represents voltage in µV. Activity for parallel surround was marginally higher than activity for orthogonal surround in Load 2. Error bars represent standard errors.*

Retrieval

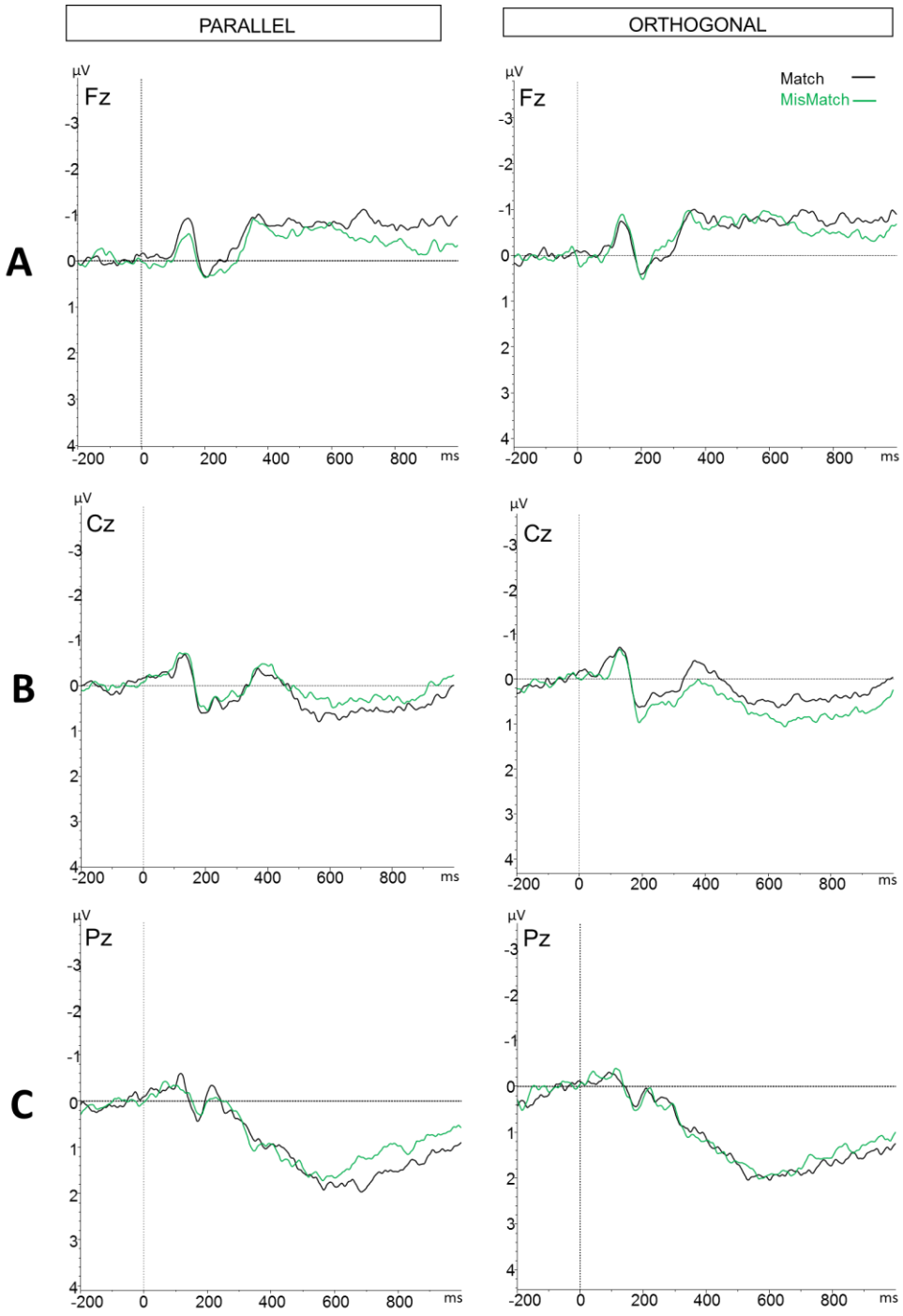


Figure 0.13 Grand Average ERPs of the parallel (left) and orthogonal surround (right) gratings during retrieval in response to the match (black) and mismatch (green) trials. The x-axis represents time in milliseconds (ms) where 0 is stimulus onset. The y-axis represents voltage in microvolts (µV). Slow wave activity was observed after stimulus offset (from 450ms onwards) at frontal (A), central (B) and parietal (C) electrodes. At parietal electrodes (C) no activity that resembled ongoing alpha was observed.

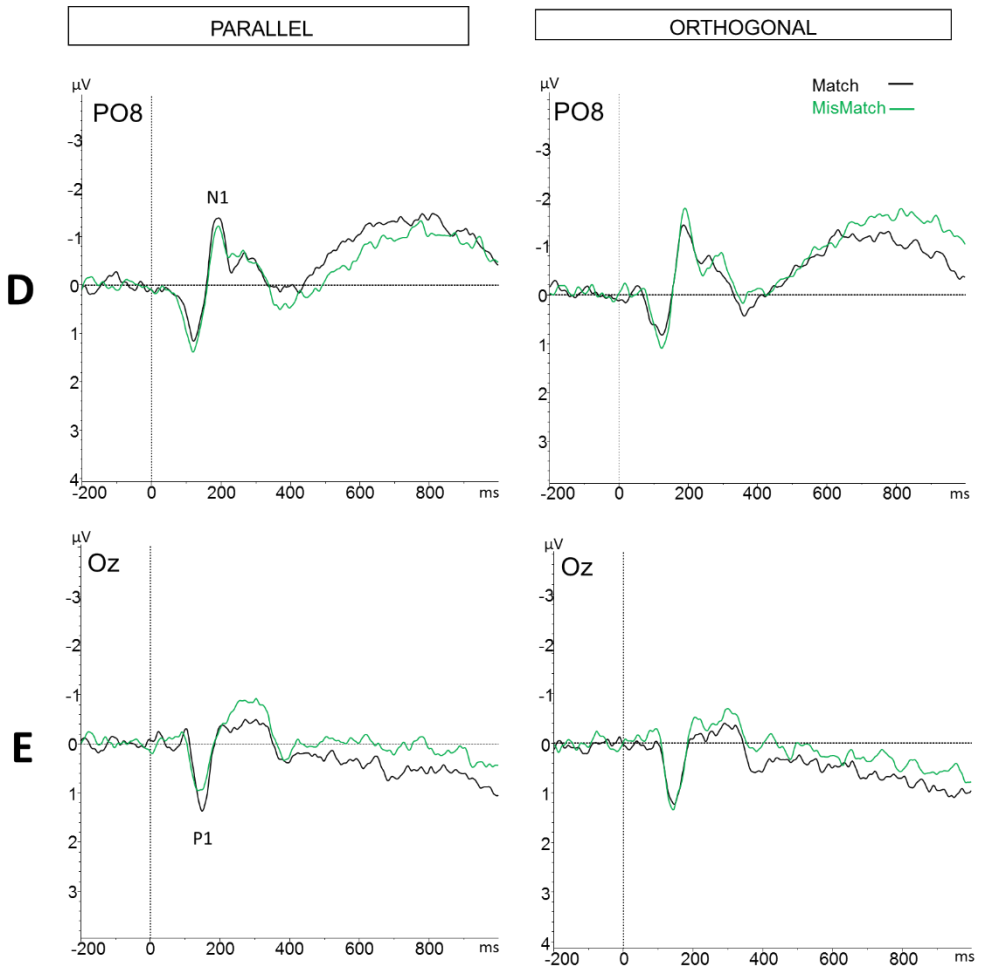


Figure 0.14 Grand Average ERPs of the parallel (left) and orthogonal surround (right) gratings during retrieval in response to the match (black) and mismatch (green) trials. The x-axis represents time in milliseconds (ms) where 0 is stimulus onset. The y-axis represents voltage in microvolts (µV). At lateral occipital electrodes, P1 and N1 were observed (D). In contrast with encoding, at central occipital electrodes, P1 was observed instead of C1 and P2 (E).

P1

P1 was observed at central (O1, O2, Oz) with a mean latency of 149ms (SD = 24) for match trials and a mean latency of 148ms (SD = 25) for mismatch trials. Significant results were found only for P1 amplitudes, but not for latency.

Amplitudes

A main effect of load was found ($F(2,34) = 5.4$, $p = 0.009$, $p\eta^2 = 0.24$). Amplitudes decreased with the increment in memory load.

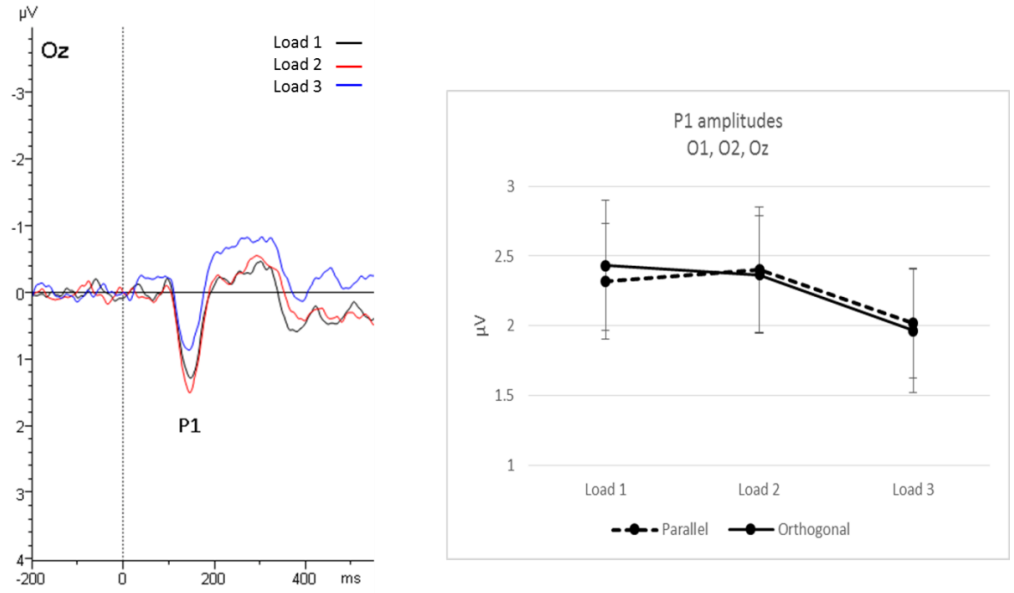


Figure 0.15. (Left) Grand average ERP waveform representing P1 at Oz electrode in response to Load 1, 2 and 3 (averaged for parallel and orthogonal condition). The x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in µV. (Right) Main effect of load for parallel and orthogonal surround for P1 amplitudes averaged for electrodes O1, O2 and Oz. The x-axis represents WM load conditions 1, 2 and 3. The y-axis represents voltage in µV. Error bars represent standard errors.

N1

N1 was observed at lateral visual electrodes (PO7, PO8, PO9, PO10) with a mean latency of 196ms (SD = 19) for match trials and a mean latency of 198ms (SD = 20) for mismatch trials.

Latency

An interaction match/mismatch*surround ($F(1,17) = 5.2$, $p = 0.04$, $p\eta^2 = 0.23$) and an interaction match/mismatch*electrode*surround ($F(3,51) = 3.4$, $p = 0.03$, $p\eta^2 = 0.17$) were found. Analysis performed at each surround revealed that N1 latencies were shorter for match compared to mismatch trials only for parallel ($F(1,17) = 4.7$, $p = 0.04$, $p\eta^2 = 0.22$) but not for the orthogonal surround.

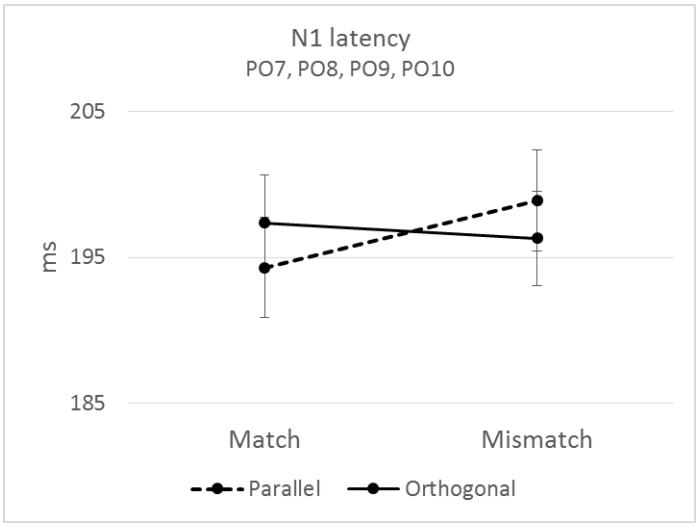


*Figure 0.16. Interaction match/mismatch*surround for N1 latency at retrieval averaged for electrodes PO7, PO8, PO9, PO10. The x-axis represents match and mismatch trials. The y-axis represents time in ms. Error bars represent standard errors.*

Amplitudes

A main effect of load ($F(2,34)= 9$, $p = 0.001$, $p\eta^2 = 0.35$) was found. N1 amplitudes increased with memory load. A trend to an interaction surround*load ($F(2,34)= 3$, $p = 0.07$, $p\eta^2 = 0.15$) was also found. Analysis performed at each surround revealed that N1 amplitudes increased with the increment of memory load only for the parallel ($F(2,34)= 16.5$, $p < 0.001$, $p\eta^2 = 0.50$) but not for the orthogonal surround. No correlations were found with WM or visual tasks.

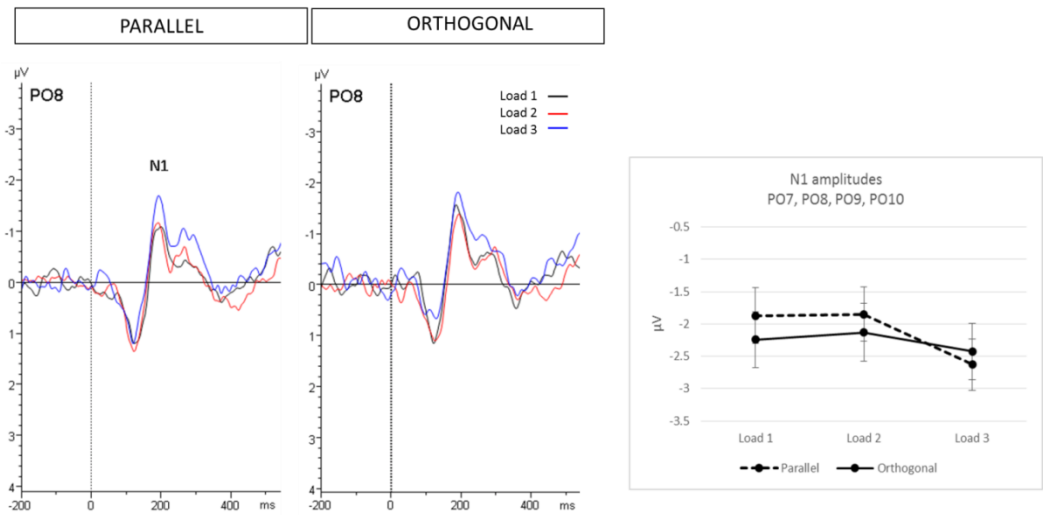


*Figure 0.17. (Left) Grand average ERP waveform representing N1 at electrode PO8 in response to Load 1, 2 and 3 for parallel and orthogonal surround conditions. The x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in µV. (Right) Interaction surround*load for N1 amplitudes averaged for electrodes PO7, PO8, PO9, PO10. The x-axis represents WM load conditions 1, 2 and 3. The y-axis represents voltage in µV. Error bars represent standard errors.*

Discussion

Behavioural results

In study 1 it has been examined whether basic visual mechanisms can influence WM. Specifically, it has been explored to what extent lateral inhibitory activity affects the formation of memory content and WM performance. Firstly, in order to analyse LI mechanisms at a perceptual level, a contrast matching (CM) task was used, in which participants had to judge whether the contrast of a target grating was higher when presented in isolation or embedded in a larger surround. An orientation discrimination (OD) task was also used to explore surround effects on orientation perception. In the task, participants had to indicate whether the grating was rotated clockwise or anti-clockwise compared to the previous interval. Crucially, in both tasks, the larger surround was either parallel or orthogonally oriented to the target in order to induce different levels of LI.

As expected, in the CM task, contrast perception of the central grating was significantly decreased in the parallel surround condition both compared to the orthogonal surround and to the reference contrast of the isolated patch. This surround suppression (SS) effect has been repeatedly found in previous studies that have interpreted this phenomenon as a reflection of LI mechanisms (Blakemore & Tobin, 1972; Dakin et al., 2005; Sachdev et al., 2012; Xing & Heeger, 2001; Yoon et al., 2009; Zenger-Landolt & Heeger, 2003). Thus, it can be assumed that the parallel surround in the contrast matching task has induced stronger LI activity compared to the orthogonal surround. Moreover, only the parallel surround condition of the CM results correlated negatively with OD, suggesting that participants showing a higher suppression in the CM also needed a lower orientation discrimination threshold.

However, orientation discrimination was not affected by the surround suppression effect. Specifically, orientation discrimination did not differ when the surround was parallel compared to when it was orthogonally oriented to the target. Previous studies have highlighted that the SS effect on orientation discrimination can be variable between participants (Clifford, 2014; Song et al., 2013b). Moreover, evidence has also shown that participants with a lower orientation discrimination threshold seem to be more immune from the SS effect (Song et al., 2013b; Wilks et al., 2014). To test this assumption, a further analysis was performed between participants from experiment 1 and participants from experiment 3 which, instead, showed a difference between the parallel and orthogonal surround in the OD task (see Chapter 5). This analysis

revealed a group effect. Specifically, participants from experiment 1 had a significantly lower orientation discrimination threshold compared to participants from experiment 3. Thus, in line with the literature, it is suggested that participants in this study did not show a surround effect in the OD task likely because they had a lower orientation discrimination threshold (Song et al., 2013b). This analysis is outlined more in-depth in the results and discussion session of Chapter 5.

In the study, it has been also explored, whether WM performance is affected by the SS effect. In a delayed matching to sample WM task, up to three gratings (embedded either in the parallel or in the orthogonal surround) were presented with different orientations and, after a delay, participants had to judge whether the orientation of a probe Gabor (shown without the surround) matched or not one of the orientations previously presented. Although response times were not influenced by the experimental manipulations, accuracy decreased with an increment in memory load. Moreover, in Load 1 condition, accuracy for the parallel surround was lower than accuracy for the orthogonal surround. This result was further confirmed by dPrime (the proportion between hits and false alarms), that is a considered as a measure of the sensitiveness of a participant in recognising a target (Haatveit et al., 2010). However, surround effects at higher memory loads, in Load 2 and 3 conditions were not found. In contrast to Load 1 condition, in which the representation of the item was isolated, in Load 2 and Load 3 conditions, the target item is encoded together with the non-target items. Thus, the surround effect at Load 1 can be interpreted as reflecting a stronger perceptual interference induced by the parallel surround which, however, was not related to WM processing. In Load 2 and 3 conditions, the representation of the items was overlaid on top of each other, and this might have probably hindered surround effects. This potential explanation will be explored more in-depth in Experiment 3 (Chapter 5), in which a task that allowed to isolate the single representation of each item has been used.

In addition, a negative correlation between OD for the orthogonal surround and WM accuracy in Load 3 condition was found. Specifically, participants that showed higher accuracy in the WM task also showed a lower threshold for OD but only for the orthogonal surround condition, and not with the parallel. Moreover, WM accuracy in Load 3 condition also negatively correlated with the overall OD performance. These correlations indicate that higher performance in orientation discrimination (i.e. lower thresholds) seems to be associated with better WM accuracy at higher loads. Thus,

this result suggests that higher basic visual skills (such as lower orientation discrimination threshold) also support WM performance. This seems to support current models of WM suggesting that basic sensory mechanisms can influence WM processing (D'Esposito & Postle, 2015; Javitt, 2009). However, since the correlations were not specific for the most suppressive surround (parallel surround), LI mechanisms seem not to improve OD skills and, consequently, WM performance. In contrast, contrast matching positively correlated specifically with correct rejections only in the parallel but not in the orthogonal surround condition. This correlation seems to suggest that higher suppression is related to higher performance in trials that required to recognise a non-matching orientation. However, since there were no surround effects on correct rejections, the relationship between CM and WM performance needs to be further investigated.

In sum, the behavioural results suggest that the parallel surround decreased contrast perception of a central target. Moreover, SS effects on WM performance were only evident at Load 1 which suggest that these were of perceptual nature. Finally, better perceptual abilities (specifically, lower orientation discrimination thresholds) seems to be related to higher WM performance. However, LI seems not to improve OD skills and their effects on WM.

EEG results

Encoding

In order to explore neural mechanisms underlying the different phases of WM, EEG data have been collected.

At encoding, C1 was observed only at electrode Oz. Since items were presented in the fovea, C1 had a negative polarity, in line with previous evidence (Hansen et al., 2016). However, C1 amplitudes or latencies were not affected by surround or memory load effects. Surround effects were observed at around 200ms after stimulus onset, with P2. Both P2 latencies and amplitudes were modulated by the surround. Specifically, P2 amplitudes and latencies were lower in the parallel compared to the orthogonal surround. Moreover, both for latencies and amplitudes, a large effect size was observed, suggesting that the effect was reasonably powerful.

In addition, P2 amplitudes positively correlated with CM in the parallel but not in the orthogonal surround condition, suggesting that higher contrast matching was associated with higher P2 amplitudes when surround suppression was stronger.

In previous studies, posterior P2 has been associated with stimulus saliency. Specifically, studies investigating contour integration have found that P2 amplitudes were lower for highly salient stimuli, i.e. when the figure-ground segregation was clearer (Machilsen et al., 2011; Straube & Fahle, 2010). It has been suggested that a stimulus is more salient when the perceived difference between the stimulus itself and its background is larger (Itti & Koch, 2001; Machilsen et al., 2011; Straube & Fahle, 2010). According to this claim, the orthogonal surround items are more salient compared to the parallel surround as the orientation difference between the target and the surround is larger. However, in contrast to previous studies, here P2 amplitudes were found to be lower for the less salient stimuli (parallel surround condition). Thus, it is suggested that the P2 amplitudes decrement with the parallel surround can be interpreted not as a saliency effect, but as a perceptual effect reflecting the more suppressive activity exerted from the parallel surround.

During late encoding, an interaction surround*load in the Slow Waves (SW) at frontal electrodes was found. However, further post-hoc t-tests were not significant. SW has been found to increase when a larger number of items need to be retained in WM (Luria et al., 2016; Vogel et al., 2005). However, these maintenance mechanisms might also depend on the perceptual characteristics of the items. Kursawe & Zimmer (2015) have found that SW activity increased with the increment of load only when more complex perceptual features had to be retained, whereas the increment of SW activity was not observed with the maintenance of simple features (Kursawe & Zimmer, 2015). However, in this study there was not a main effect of surround that would have been in line with this evidence. Instead, the effect was not found throughout all the memory loads, but only weakly in Load 2 condition. Thus, the SW results suggest that the maintenance of memory representations is not affected by the surround modulation.

In sum, ERPs results at encoding showed that P2 amplitudes are modulated by the SS effects. This seems to be confirmed by the correlations between P2 amplitudes and the CM tasks. However, we could not find direct correlations between ERPs and WM behavioural results suggesting that encoding mechanisms did not directly influence the overall WM performance.

Retrieval

At retrieval, the probe stimulus was shown without the surround. Here, ERPs responses to match and mismatch trials were analysed. Specifically, trials in which participants correctly identified that the orientation of the probe was the same as the target item at encoding were considered match trials. Trials in which participants correctly identified that the orientation of the probe was not the same as the target item at encoding were considered mismatch trials.

At central posterior electrodes, P1 was observed instead of C1 and P2. It was found that P1 amplitudes decreased with higher loads. Load effects on P1 amplitudes were associated with a large effect size, suggesting a substantial magnitude of the effect. Previous research has associated P1 amplitudes with attentional mechanisms (Kappenman & Luck, 2012a). For example, in studies testing spatial cueing (Luck et al., 1994; Luck & Hillyard, 1995), participants had to report the presence or the absence of a stimulus. In some trials, a cue arrow highlighted the location in which the stimulus was about to appear (valid-cue) or another location (invalid-cue). In a neutral-cue condition, none of the positions was highlighted. P1 was enhanced in invalid compared to neutral trials. The authors interpreted this result as reflecting the suppression of irrelevant information (Hillyard et al., 1998; Luck et al., 1994; Luck & Hillyard, 1995). Although these studies have tested spatial attention, the result in the current study might be in line with this interpretation. The decrement of P1 amplitudes from memory Load 1 to memory Load 3 might reflect the suppression of an increasing number of irrelevant information.

Although at retrieval the surround was not physically present, ERPs activity was still modulated by the surround. Specifically, N1 latencies were lower for match compared to the mismatch trials, but only in the parallel and not in the orthogonal surround condition. Moreover, N1 amplitudes increased with the increment in memory load only for the parallel but not for the orthogonal surround. This effect appeared to be statistically powerful since it was associated with a large effect size. N1 has been previously associated with stimulus discrimination (Machilsen et al., 2011; Vogel & Luck, 2000) and with enhanced attentional mechanisms (Griffin & Nobre, 2003; Hillyard et al., 1998; Luck et al., 1994; Luck & Hillyard, 1995). Moreover, in a delayed matching to sample WM task, Pinal, Zurron, & Diaz (2014) also found increased activity with memory load at retrieval, but with N2 instead of N1. In a delayed matching to sample WM task, they showed to participants a domino tile filled with up to six black

dots. At retrieval, another domino tile was showed and participants had to judge whether the dots matched or did not match the ones at encoding. Memory load was modulated by increasing the number of black dots. They found that at retrieval, N2 amplitudes increased with the increment of memory load. The increment in N2 amplitudes was interpreted as reflecting enhanced attentional demand at higher memory loads. Moreover, the authors interpreted the result as reflecting comparison processes between the presented probe and the internal memory representation (Pinal et al., 2014). Although they found a memory load effect with N2 instead of N1, different presentation times (three seconds instead of one second) and different stimuli (domino tiles) might explain the discrepancy with the current result. Thus, in line with this evidence, it is suggested that N1 surround modulation might reflect some sort of discriminatory processes between the probe (shown without the surround) and the test item (shown with the surround). Moreover, the increment of N1 amplitudes only for the parallel, but not for the orthogonal surround can be interpreted as reflecting a larger deploy of attention for stimuli that were presumably less perceptually salient (Itti & Koch, 2001; Machilsen et al., 2011; Straube & Fahle, 2010).

In sum, at retrieval P1 amplitudes decreased with memory load, suggesting increasing inhibition of irrelevant items. In contrast, N1 amplitudes increased with load only for the parallel surround. It is suggested that these results reflect comparison processes between the internal memory trace and the presented probe.

Overall, Experiment 1 replicated previous results regarding the SS effect on contrast perception. The contrast was perceived as significantly decreased when LI was stronger. However, it was not found a direct influence of LI mechanisms on WM performance. Specifically, only in Load 1, WM accuracy was decreased when LI was stronger. This result seems to somewhat contradict the idea that surround suppression enhances the precision of items perception (Sachdev et al., 2012). More specifically, it seems that the identification of the targets over a continuous background supported by SS activity is associated with a cost in the precision of the target representation. Nevertheless, since LI effects were not found at higher WM loads, it seems that LI does not interfere with WM processing. Moreover, orientation discriminations skills seem to negatively correlate with WM performance, suggesting that higher basic perceptual

skills support WM accuracy. However, LI mechanisms seem not to improve OD abilities and WM performance.

ERPs results showed that at encoding, P2 amplitudes in the parallel surround condition were decreased and positively correlated with CM. It is proposed that this result reflects the stronger suppressive activity induced by the parallel surround. At retrieval, although the surround was not physically present, an increment of N1 amplitudes with the memory load was found in the parallel surround condition, but not in the orthogonal. This result might reflect increased attentional demand for less perceptually salient stimuli, and comparison processes between the probe and the internal memory content.

To conclude, the contextual modulation exerted by LI mechanisms seems to decrease contrast perception of a central target. However, in this experiment LI activity seems not to have directly affected WM performance. Future studies might attempt to clarify the effects of LI on WM. For example, future studies might explore whether the simple presence of a surround (independently of a parallel or orthogonal condition) might impair WM representations compared to a condition in which the SS effect is absent (a “no-surround” condition).

The following chapter will explore the contribution of an impaired LI system to WM deficits in clinical populations, such as schizophrenia.

Chapter 4: Working Memory and schizophrenia

Introduction

Difficulties in everyday life and social interactions are persistent in people affected by schizophrenia (SZ), also when they are not experiencing acute psychiatric symptoms. Several studies have shown that poor cognitive performance in patients can be a predictor of limitations of general everyday living such as employment status (Meltzer*, et al*., 1996) or social functioning (Green, *et al.*, 1996). In fact, cognitive deficits have been associated with poor quality of life in patients with schizophrenia (Green, 1996; Meitzer et al., 1996; Shamsi et al., 2011).

Poor quality of life is persistent in people affected by schizophrenia, even when clinical symptoms are reduced with medications intake. Quality of life has been traditionally assessed with objective sociodemographic factors such as age, level of education, housing, income and access to the community (Lehman, 1983). However, these measures do not account for the patients' personal evaluation (Lehman, 1983; Priebe & Fakhoury, 2008). Therefore, recent measurement of quality of life includes a direct patients' self-evaluation of subjective factors such as leisure time, family, work and social relationship (Priebe, Huxley, Knight, & Evans, 1999; Priebe et al., 2010, 2011). It has been shown that improvements in the subjective rating of the quality of life were associated with a reduction of clinical symptoms (Priebe et al., 2011). Moreover, it has been proposed that the subjective evaluation of patients' quality of life might lead to better management of the disease and to the development of more targeted care programs (Priebe & Fakhoury, 2008). Thus, it is now believed that the quality of life needs to be constantly monitored in order to ensure patients' wellbeing in the long-term (Priebe & Fakhoury, 2008; Priebe et al., 1999; Priebe et al., 2010, 2011).

Moreover, Shamsi and colleagues (2011) found that aspects of quality of life are related to specific cognitive deficits: verbal memory predicted residential status, social cognition predicted social functioning and working memory predicted work/education status. Since cognitive deficits seem to be fairly independent of positive and negative symptoms, they are now considered as a core feature of the disease (Barnett et al., 2010). A range of cognitive deficits has been reported in people with schizophrenia, such as poor attention, speed of processing, sensory processing, motor functions,

social cognition, problem solving and working memory (Barch & Ceaser, 2012; Keefe, 2008; Nuechterlein et al., 2004). For this reason, the National Institute of Mental Health sponsored the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) programme in order to specifically target cognitive deficits and to develop cognitive training as treatments (Barnett et al., 2010; Green et al., 2004). As a consequence, a neuropsychological battery of tests, the MATRICS Consensus Cognitive Battery (MCCB), has been implemented and validated to address cognitive deficits in the disease (Nuechterlein et al., 2008). Although the MCCB has been widely used, recently the Cambridge Neuropsychological Test Automated Battery (CANTAB) for schizophrenia, has been proposed as an alternative battery which could be more suitable for testing new pharmacological treatments. The CANTAB battery for schizophrenia contains eight neuropsychological tests which together assess the domains recommended by MATRICS (Barnett et al., 2010). However, differently from the MCCB, it has been shown that the tests of the CANTAB battery are sensitive to pharmacological interventions that attempt to target cognitive dysfunctions (Fagerlund, Mackeprang, Gade, Hemmingsen, & Glenthøj, 2004; Fagerlund, Søholm, Fink-Jensen, Lublin, & Glenthøj, 2007; McCartan et al., 2001; Potvin et al., 2006; Tyson, Roberts, & Mortimer, 2004). Thus, it seems that the CANTAB battery might be particularly important for clinical trials testing the efficacy of a pharmacological treatment to improve cognitive deficits in schizophrenia (Barnett et al., 2010).

Within cognitive deficits, dysfunctions related to working memory seem to represent a particularly crucial issue, given the importance of working memory in many of day-to-day activities such as learning, reasoning and language comprehension (Hubacher et al., 2013; Lee & Park, 2005; Shamsi et al., 2011). WM deficits in schizophrenia have been consistently found in many experiments (Barch, 2006; Haenschel & Linden, 2011; Hubacher et al., 2013; Lee & Park, 2005). However, the underlying source of these deficits is still not fully clear. It has been proposed that WM impairments in schizophrenia are mostly related to storage, maintenance and retrieval abilities (Barch, 2006; Hartman et al., 2002; Lee & Park, 2005). This is supported by studies that have found deficits in manipulation (Gold et al., 1997; Kim et al., 2004), interference control (Fleming et al., 1995; Goldberg et al., 1998), and information updating (Ganzevles & Haenen, 1995; Goldberg et al., 2003; Perlstein et al., 2003), and attention (Barch, 2006; Barch et al., 2001; Braver, Barch, & Cohen, 1999; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Cohen & Servan-Schreiber, 1992).

For example, evidence has shown that patients with SZ fail to distribute their attention evenly to all the memory representations but they tend to hyperfocus on a subset of information (Gray et al., 2014; Hahn et al., 2012; Kreither et al., 2017; Leonard et al., 2013b). Leonard et al. (2013) conducted an EEG study using a change detection WM paradigm. A group of patients with SZ and healthy controls saw two groups of coloured shapes appeared both on the right and on the left side of the screen. Participants were instructed to memorise the colours of the objects only one of the two sides. After a delay, the shapes re-appeared on the screen and participants had to judge whether the colour of one of the two shapes in the target side had changed or not. They found that when only one item had to be retained, patients showed a larger contralateral delayed activity (CDA) compared to controls. Moreover, whereas for controls CDA tended to increase at higher memory loads, in patients CDA tended to decrease. The authors suggested that patients are unable to allocate attentional resources broadly, but they would hyperfocus only on a subset of memory representations. This would lead to poorer behavioural performance, since the inability to retain multiple memory information (Leonard et al., 2013a).

WM behavioural impairments observed in SZ have been mostly associated with aberrant dorsolateral pre-frontal cortex (DLPFC) activity in schizophrenia, especially during the late phases of maintenance and retrieval (Barch, 2006; Glahn et al., 2005; Goldman-Rakic, 1995a, 1996; Tan et al., 2007). However, recent evidence has shown that dysfunctions can start already during the encoding phase of WM (Haenschel & Linden, 2011; Lee & Park, 2005). For example, Hartman and colleagues (2002) were able to demonstrate that slowed encoding processing, rather than diminished abilities in holding memory information, might be directly linked to WM deficits (Hartman et al., 2002). They tested participants with SZ and healthy controls on a delayed matching to sample task. Participants saw three coloured rectangles and, after a delay of either 500ms or 6 seconds, they had to recognise whether a probe was present or not in the previously encoded set. Crucially, the authors also manipulated the encoding duration. Firstly, they performed the task to calculate an optimal encoding time for all participants (both patients and controls). At this stage, presentation times at encoding were varied until 80% of accuracy was reached. Afterwards, participants performed the main WM task with the previously assessed optimal subjective presentation time. This procedure was aimed to ensure that all participants had sufficient time to encode the WM items. They found that patients needed a fivefold increment in presentation

time in order to reach the same level of performance as controls. However, in the main WM task, when the encoding time was subjectively adjusted, patients' performance did not differ from controls. This was also not the case during the long delay condition. The authors proposed that in patients with schizophrenia the process of encoding and forming a stable internal representation is slower compared to controls (Hartman et al., 2002). However, further studies have highlighted that even increasing presentation times at encoding, perceptual deficits can still have an impact on WM performance (Tek et al., 2002). Tek, Gold, Blaxton, & Wilk (2002) used a delayed matching to sample WM task, in which several abstract polygon shapes were presented in different locations. After a delay, participants had to judge whether a probe shape matched the previously encoded stimulus either in terms of object (same object) or location (same location). Presentation times of the stimulus varied, in order to allow different levels of encoding duration. They found that patients performed significantly lower than controls. However, this impairment was independent of the increment in the exposure period of the stimulus. Specifically, even increasing the presentation time at encoding, performance was still lower in the spatial, but not in the object condition. The authors concluded that the WM deficits observed in SZ are not solely attributable to sluggish encoding processing but they might also be driven by perceptual dysfunctions in retaining visuo-spatial information (Tek et al., 2002).

WM behavioural impairments in SZ have been associated with deficits in early sensory processing. For example, Haenschel and colleagues (2007) analysed ERP signals and compared WM performance of a population of adolescents with early-onset schizophrenia with healthy control participants on a delayed matching to sample task in which up to three abstract shapes were presented and, after a brief delay, participants had to decide whether a probe shape matched or not with the previous test set. They found that P1 at visual electrodes was reduced in patients. Moreover, P1 amplitudes increased with memory load only in controls, but not in patients. Interestingly, P1 amplitudes correlated with WM performance only in healthy controls but not in participants with schizophrenia (Haenschel et al., 2007). More recently, Dias and colleagues (2011) also found reduced ERPs signals in schizophrenia both at occipital and frontal electrodes. They measured EEG of participants with schizophrenia and healthy controls performing the AX Continuous Performance Task (AX-CPT). In this working memory task, letters are displayed on the screen and participants have to indicate when the letter A is followed by the letter X, while all the other conditions

need to be ignored. They found that visual P1 and N1 at posterior electrodes and N2 and Slow Waves at frontal electrodes were reduced in patients compared to controls. However, only increased N1 was associated with higher WM performance for patients, but not the frontal components. The authors suggested that although both frontal and visual ERPs were reduced in patients, the visual ERPs were more directly related to a reduced WM performance (Dias, Butler, Hoptman & Javitt, 2011).

In sum, these studies suggest that encoding deficits can directly affect WM performance in SZ. However, it is unclear how basic perceptual mechanisms contribute to these encoding deficits. A considerable number of studies show that basic sensory mechanisms are abnormal in schizophrenia (Butler et al., 2008; Javitt, 2009; Silverstein, 2016; Silverstein & Keane, 2011b). One of the visual dysfunctions found in schizophrenia is related to lateral inhibitory mechanisms, in which the vast majority of neurons in V1 undergo through a suppression by their neighbouring cells (Blakemore & Tobin, 1972; Butler et al., 2008; Xing & Heeger, 2001; Zenger-Landolt & Heeger, 2003). Evidence has shown that lateral inhibition (LI) seems to be weakened in schizophrenia. Dakin and colleagues (2005) tested people with schizophrenia and healthy controls on a contrast matching task. Participants had to judge whether a circular patch had a higher contrast when it was presented embedded in a larger surround compared to when it was seen in isolation. Surprisingly, the patients' cohort was significantly more accurate than controls, since their contrast perception was not decreased by the presence of the surround. The authors explained this result as reflecting basic sensory failures related to a weakened lateral inhibitory system (Dakin et al., 2005).

In addition, LI failures in SZ seems to be specific for orientation. Yoon and colleagues (2009) tested a population of schizophrenia patients and healthy controls on a task in which a circular annulus was divided into eight segments and participants had to judge whether or not one of the segments had decreased contrast compared to the others. In order to test the orientation specificity of the surround suppression effect, the authors presented the annulus embedded in a larger surround which was either vertically (parallel condition) or horizontally oriented to the annulus (orthogonal condition). Contrast perception of both patients and controls did not differ in the orthogonal surround condition. However, only controls but not patients, showed a significant decrement in contrast perception in the parallel surround condition.

According to the authors, this result indicated that the suppression induced by the parallel surround was lower in the patients' cohort compared to controls (Yoon et al., 2009). The authors proposed that the surround suppression abnormalities observed in schizophrenia might be related to lateral inhibitory activity in the primary visual cortex. They tested this claim in a follow-up study in which they used the same experimental task in a group of schizophrenia patients and healthy controls but they also collected measures of ɣ-aminobutyric acid (GABA) levels with high field magnetic resonance spectroscopy (MRS) (Yoon et al., 2010). GABA interneurons regulate inhibition in the brain (Moghaddam & Javitt, 2012; Yoon et al., 2010). They found that GABA levels in patients' visual cortex were reduced compared to controls. Moreover, GABA levels in the visual cortex positively correlated with the magnitude of the surround suppression effect only in control population (Yoon et al., 2010). Thus, the authors concluded that a reduction in GABA levels in schizophrenia is related to perceptual processing involving inhibition (Moghaddam & Javitt, 2012; Yoon et al., 2010).

This evidence seems to suggest that a weakened LI system might be at the basis of perceptual dysfunctions that can also affect natural vision. For example, deficits in LI can results in failures in creating a unified and coherent representation of visual items (Butler et al., 2008; Silverstein & Keane, 2011b; Yoon et al., 2009). Moreover, it has been proposed that these basic visual dysfunctions might also underlie higher cognitive processing, including working memory (Javitt, 2009; Javitt & Freedman, 2014). Although it seems that WM performance in schizophrenia can be directly related to encoding deficits (Bittner et al., 2015; Haenschel et al., 2007), whether impaired LI mechanisms can contribute to these dysfunctions, to my knowledge, has not yet been tested. Therefore, this chapter will explore whether dysfunctions in the LI system observed in SZ affect WM performance.

Experiment 2: aims and predictions

The aim of Experiment 2 was to test the effects of diminished LI in schizophrenia on working memory performance. The SS effect was used as a measure of LI.

Here a population of people with schizophrenia and healthy matched controls have been tested. Similarly to experiment 1, a WM task in which items induced two different levels of SS was used. Specifically, in a parallel surround condition (stronger LI) the surround was vertically oriented to the target, whereas in an orthogonal surround

condition (lower LI) the surround was horizontally oriented to the central grating (see methods section for a detailed description). To test LI effects on perceived contrast and orientation the same stimuli were used in a contrast matching and an orientation discrimination task. To test LI effects on working memory the same stimuli were used in a delayed matching to sample WM task. During the WM task, event-related potentials (ERPs) were also measured in order to explore visual mechanisms during WM encoding and retrieval.

Moreover, participants have been tested on two neuropsychological tests taken from the CANTAB schizophrenia battery. Among the eight tests contained in the CANTAB schizophrenia battery, two tests that target visual short term memory and working memory abilities were chosen (Barnett et al., 2010). These tests allowed to verify whether WM results of the current study could be associated with standardised tests of visual memory and spatial working memory for schizophrenia. For the patient's population, measures of clinical symptoms and quality of life were also collected.

In light of the literature background and to the results of experiment 1 it was expected:

- The parallel surround to induce a stronger surround suppression compared to the orthogonal surround only in control population but not in patients, in line with previous studies.
- WM performance to be decreased and reaction times to be slower in patients compared to controls.
- In control population, but not in patients, WM performance to be higher in the parallel compared to the orthogonal surround in Load 1 condition, in line with experiment 1.
- Visual ERPs to be reduced in patients compared to controls.
- Performance in the CANTAB tests to be decreased in patients compared to controls. Patients' performance in these tests was expected to positively correlate with accuracy in our WM task.
- WM performance in patients to positively correlate with the quality of life measures.

Methods

Participants

Twenty-three people with Schizophrenia (8 females and 15 males, mean age = 36.82 year, SD = 9.7) and twenty healthy controls (8 females, 12 males, mean age = 34.95, SD = 10.75) were recruited for this study. Patients with a diagnosis of Schizophrenia according to the International Classification of Diseases-Tenth revision (ICD-10) criteria were recruited from the East London NHS Trust as outpatients. Patients were clinically stable at the time of the experiment and treated with commonly used second-generation antipsychotics (see Table 4.1). Current clinical symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). Patients with a history of substance abuse in the six months preceding the study, those with learning disabilities or communication difficulties and those with additional neuropsychiatric or neurological diagnoses were excluded from the study. Healthy control participants were demographically matched in terms of gender, age and years of education. Exclusion criteria for controls were history or family history of a psychiatric or neurological disease and the use of psychiatric drugs. These exclusion criteria for controls were assessed on self-report. All participants had normal or corrected to normal vision. Handedness was assessed with the Edinburgh Handedness Inventory Questionnaire (Oldfield, 1971). Only one patient was left-handed. This study was approved by the NHS Research Ethics Committee and adopted by the NHS portfolio. All participants signed an informed consent before participation.

After inspection of the collected data, four patients (four males) were less than 50% accurate in our working memory task. Therefore, they were excluded from the analysis (behavioural and EEG) as the reliability of the data was doubtful. Therefore, the final sample is of 19 patients (8 females and 11 males, mean age = 36.7 years, SD = 9.9) and 20 controls.

	Patients with Schizophrenia (N = 19)	Control participants (N = 20)
Mean Age (years)	36.7 *(SD = 9.9)*	34.95 *(SD = 10.75)*
Gender (N)		
Females	8	8
Males	11	12
Mean Education (years)	13.4 *(SD = 1.9)*	13.4 *(SD = 1.8)*
Handedness (N)		
Right	18	20
Left	1	0
Years of diagnosis (mean)	4.55 *(SD = 3.28)*	
Mean PANSS score	1.27 *(SD = 0.39)*	
Antipsychotic medication use (N)		
Amisulpride	3	
Aripiprazole	4	
Clozapine	3	
Olanzapine	4	
Quetiapine	2	
Risperidone	2	
Risperidone (DEPOT)	1	
Mean chlorpromazine equivalents (mg)	847	

Table 0.1 Participants' demographic details and patients clinical characteristics. First row: mean age (and SD) for patients and control populations. Second row: number of female and male participants for patients and control population. Third row: education level for patients and control populations expressed in mean (and SD) years of study. Fourth row: number of right and left-handed participants in the patients and control populations. Fifth row: mean (and SD) of the number of years patients received the diagnosis. Sixth row: mean (and SD) PANSS score for the patients population. Scores of different PANSS scales can be found in table 4.2. Seventh row: list of antipsychotic medications used by the patients and number of patients for each medication. Eighth row: average of chlorpromazine equivalent in milligrams (mg).

Chlorpromazine equivalent

Chlorpromazine (CPZ) equivalent was calculated per each patient based on conversion factors described previously (Gardner, Murphy, O'Donnell, Centorrino, & Baldessarini, 2010; Leucht et al., 2014; Woods, Gueorguieva, Baker, & Makuch, 2005). Specifically, equivalent doses of 100mg of CPZ for amisulpride were 0.86mg per day, for aripiprazole 4mg per day, for clozapine 120mg per day, for olanzapine 3mg per day, for quetiapine 60mg per day, for risperidone were 0.8mg per day and for risperidone

(depot) 14 mg per 14 days. The calculated equivalent was inserted as a covariate in the ANOVAs for patients.

Positive and Negative Syndrome Scale (PANSS)

Clinical symptoms for the patients' cohort were assessed with the Positive and Negative Syndrome Scale (PANSS). PANSS is a highly validated scale to assess clinical symptoms of Schizophrenia. Specifically, it evaluates the acuteness of positive and negative symptoms, the response to medications but also general psychopathology issues and how they interact with the severity of positive and negative symptoms (Kay et al., 1987). The scale consists of a Positive Scales and a Negative Scale of seven items each, and a General Psychopathology Scale of 16 questions, for a total of 30 items all assessed on a seven points Likert scale representing increasing levels of psychopathology where:

1 = absent; 2 = minimal; 3 = mild; 4 = moderate; 5 = moderate severe; 6 = severe; 7 = extreme

Higher scores indicated higher severity of symptoms on each scale. In order to assess the degree of severity of symptoms, a rating point was calculated per each participant as the summed score divided by the number of items for each scale. Specifically, for the positive scale and negative scale, the summed score per each participant was divided by seven. For the general scale, the summed score per each participant was divided by 16. For the total score, the summed score per each participant was divided by 30. The rating point obtained was then referred to the above Likert scale.
See Appendix 1 for a description of each item of the scale.

PANSS results showed that, overall, patients scored between 1 and 2 on the increasing levels of psychopathology rating scale in the positive symptoms, negative symptoms and general psychopathology scales. The average total score for PANSS was also between 1 and 2 on the Likert scale (see Table 4.2). Thus, clinical symptoms of this patients' cohort were between absent and minimal.

	MINIMUM AND MAXIMUM VALUES (1)	MEAN SUMMED SCORE (2)	MEAN RATING SCORE (3)
PANSS Positive scale	Min = 7 Max = 49	10 *(SD = 6.2)*	1.42 *(S.D. = 0.89)*
PANSS Negative scale	Min = 7 Max = 49	7.6 *(SD = 1.3)*	1.08 *(S.D. = 0.19)*
PANSS General Scale	Min = 16 Max = 112	20.5 *(SD = 4.7)*	1.28 *(S.D. = 0.29)*
PANSS Total	Min = 30 Max = 210	38 *(SD = 11.6)*	1.27 *(S.D. = 0.39)*

Table 0.2. PANSS results for patients' cohort. Column (1) represents the minimum and maximum score a single participant could obtain on each scale. Column (2) represents the mean (and SD) summed score for each scale. Column (3) represents the mean rating score obtained at each scale according to the seven points levels of psychopathology Likert scale (see Methods for details).

Edinburgh Handedness Inventory Questionnaire

The Edinburgh Handedness Inventory Questionnaire is a quantitative scale aimed to assess the dominant hand. The scale consists of 20 items describing common actions (such as writing and drawing, using scissors or a toothbrush) which could be answered with either "Right hand" or "Left hand". Handedness is then determined by the hand that obtained the highest score (Oldfield, 1971). Only one participant from the patients' cohort was left-handed. See Appendix 3 for the full questionnaire.

Stimuli and design

For all four tasks, circular grating items embedded in larger surrounds were generated using Matlab software and Psychtoolbox 3.0.12 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) and presented centrally on a grey background CRT monitor with a gamma correction of 2.2 at a viewing distance of 58cm. A detailed description of stimuli and parameters is outlined in Chapter 2.

Tasks

Participants sat in a dark and soundproof Faraday cage. Participants performed a Two-Interval Forced Choice Detection task (2IFCD), a contrast matching task (CM), an orientation discrimination task (OD) and a working memory task. In addition, EEG was

recorded only during the Working Memory task. A detailed description of each task and stimulus parameters is outlined in Chapter 2.

Control participants and schizophrenia patients performed (in this order) three CANTAB tests (Motor Screening Test, Paired Associate Learning and Spatial Working Memory). Schizophrenia patients also completed a questionnaire that assessed the quality of life (MANSA).

Cambridge Neuropsychological Test Automated Battery (CANTAB)

The CANTAB schizophrenia battery includes eight computerised neuropsychological tests that target cognitive deficits in schizophrenia considered relevant according to the international MATRICS consensus (Barnett et al., 2010). Moreover, these tests have been found to be sensitive to pharmacological treatments to target cognitive deficits in schizophrenia (Fagerlund et al., 2004, 2007; McCartan et al., 2001; Potvin et al., 2006; Tyson et al., 2004). Since this study is aimed to test WM performance in schizophrenia, the Paired Associate Learning and a Spatial Working Memory tests were selected from the battery because they specifically assess visual short-term memory and working memory abilities (Barnett et al., 2010). Moreover, we performed these tests in order to verify whether our WM results could be related to more standardised measures of WM. A Motor screening test was also performed in order to allow participants to familiarise with the touchscreen tablet.

Motor Screening test (MOT)

This test was administered at the beginning of the CANTAB testing session. Participants had to touch with the forefinger of the dominant hand a series of crosses appearing in different locations of the screen. Since this test was mainly performed with the aim of introducing participants to the use of a touchscreen computer, data from this test were not analysed.

Paired Associate Learning (PAL)

This test is aimed to assess visual memory and associative learning skills (Sahakian et al., 1988). Six to eight boxes opened one by one on the screen in random order. One or more boxes contained a pattern (Figure 4.1). Once the boxes have all been opened, the patterns appeared in the middle of the screen, one at a time in random order.

Participants had to indicate the box in which they previously saw the pattern. If errors were made, the patterns were displayed again. Participants had up to ten attempts to locate all the patterns in their boxes. When all the answers were correct, the test proceeded to the next level. Difficulties constantly increased by adding the number of patterns to remember. Independent sample t-test was performed to compare patients and controls on the total number of errors (PAL_total error) made on the PAL. Total number of errors score was also correlated with overall WM accuracy.

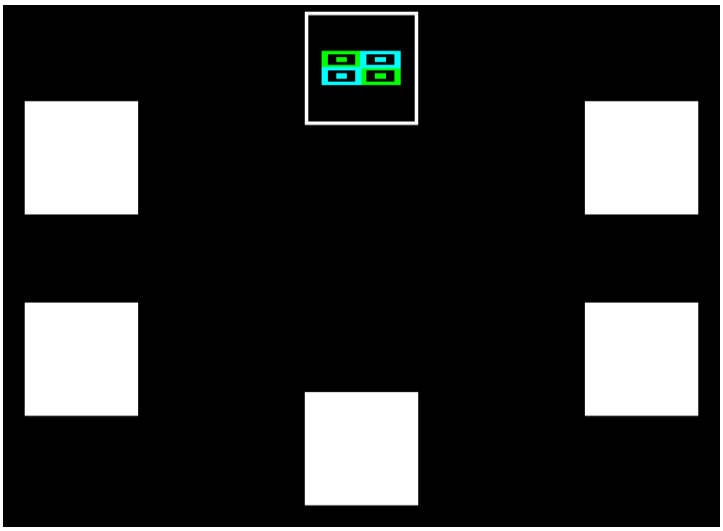


Figure 0.1. Example of a trial in the Paired Associate Learning (PAL) test. Participants were asked to remember the pattern showed in the upper box.

Spatial Working Memory (SWM)

This test is aimed to evaluate the ability to recall and manipulate spatial information held in working memory. It also assesses the skill of developing a strategy in order to solve the task (Sahakian et al., 1988). Participants were presented with a set of coloured boxes. The aim was to touch each box in order to find a blue token, which, once found, was put inside a column on the right side of the screen (Figure 4.2). The token then had to be found in any of the other boxes until the column was filled. Participants had to retrospectively remember not to touch anymore the boxes in which they already found the token. The score for this test was calculated as a Total number of errors (SWM_total error), intended as the total number of times in which a box where the blue token had already been found was touched. This test can be solved by using a heuristic strategy. Specifically, the best strategy to solve the task is to start a new search by touching always the same box (Owen, Downes, Sahakian, Polkey, & Robbins, 1990). Therefore, we also analysed a "strategy value" calculated as the

number of times in which the participant began a new search with a different box, in the six and eight box trials only. The minimum possible strategy score is one, whereas the maximum is 56. Higher strategy value score indicates a poor strategy (since it indicates that the participant started the new search from a different box than the previous trials) while a lower strategy value score indicates a good strategy. Independent sample t-tests were computed in order to compare patients and controls. Total number of errors score and strategy value were also correlated with overall WM accuracy.

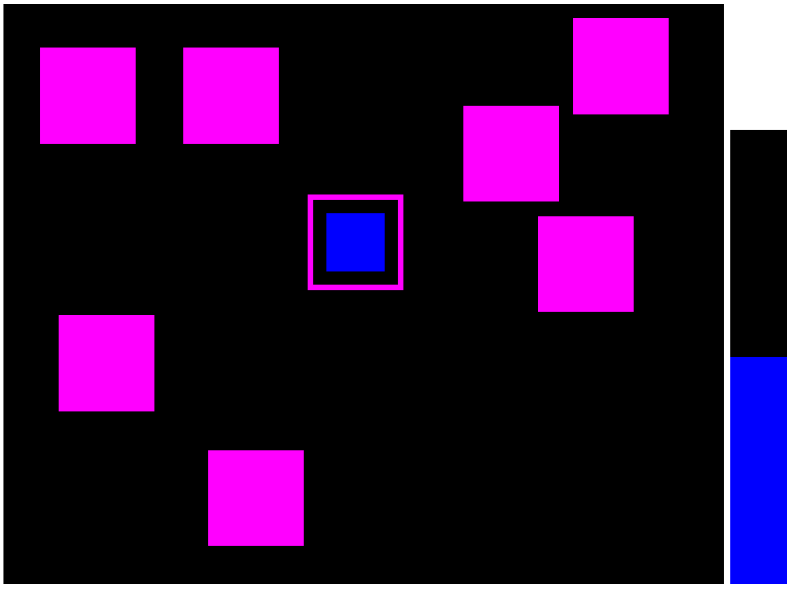


Figure 0.2. Example of a trial in the Spatial Working Memory (SWM) test. When the blue token was found, participants moved it in the black bar on the right-hand side of the screen. After, participants had to find the token in one of the other magenta squares without touching the central square, where the token was already found. The trial terminated once the black bar on the right-hand side of the screen was filled with all the blue tokens.

The Manchester Short Assessment of Quality of Life (MANSA)

The MANSA is a short and effective questionnaire that assesses the quality of life. It is widely used in mental health research as it provides a highly reliable measure. Moreover, it includes both objective and subjective evaluation of the quality of life (Priebe et al., 1999; Priebe et al., 2010, 2011).

The questionnaire is divided into three sections which address respectively demographic details (date of birth, gender, ethnic origin, and diagnosis); personal details that may change over time (education, current employment, income, living situation); objective and subjective aspects of everyday life, assessed with a set of 16

questions. Four objective questions are answered on a yes/no basis and deal with: the existence of friends and number of contact with friends per week, accusation or victimisation of a crime or physical violence. The remaining 12 items are subjective questions are aimed to assess: overall life satisfaction, work and financial situation, living situation, use of free time, quantity and quality of family and friends relationships, personal safety, sex life, physical and mental health (Priebe et al., 1999; Priebe et al., 2010, 2011). The answer to these items are assessed on a seven points Likert type rating scale representing increasing levels of life satisfaction where:

1 = Couldn't be worse; 2 = Displeased; 3 = Mostly dissatisfied; 4 = Mixed; 5 = Mostly satisfied; 6 = Pleased; 7 = Couldn't be better

Higher scores indicated higher evaluation of the quality of life. Rating scores from the twelve Likert scale items were correlated with the visual tasks and working memory accuracy. See Appendix 2 for the full questionnaire.

ERP Data acquisition, processing and analysis

During the WM task, a 64 electrode cap (actiCAP, Brain Products GmbH) was fitted on the participants' heads according to the international 10-20 system (Jasper, 1958), with the ground electrode at the middle anterior frontal electrode, the reference at the middle frontocentral electrode, and an additional vertical electro-oculogram electrode below the left eye. Pre-processing analysis is outlined in details in chapter 2. Time windows for ERPs analysis were chosen based on visual inspection of the Grand Averages of patients and controls overlaid. Therefore, for some components time windows were slightly adjusted compared to experiment 1.

Encoding

During encoding, peak amplitudes and latencies of C1 at electrode Oz (central occipital electrode) were defined in the interval between 65ms and 140ms, P1 at lateral visual electrodes (PO7, PO8, PO9, PO10) between 70 and 130ms, N1 at lateral visual electrodes (PO7, PO8, PO9, PO10) between 100 and 213ms, and P2 at electrodes O1, O2 and Oz (central occipital electrode) between 190ms and 277ms after stimulus onset. Mean averaged Slow Wave activity was analysed at frontal (F1, F2, Fz) and

lateral visual electrodes (PO7, PO8, PO9, PO10) in the time interval between 450 and 900ms after stimulus onset.

Retrieval

At retrieval, correct trials related to match and mismatch conditions were analysed. We analysed correct trials in which the probe orientation matched one of the orientations in the previous test set as "match" trials whereas correct trials in which the probe orientation did not match one of the orientations in the previous test were analysed as "mismatch" trials.

For both match and mismatch trials, peak amplitudes and latencies of P1 were extracted at central occipital electrodes (Oz, O1, O2) in the time interval between 90ms and 163ms, and N1 at lateral electrodes (PO7, PO8, PO9 and PO10) between 149ms and 264ms after probe onset.

Statistical analysis

Orientation Discrimination

2x2 repeated measure ANOVA with "surround" as two levels within-participants factor and "group" as two levels between-participants factor was used to detect any differences between the two groups. Further paired sample t-tests were also applied. For the orientation discrimination task, the mean orientation of the last five trials was calculated excluding the values that were above seven. An inspection of the data revealed that for four participants in the patients' sample the mean could not be calculated as all values were all above seven. Therefore, only for the analysis of the orientation discrimination task, t-test and correlations were performed with 15 patients and 20 controls.

Contrast Matching

2x2 repeated measure ANOVA with "surround" as two levels within-participants factor and "group" as two levels between-participants factor was used to detect any differences between the two groups. Further paired sample t-tests were also performed.

Working Memory

A 2x3x2 repeated measure ANOVA with "surround" as within-participants factor with two levels (parallel and orthogonal), "load" as within-participants factor with three levels (load 1, 2 and 3), and "group" as between-participants factor with two levels (patients and controls) was performed for WM accuracy, dPrime, hit rate, correct rejections rate and response times. WM accuracy, dPrime, hit rate, correct rejections rate and response times were cleaned as described in chapter 2. Only significant main effects and interactions were reported. If sphericity was not assumed, Greenhouse-Geisser correction was applied. If group effects were significant, further ANOVAs were performed separately for the two groups. If main effects or interactions were significant, further pairwise comparisons were performed with Bonferroni correction.

To perform bivariate correlations, WM accuracy was averaged within all conditions and within Load 1, 2 and 3 both for parallel and orthogonal surround, separately for each population. WM was also averaged within parallel and orthogonal surround respectively for Load 1, 2 and 3. Then, we performed bivariate correlations between WM averaged accuracy and CM and OD for parallel and orthogonal surrounds, separately for each cohort. In addition, a correlation between overall WM accuracy and overall OD performance (averaged between parallel and orthogonal surround) was also performed.

ERPs

At encoding a 3x2x3x2 (4x2x3x2 when 4 electrodes were loaded) (electrode, surround condition, WM load and group), whereas at retrieval a 2x3x2x3x2 (2x4x2x3x2 when 4 electrodes were loaded) (match/mismatch, electrode, surround condition, WM load and group) repeated-measures multivariate analysis of variance was used to test the effects within participants on all dependent measures.

Main effects and interactions were reported only if significant. If group effects were found, patients and controls were analysed separately. In the case of significant main effects or interactions, we also performed bivariate correlations between ERPs amplitude at encoding and WM accuracy, CM and OD performance. Moreover, ERPs amplitudes for match trials at retrieval were correlated with CM, OD, and Hit rate, whereas ERPs amplitudes for mismatch trials at retrieval were correlated with CM, OD, and correct rejections rate.

Comparison between controls and participants from Study 1

Since dissimilarities emerged between the results of controls and of participants from experiment 1, it was verified whether group differences occurred between these two samples. Both for the behavioural and for the ERPs data, controls and participants from experiment 1 were analysed in the same ANOVA. Specifically, the same ANOVAs described above was performed by adding group (experiment 1 sample and controls) as a between-participants factor. If group differences were found, it was explored whether these could be attributed to the factors used as inclusion criteria for controls recruitment, i.e. age, gender and years of education. Specifically, in the case of group effects, further ANCOVAs were performed by inserting age, gender and years of education as covariates.

For both behavioural and ERPs results, measures of effect size are reported in terms of partial eta squared ($p\eta^2$) (Cohen, 1988; Cohen, 1973). The magnitude of the effect size will be interpreted as small with $p\eta^2 = 0.01$ circa, medium with $p\eta^2 = 0.06$ circa and large with $p\eta^2 = 0.14$ circa (Cohen, 1988; Levine & Hullett, 2002; Norouzian & Plonsky, 2018).

Results

Behavioural results

Orientation Discrimination

A main effect of group was found ($F(1,33) = 13.6$, $p = 0.001$, $p\eta^2 = 0.29$). Patients showed a higher orientation threshold compared to controls. However, the thresholds needed to discriminate two orientations were not significantly different for the two surrounds conditions for each group.

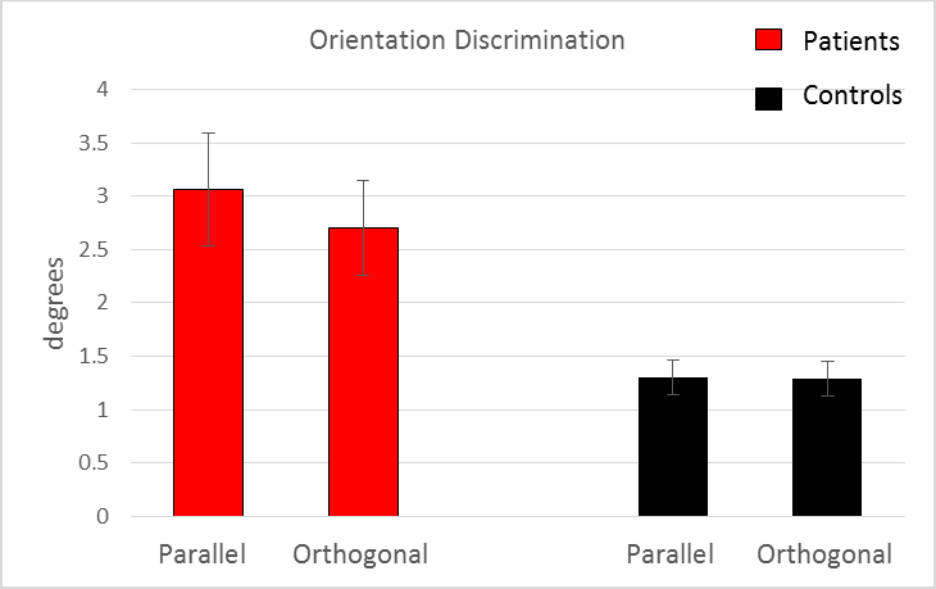


Figure 0.3. Orientation discrimination results for parallel and orthogonal surround for patients (red) and control participants (black). The x-axis indicates parallel and orthogonal surround conditions. Values on the y-axis represent orientation discrimination thresholds expressed in degrees. Error bars indicate standard errors.

Contrast Matching

An interaction contrast matching*group ($F(1,37) = 4$, $p = 0.056$, $p\eta^2 = 0.1$) was found. Further analysis performed separately for the two groups revealed that, in line with experiment 1, contrast matching for parallel surround was higher compared to the orthogonal surround for control participants ($t(19) = 3.5$, $p = 0.003$), but not for patients ($t(18) = -0.8$, $p = 0.42$). In addition, contrast matching for the parallel surround differed from the reference only for control participants ($t(19) = 5.5$, $p < 0.001$) but not for patients ($t(18) = 0.96$, $p = 0.35$). Finally, contrast matching for orthogonal surround did not differ from the reference both for controls ($t(19) = 1.7$, $p = 0.10$) and patients ($t(18) = 1.4$, $p = 0.17$).

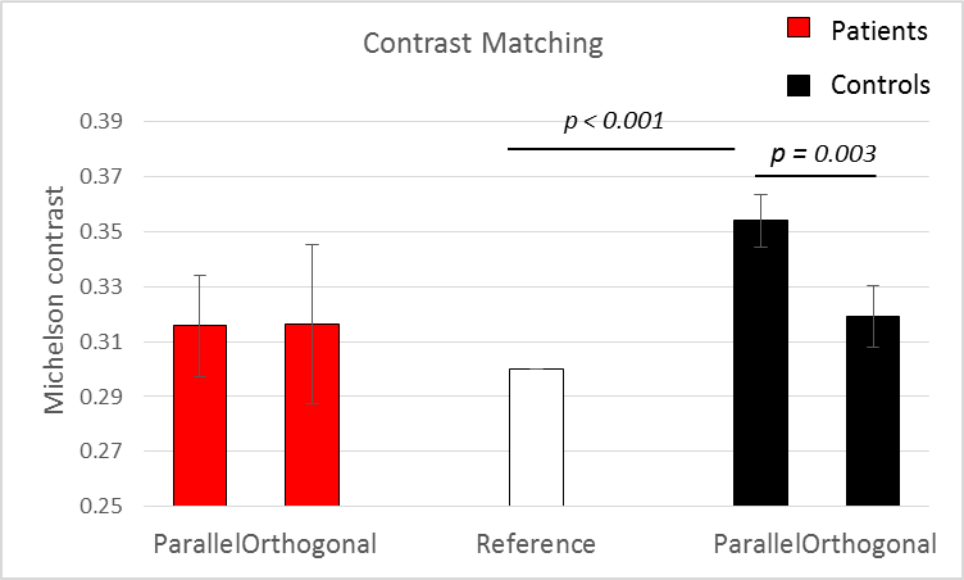


Figure 0.4. Contrast matching results for parallel and orthogonal surround conditions for patients (red) and control participants (black). The x-axis represents the parallel and orthogonal surround conditions. The white bar represents the reference contrast of the isolated patch which was constant throughout the task (30% Michelson contrast). Values on the y-axis represent contrast matching expressed in Michelson contrast. Horizontal black lines represent significant differences found between the parallel and orthogonal surround and between the parallel surround condition and the reference only in the control population. Error bars indicate standard errors.

Working Memory

	Load 1 Parallel	Load 1 Orthogonal	Load 2 Parallel	Load 2 Orthogonal	Load 3 Parallel	Load 3 Orthogonal
Accuracy Mean *(SD)* Patients	0.74 *(0.21)*	0.76 *(0.18)*	0.69 *(0.19)*	0.68 *(0.17)*	0.63 *(0.13)*	0.64 *(0.16)*
Controls	**0.93** * ***(0.07)***	**0.96** ***(0.06)***	0.87 *(0.11)*	0.86 *(0.09)*	**0.79** * ***(0.10)***	**0.75** ***(0.12)***
dPrime Mean *(SD)* Patients	1.74 *(1.61)*	1.81 *(1.50)*	1.31 *(1.38)*	1.18 *(1.30)*	0.80 *(0.90)*	0.89 *(0.99)*
Controls	3.27 *(0.80)*	3.50 *(0.71)*	2.51 *(0.95)*	2.41 *(0.83)*	**1.80** * ***(0.80)***	**1.55** ***(0.90)***
Hits Mean *(SD)* Patients	0.80 *(0.20)*	0.78 *(0.21)*	0.73 *(0.21)*	0.75 *(0.18)*	0.66 *(0.21)*	0.68 *(0.20)*
Controls	0.94 *(0.10)*	0.97 *(0.06)*	0.88 *(0.14)*	0.91 *(0.09)*	0.81 *(0.13)*	0.79 *(0.15)*
Correct Rej. Mean *(SD)* Patients	0.68 *(0.27)*	0.72 *(0.20)*	0.66 *(0.21)*	0.60 *(0.22)*	0.60 *(0.16)*	0.61 *(0.19)*
Controls	0.92 *(0.11)*	0.94 *(0.12)*	**0.86** * ***(0.12)***	**0.80** ***(0.14)***	**0.77** * ***(0.13)***	**0.71** ***(0.14)***
Response Times Mean (seconds) *(SD)* Patients	**0.82** * ***(0.33)***	**0.93** ***(0.37)***	**0.76** * ***(0.28)***	**0.68** ***(0.24)***	**0.58** * ***(0.18)***	**0.68** ***(0.25)***
Controls	**0.55** * ***(0.15)***	**0.47** ***(0.11)***	0.45 *(0.09)*	0.44 *(0.08)*	0.44 *(0.08)*	0.44 *(0.09)*
* $p < 0.05$						

Table 0.3. Working Memory behavioural results for each condition for patients and control participants. Mean and standard deviations (in brackets) are displayed for accuracy, dPrime, hits, correct rejections, and response times. For response times, means and standard deviations are expressed in seconds. Numbers in bold with asterisks represent conditions in which a significant difference (with $p < 0.05$) was found.

Mean and standard deviations for working memory behavioural results are reported in Table 4.3, both for patients and controls. Overall, patients' accuracy ($F(1,37) = 17.4$, $p < 0.001$, $p\eta^2 = 0.32$), dPrime ($F(1,37) = 15$, $p < 0.001$, $p\eta^2 = 0.29$), hit rate ($F(1,37) = 10.2$, $p = 0.003$, $p\eta^2 = 0.22$) and correct rejections rate ($F(1,37) = 15$, $p < 0.001$, $p\eta^2 =$

0.30) were significantly lower compared to controls. Moreover, patients' response times were slower compared to controls ($F(1,37) = 19$, $p < 0.001$, $p\eta^2 = 0.34$).

A main effect of load was found for accuracy ($F(1.6,59.3) = 70.6$, $p < 0.001$, $p\eta^2 = 0.66$), dPrime ($F(1.7, 61.5) = 86$, $p < 0.001$, $p\eta^2 = 0.70$), hits ($F(1.5, 55.6) = 33.5$, $p < 0.001$, $p\eta^2 = 0.48$), correct rejections ($F(1.6, 59.1) = 3.3$, $p = 0.05$, $p\eta^2 = 0.08$) and response times ($F(1.3,48.5) = 55.4$, $p < 0.001$, $p\eta^2 = 0.60$). Overall, both performance and response times decreased with the increment of memory load.

In addition, interactions load*group were found for accuracy ($F(1.6,59.3) = 3.6$, $p = 0.043$, $p\eta^2 = 0.088$), dPrime ($F(1.6, 61.5) = 7.3$, $p = 0.003$, $p\eta^2 = 0.17$) and correct rejections ($F(1.6, 59.1) = 3.3$, $p = 0.05$, $p\eta^2 = 0.08$). Since we found load*group interactions we also analysed the two groups separately. Interactions surround*load for accuracy ($F(2,38) = 7.2$, $p = 0.002$, $p\eta^2 = 0.27$), dPrime ($F(2,38) = 3.9$, $p = 0.03$, $p\eta^2 = 0.17$), and correct rejections ($F(2,38) = 5.3$, $p = 0.009$, $p\eta^2 = 0.22$) were found only for controls, but not for patients. Moreover, for correct rejections, a main effect of surround ($F(1,19) = 9.1$, $p = 0.007$, $p\eta^2 = 0.32$) was additionally found only in control population, but not for patients. Further paired sample t-tests performed for control participants revealed that, in line with experiment 1, for Load 1 accuracy was lower for parallel compared to the orthogonal surround ($t(19) = 2.6$, $p = 0.019$). However, for Load 3, accuracy ($t(19) = 2.8$, $p = 0.011$), correct rejections ($t(19) = 3$, $p = 0.008$) and, marginally, dPrime ($t(19) = 2$, $p = 0.06$) for parallel surround were higher compared to orthogonal surround condition. In addition, correct rejections rate was higher for parallel compared to orthogonal surround also for Load 2 condition ($t(19) = 3$, $p = 0.007$).

For response times an interaction surround*load*group was found ($F(2,74) = 36.4$, $p < 0.001$, $p\eta^2 = 0.50$). Further analysis performed separately for each group revealed that the interaction surround*load was found both for patients ($F(2,36) = 29$, $p < 0.001$, $p\eta^2 = 0.62$) and controls ($F(1.5,28) = 20$, $p < 0.001$, $p\eta^2 = 0.51$). Specifically, for patients, response times for parallel surround were faster than orthogonal surround both in Load 1 ($t(18) = 4.4$, $p < 0.001$) and in Load 3 ($t(18) = 4.6$, $p < 0.001$), but they were slower than orthogonal surround in Load 2 ($t(18) = 6$, $p < 0.001$). In contrast, for controls, response times for parallel surround were slower than orthogonal surround only in Load 1 condition ($t(19) = 5.4$, $p < 0.001$).

Comparison between controls and participants from Study 1

No group differences were found for accuracy, dPrime, hits and correct rejection rate. However, a group effect was found for the reaction times ($F(1,36) = 6.3$, $p = 0.02$, $p\eta^2 = 0.15$). Control participants performed slower than participants from experiment 1. After controlling for age, gender and years of education, the group effect became non-significant ($F(1,33) = 2.2$, $p = 0.15$, $p\eta^2 = 0.06$). However, none of the covariates was significant.

Correlations

Orientation Discrimination and Contrast Matching

No correlations were found between OD and CM both for patients and controls.

Orientation Discrimination and Working Memory

Only for patients population we found a negative correlations between OD and WM accuracy both for parallel ($r = -0.9$, $p < 0.001$) and orthogonal surround ($r = -0.82$, $p < 0.001$). Moreover, overall OD correlated with overall WM accuracy only for patients ($r = -0.9$, $p < 0.001$). Differently from experiment 1, no correlations were found between OD and WM accuracy for controls. For controls, partial correlations were also performed controlling for age, gender and years of education. However, these were also not significant.

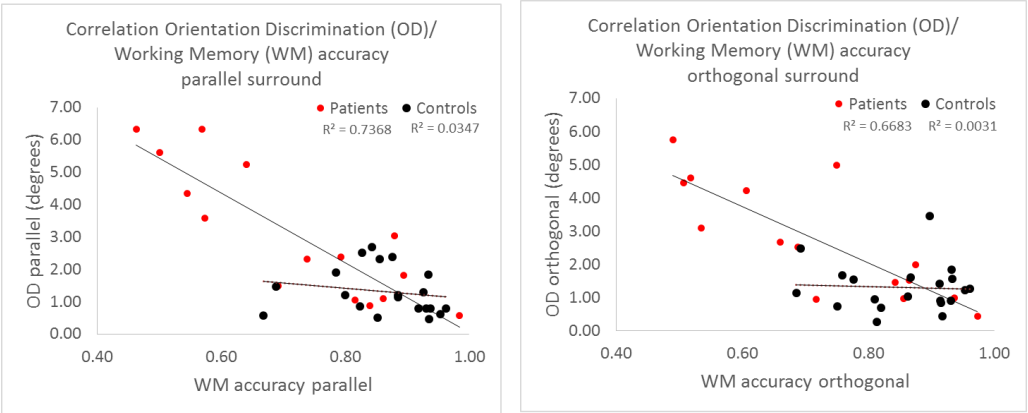


Figure 0.5. Correlations between WM accuracy (x-axis) and orientation discrimination (y-axis) for the parallel (left) and orthogonal surround (right). The correlations were significant only for patients (red) but not for controls (black). R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

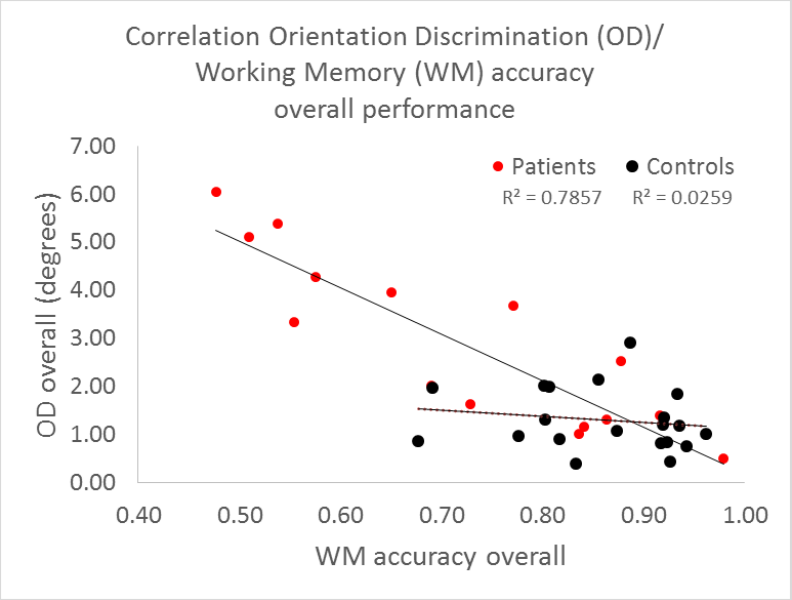


Figure 0.6. Correlation between WM accuracy (x-axis) and orientation discrimination (y-axis) for the overall performance. The correlation was significant only for patients (red) but not for controls (black). R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

Contrast Matching and Working Memory

Correlations between contrast matching and working memory accuracy were not significant both for patients and controls.

ERPs results

Encoding

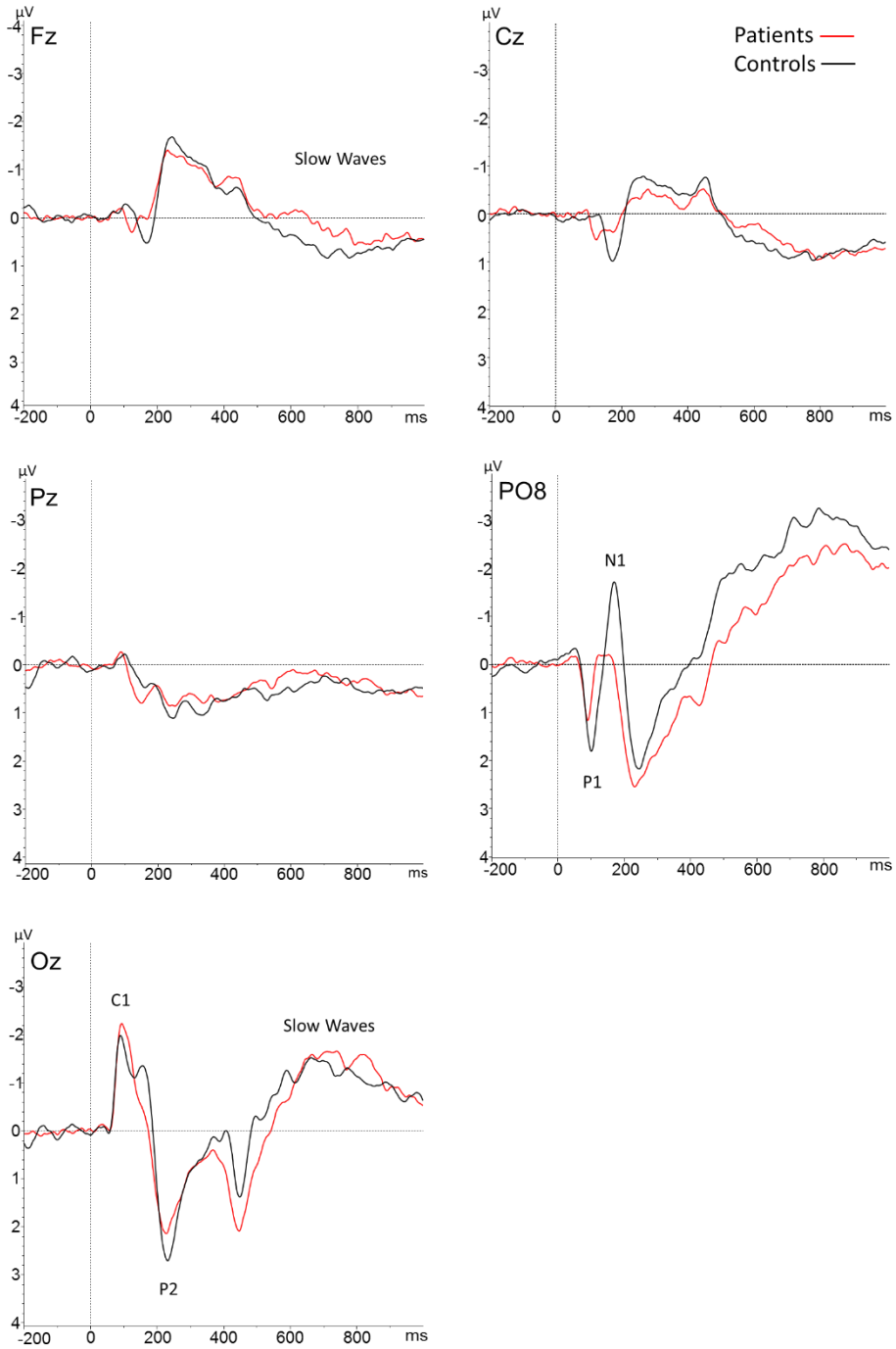


Figure 0.7. Grand Average ERPs of all working memory conditions averaged for patients (red) and controls (black) at electrodes Fz, Cz, Pz, PO8 and Oz at encoding. The x-axis represents time in milliseconds (ms) where 0 is stimulus onset. The y-axis represents voltage in microvolts (µV). The grating with the surround elicited P1 and N1 at lateral occipital electrodes (PO8) and C1 and P2 at central occipital electrodes (Oz). Slow wave activity was observed after stimulus offset (from 450ms onwards) throughout all the electrodes. The positive peak arising after 400ms at central occipital electrodes (Oz) has been interpreted as related to stimulus offset (300ms) and therefore it was not analysed.

C1

The stimuli elicited C1 with a negative polarity at the central occipital electrode (Oz) with a mean latency of 112 ms (SD = 28ms) for patients and of 114 ms (SD = 31ms) for controls. Significant effects were found only for C1 amplitudes, but not for latencies.

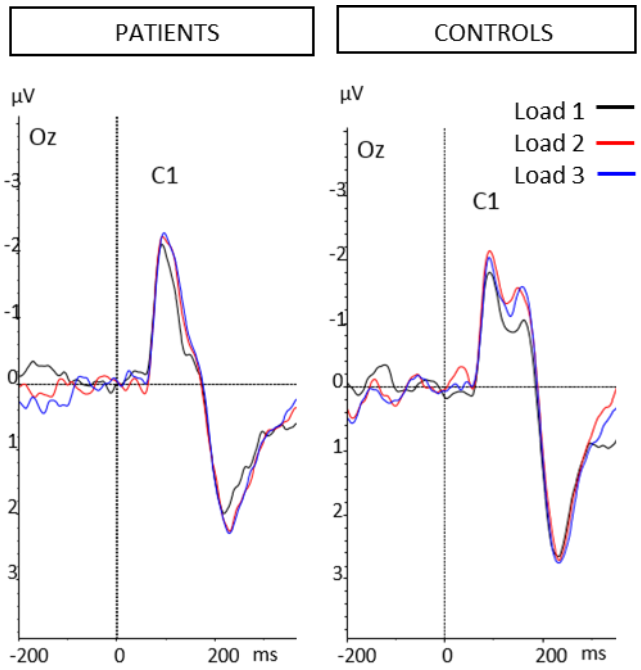


Figure 0.8. Grand average ERP waveform representing C1 component at electrode Oz in response to Load 1, 2 and 3 (averaged for parallel and orthogonal surround condition) for patients (left) and control participants (right). The x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in μV.

Amplitudes

There was no significant group effect at electrode Oz. However, in contrast with experiment 1, a main effect of load was found ($F(1.6,60.6) = 5.6$, $p = 0.009$, $p\eta^2 = 0.13$). C1 amplitudes increased with the increment in memory load. No correlations were found between C1 amplitudes and WM accuracy or visual tasks both for patients and controls. Patients results were not affected by medications ($F(1,17) = 0.14$, $p = 0.72$, $p\eta^2 = 0.008$).

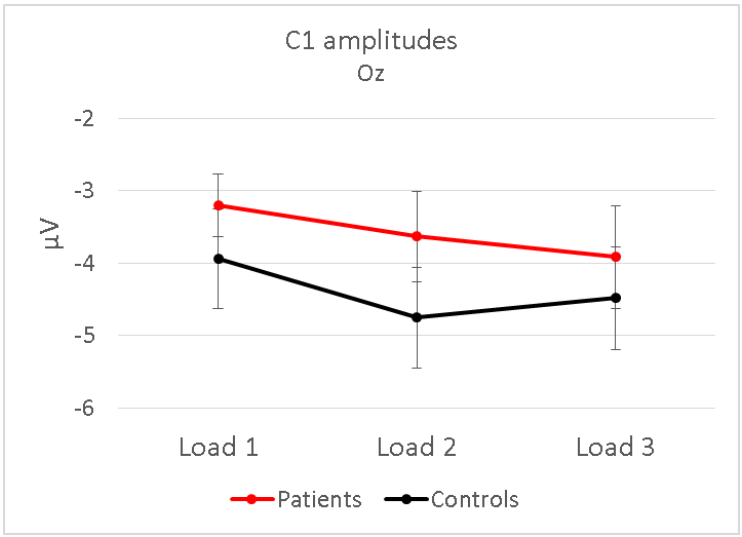


Figure 0.9. Main effect of load for C1 amplitudes at electrode Oz for patients (red) and control participants (black). The x-axis represents WM load conditions 1, 2 and 3. The y-axis indicates voltage in µV. Error bars represent standard errors.

P1

P1 was observed at lateral occipital electrodes (PO7, PO8, PO9, PO10) with a mean latency of 98ms (SD = 20) for patients and of 102ms (SD = 18) for controls.

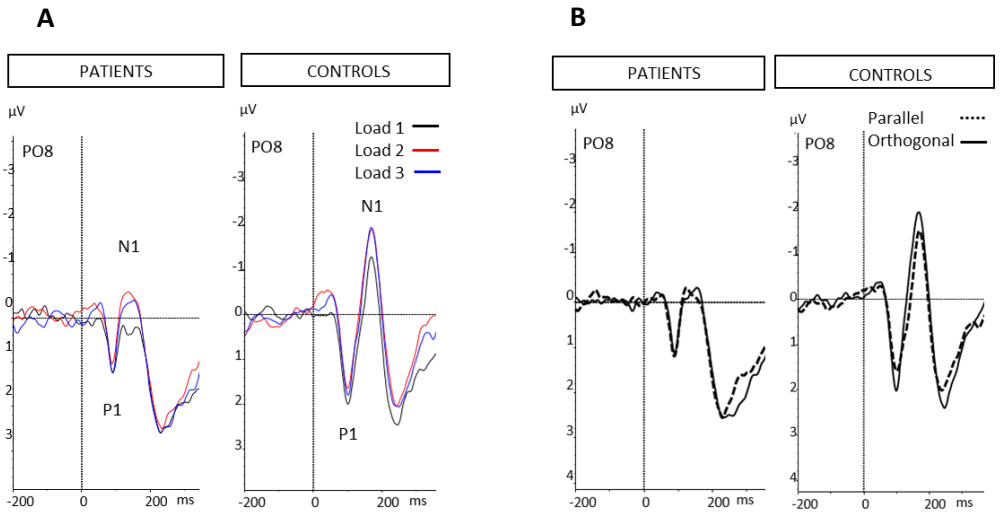


Figure 0.10. (A) Grand average ERP waveform representing P1 and N1 at electrode PO8 in response to Load 1, 2 and 3 (averaged for parallel and orthogonal surround condition) for patients (left) and control participants (right). (B) Grand average ERP waveform representing P1 and N1 at electrode PO8 in response to the parallel and orthogonal surround (averaged for Load 1, 2 and 3 conditions) for patients (left) and control participants (right). In both A and B, The x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in µV.

Latency

P1 latencies did not differ between the two groups. A main effect of load was found ($F(2,74) = 3.6$, $p = 0.03$, $p\eta^2 = 0.09$). Specifically, latency for Load 1 was larger than latency for Load 2. Results for patients were not influenced by medication intake ($F(1,17) = 0.5$, $p = 0.5$, $p\eta^2 = 0.03$).

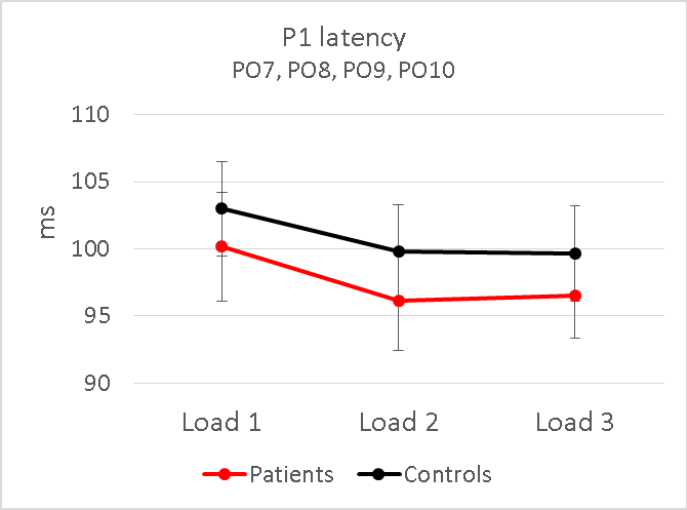


Figure 0.11. Main effect of load for P1 latency averaged for electrodes PO7, PO8, PO9, PO10 for patients (red) and control participants (black). The x-axis represents WM load conditions 1, 2 and 3. The y-axis indicates time in ms. Error bars represent standard errors.

Amplitudes

P1 amplitudes did not differ between the two groups. Contrary to experiment 1, a trend to a main effect of surround ($F(1,37) = 3.7$, $p = 0.06$, $p\eta^2 = 0.09$) was found. Peaks for parallel surround were lower compared to the orthogonal. A main effect of load ($F(2,74) = 6.3$, $p = 0.003$, $p\eta^2 = 0.15$) was also found. P1 amplitudes decreased with from Load 1 to higher loads. P1 amplitudes were not affected by medications ($F(1,17) = 0.23$, $p = 0.6$, $p\eta^2 = 0.013$).

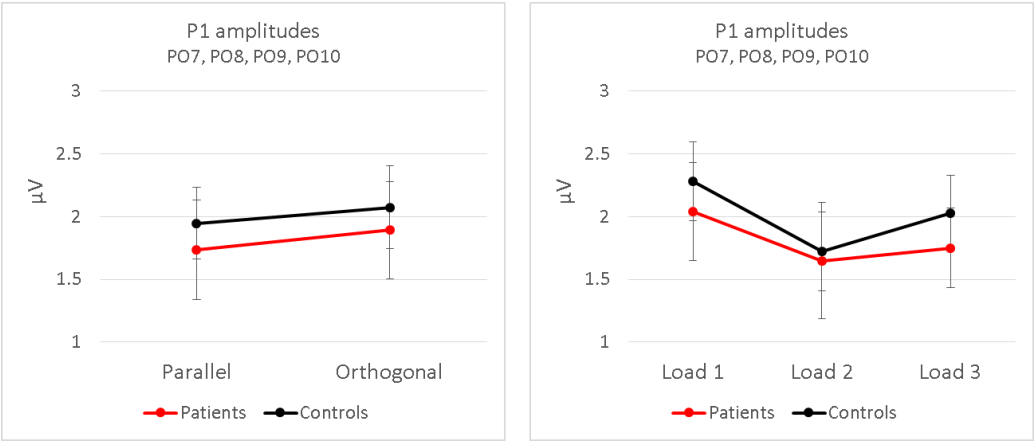


Figure 0.12. Main effect of surround (left) and main effect of load (right) for P1 amplitudes averaged for electrodes PO7, PO8, PO9, PO10 for patients (red) and control participants (black). The x-axis represents parallel and orthogonal surround conditions (left) and WM load conditions 1, 2 and 3 (right). The y-axis indicates voltage in µV (left and right). Error bars represent standard errors.

N1

N1 was elicited with a negative polarity at lateral visual electrodes (PO7, PO8, PO9 and PO10) with a mean latency of 146 ms (SD = 31 ms) for patients and 158 ms (SD = 27 ms) for controls.

Latency

N1 latency was shorter in the patients cohort compared to controls ($F(1, 37) = 4.7$, $p = 0.036$, $p\eta^2 = 0.11$). Moreover, a main effect of load was found ($F(2,74) = 5.2$, $p = 0.008$, $p\eta^2 = 0.12$). Latencies increased with the increment of load. For patients, results were not influenced by medications ($F(1,17) = 0.001$, $p = 0.97$, $p\eta^2 = 0$).

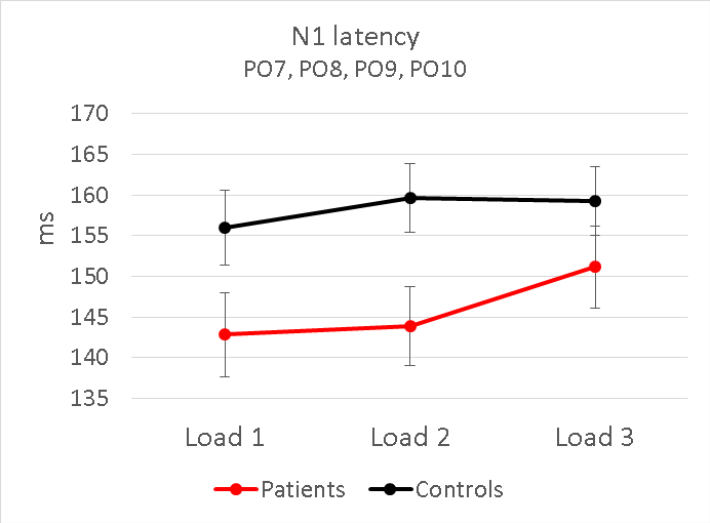


Figure 0.13. Main effect of load for N1 latency averaged for electrodes PO7, PO8, PO9, PO10 for patients (red) and control participants (black). The x-axis represents WM load conditions 1, 2 and 3. The y-axis indicates time in ms. Error bars represent standard errors.

Amplitudes

N1 amplitudes did not differ between groups ($F(1, 37) = 0.01$, $p = 0.92$, $p\eta^2 = 0.00$). A main effect of surround ($F(1, 37) = 5.2$, $p = 0.028$, $p\eta^2 = 0.12$) was found. Amplitudes were lower for the parallel compared to the orthogonal surround. A main effect of load ($F(2,74) = 9.1$, $p < 0.001$, $p\eta^2 = 0.20$) was also found. N1 amplitudes increased with the increment of memory load. Patients' results were not influenced by medication intake ($F(1,17) = 0.35$, $p = 0.56$, $p\eta^2 = 0.02$).

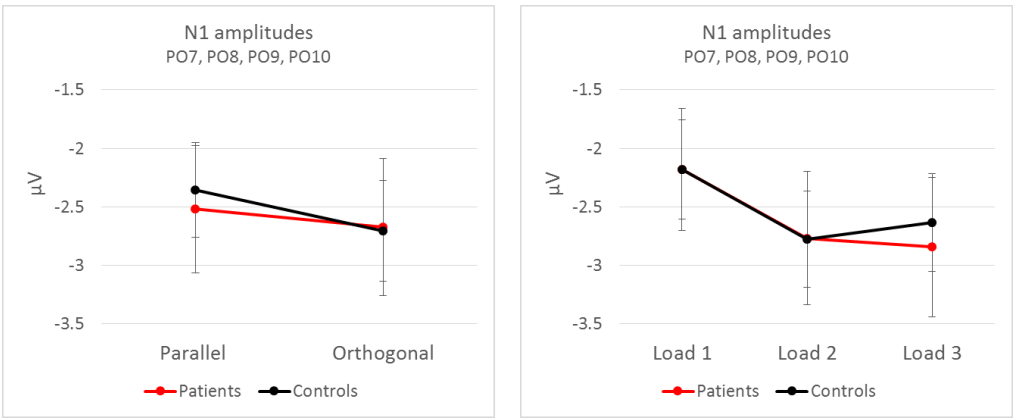


Figure 0.14. Main effect of surround (left) and main effect of load (right) for N1 amplitudes averaged for electrodes PO7, PO8, PO9, PO10 for patients (red) and control participants (black). The x-axis represents parallel and orthogonal surround conditions (left) and WM load conditions 1, 2 and 3 (right). The y-axis indicates voltage in µV (left and right). Error bars represent standard errors.

P2

P2 was elicited with a positive polarity at central visual electrodes (Oz, O1 and O2) with a mean latency of 233 ms (SD = 25 ms) for patients and 232 ms (SD = 20 ms) for controls.

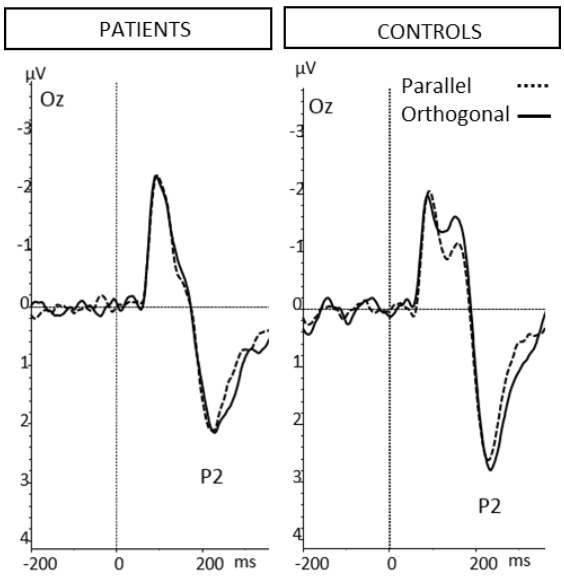


Figure 0.15. Grand average ERP waveform representing P2 at electrode Oz in response to the parallel and orthogonal surround (averaged for Load 1, 2 and 3 conditions) for patients (left) and control participants (right). The x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in μV.

Latency

There was no significant group effect. However, a main effect of surround was found ($F(1,37) = 8.8$, $p = 0.005$, $p\eta^2 = 0.19$). P2 latencies for parallel surround were shorter compared to orthogonal surround. A medication effect was also found for patients ($F(1,17) = 5.3$, $p = 0.03$, $p\eta^2 = 0.24$). After controlling for medications effects, no surround effect was found for patients.

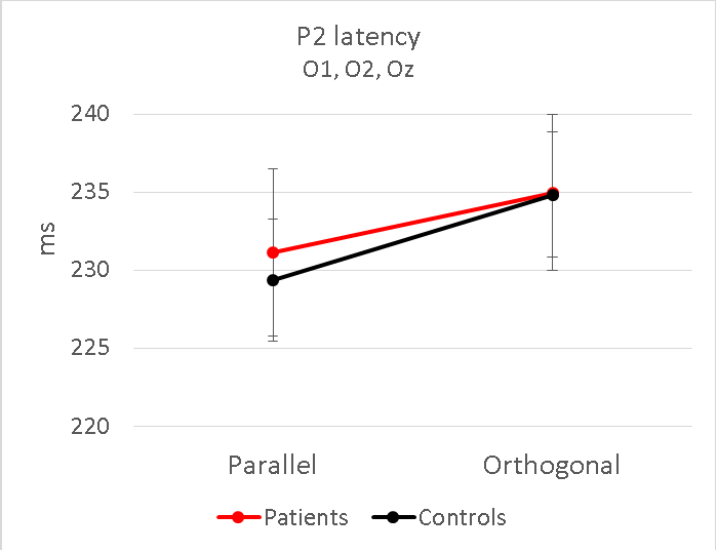


Figure 0.16. Main effect of surround for P2 latency averaged for electrodes O1, O2 and Oz for patients (red) and control participants (black). The x-axis represents the parallel and orthogonal surround conditions. The y-axis indicates time in ms. Error bars represent standard errors.

Amplitudes

P2 amplitudes did not differ between the two groups. However, an interaction electrode*load*group ($F(2.6,97.3) = 2.7$, $p = 0.055$, $p\eta^2 = 0.07$) was found, along with a main effect of electrode ($F(1.4,51.4) = 7.7$, $p = 0.004$, $p\eta^2 = 0.17$). Analysis performed separately for each group revealed only a main effect of electrode ($F(1.4,25) = 6.2$, $p = 0.013$, $p\eta^2 = 0.26$) for patients. For controls, a marginal interaction surround*load ($F(1.5,28) = 3.4$, $p = 0.06$, $p\eta^2 = 0.15$) was found. Follow up analysis performed at each load only for control participants revealed that P2 amplitudes for parallel surround were lower compared to orthogonal surround in Load 2 condition (main effect of surround: ($F(1,19) = 4.8$, $p = 0.04$, $p\eta^2 = 0.20$)).

Patients results were not influenced by medication intake ($F(1,17) = 0.13$, $p = 0.73$, $p\eta^2 = 0.007$).

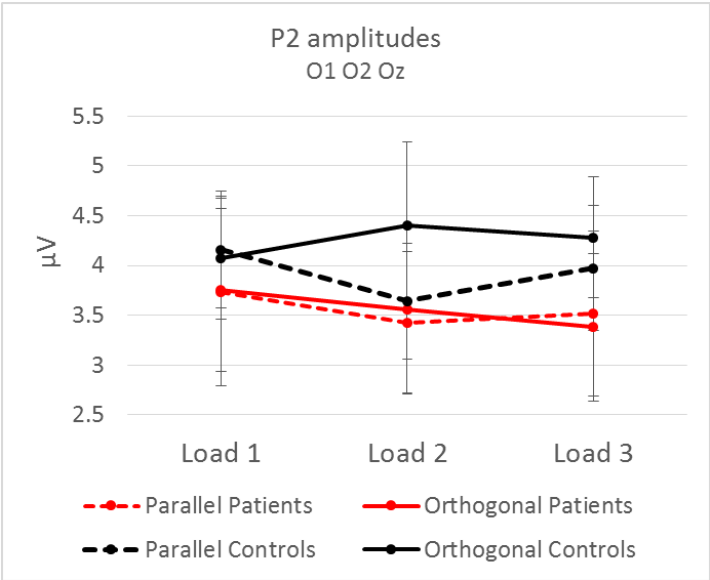


*Figure 0.17. Interaction surround*load for P2 amplitudes averaged for electrodes O1, O2 and Oz for patients (red) and control participants (black). The x-axis represents WM load conditions 1, 2 and 3. The y-axis indicates voltage in µV. Error bars represent standard errors.*

Since significant results were found only for controls, but not for patients, correlations with behavioural results were performed only for controls population. In line with experiment 1, a positive correlation was found between CM and P2 amplitudes in the parallel surround condition (r = 0.60, p = 0.006). In contrast with experiment 1, we also found a positive correlation between CM and P2 amplitudes for the orthogonal surround condition (r = 0.47, p = 0.04). No correlations were found with WM accuracy.

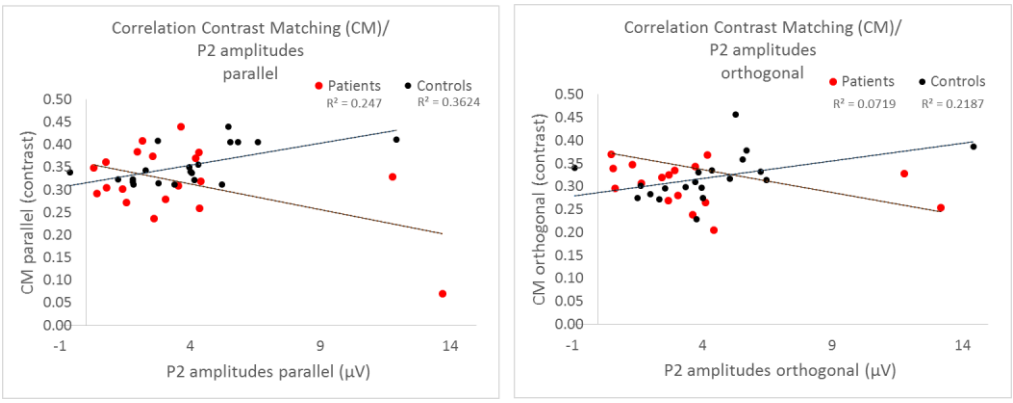


Figure 0.18. Correlations between P2 amplitudes (x-axis) and contrast matching (y-axis) for the parallel (left) and orthogonal surround (right) for patients and control participants. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

Slow Waves

Slow wave activity was observed in the time window between 450 and 900 ms after stimulus onset and analysed at frontal and visual electrodes.

Frontal electrodes

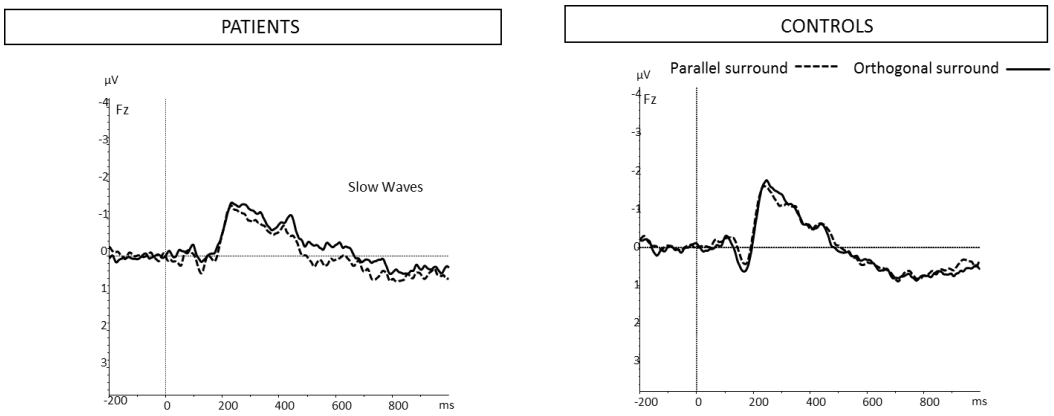


Figure 0.19. Grand average ERP waveform representing Slow Wave activity at electrode Fz in response to the parallel and orthogonal surround (averaged for Load 1, 2 and 3 conditions) for patients (left) and control participants (right). The x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in μV.

A main effect of surround ($F(1,37) = 5.1$, $p = 0.03$, $p\eta^2 = 0.12$) was found. SW activity for parallel surround was larger compared to orthogonal surround. Even though there was no difference between the two groups, an interaction surround*load*group ($F(1.7,61.1) = 6.4$, $p = 0.005$, $p\eta^2 = 0.15$) was found. Further analysis performed separately for each group revealed a trend to a main effect of surround ($F(1,18) = 4.1$, $p = 0.06$, $p\eta^2 = 0.19$) and an interaction surround*load ($F(1.5,27) = 4.8$, $p = 0.024$, $p\eta^2 = 0.21$) for patients. Analysis performed separately at each load for patients, revealed that SW activity was higher for parallel compared to orthogonal surround in Load 1 condition (main effect of surround: $F(1,18) = 9$, $p = 0.008$, $p\eta^2 = 0.34$). Moreover, analysis performed for each surround revealed a main effect of load only for parallel surround ($F(2,36) = 3.8$, $p = 0.03$, $p\eta^2 = 0.18$) but not for the orthogonal surround. For controls, only a main effect of load was found ($F(2,38) = 4.5$, $p = 0.02$, $p\eta^2 = 0.19$). Activity was larger for Load 2 compared to Load 3 (MD = 0.51, SE = 0.17, $p = 0.023$). No medications effect was found ($F(1,17) = 0.6$, $p = 0.45$, $p\eta^2 = 0.04$).

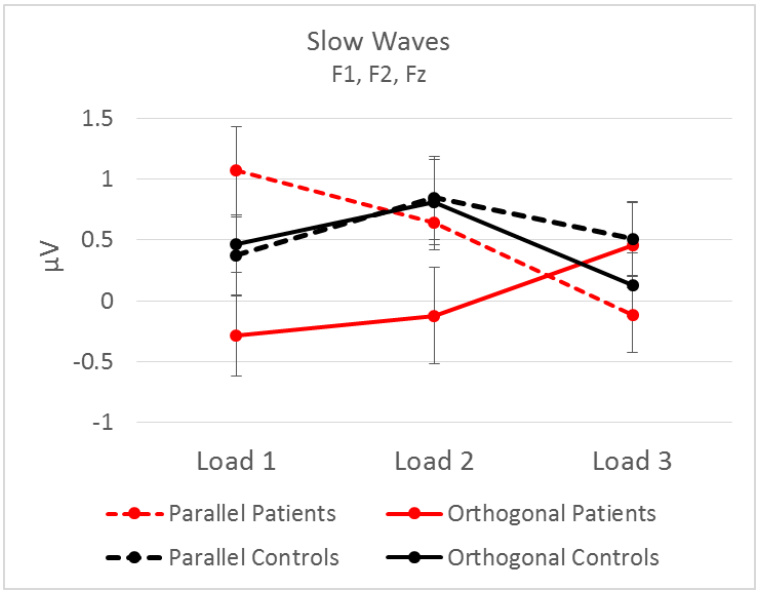


*Figure 0.20. Interaction surround*load for Slow Wave activity averaged for electrodes F1, F2 and Fz for patients (red) and control participants (black). The x-axis represents WM load 1, 2 and 3. The y-axis indicates voltage in µV. Error bars represent standard errors.*

Visual electrodes

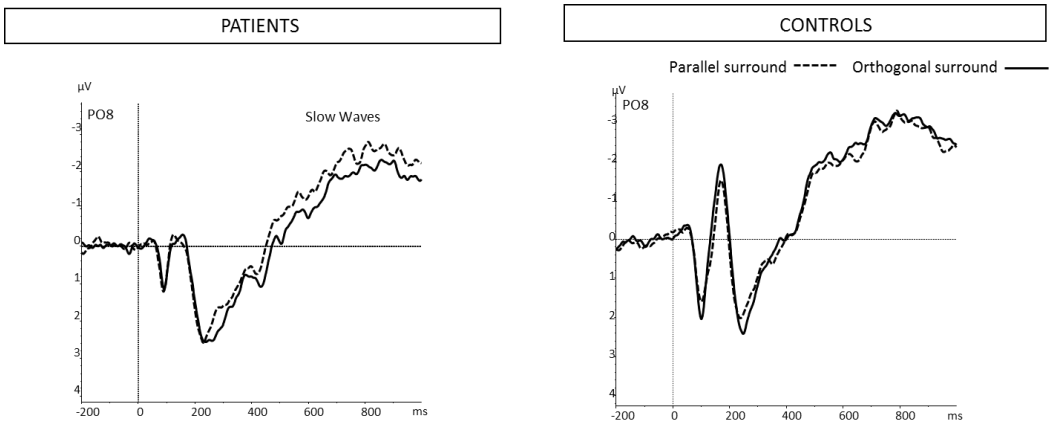


Figure 0.21. Grand average ERP waveform representing Slow Wave activity at electrode PO8 in response to the parallel and orthogonal surround (averaged for Load 1, 2 and 3 conditions) for patients (left) and control participants (right). The x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in µV.

SW activity at visual electrodes did not differ between groups ($F(1,37) = 1.3$, $p = 0.26$, $p\eta^2 = 0.034$). However, an interaction surround*load ($F(1.4,52.4) = 3.7$, $p = 0.045$, $p\eta^2 = 0.09$), an interaction surround*load*group ($F(1.4,52.4) = 3.8$, $p = 0.043$, $p\eta^2 = 0.09$) and a main effect of electrode ($F(2,73.5) = 5.7$, $p = 0.005$, $p\eta^2 = 0.13$) were found. Further analysis performed separately for the two groups revealed an interaction surround*load ($F(1.3,24) = 4.2$, $p = 0.04$, $p\eta^2 = 0.19$) for patients. Specifically, SW

activity was higher for parallel compared to orthogonal surround in Load 1 condition (main effect of surround: ($F(1,18) = 6.3$, $p = 0.02$, $p\eta^2 = 0.26$)).

For control participants a main effect of load ($F(2,38) = 4.8$, $p = 0.013$, $p\eta^2 = 0.20$) and a main effect of electrode ($F(2,37) = 3.5$, $p = 0.04$, $p\eta^2 = 0.16$) were found. Slow Waves activity for Load 2 was higher compared to Load 3 (MD = -0.55, SE = 0.17, $p = 0.011$). These effects were not influenced by medications ($F(1,17) = 0.92$, $p = 0.35$, $p\eta^2 = 0.05$).

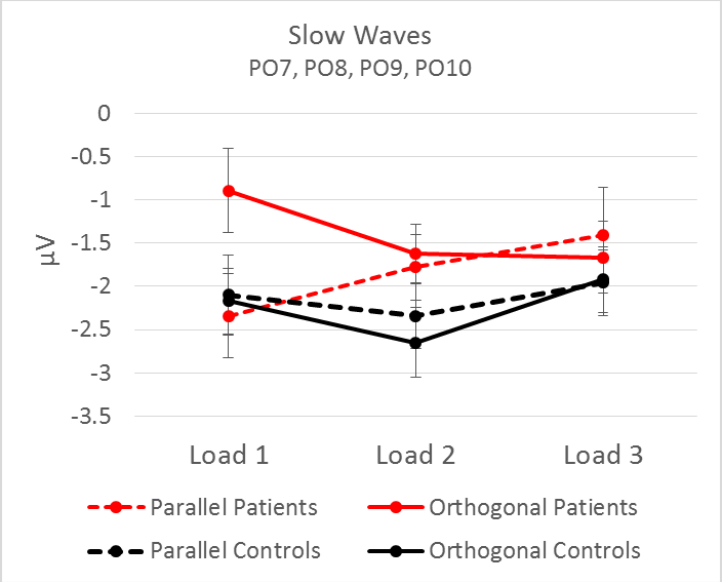


*Figure 0.22. Interaction surround*load for Slow Wave activity averaged for electrodes PO7, PO8, PO9 and PO10 for patients (red) and control participants (black). The x-axis represents WM load 1, 2 and 3. The y-axis indicates voltage in µV. Error bars represent standard errors.*

Retrieval

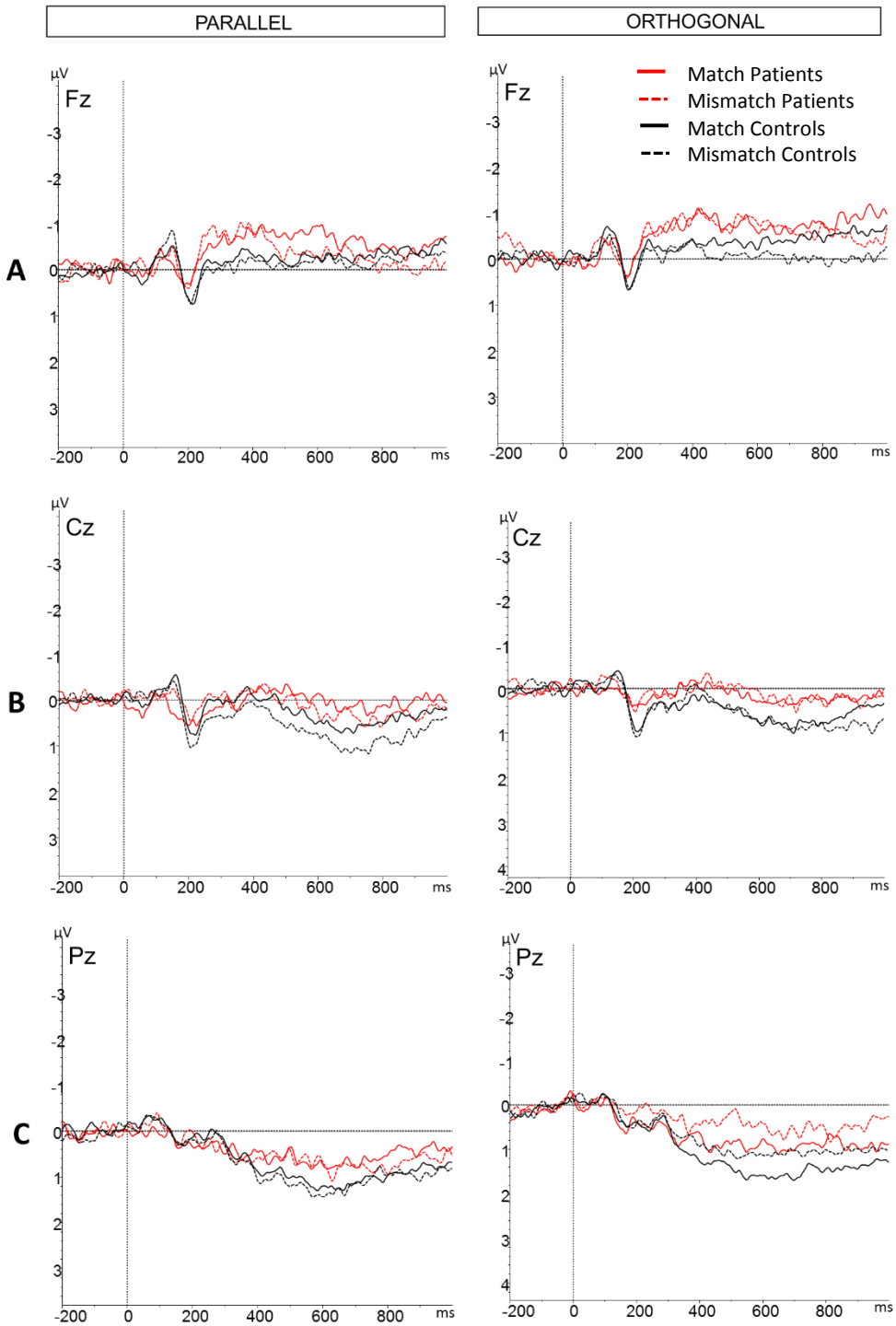


Figure 0.23. Grand Average ERPs of match (continuous line) and mismatch trials (dotted line) in response to the parallel (left) and orthogonal (right) gratings during retrieval for patients (red) and control participants (black). The x-axis represents time in milliseconds (ms) where 0 is stimulus onset. The y-axis represents voltage in microvolts (μV). Slow wave activity was observed after stimulus offset (from 450ms onwards) at frontal (A), central (B) and parietal (C) electrodes.

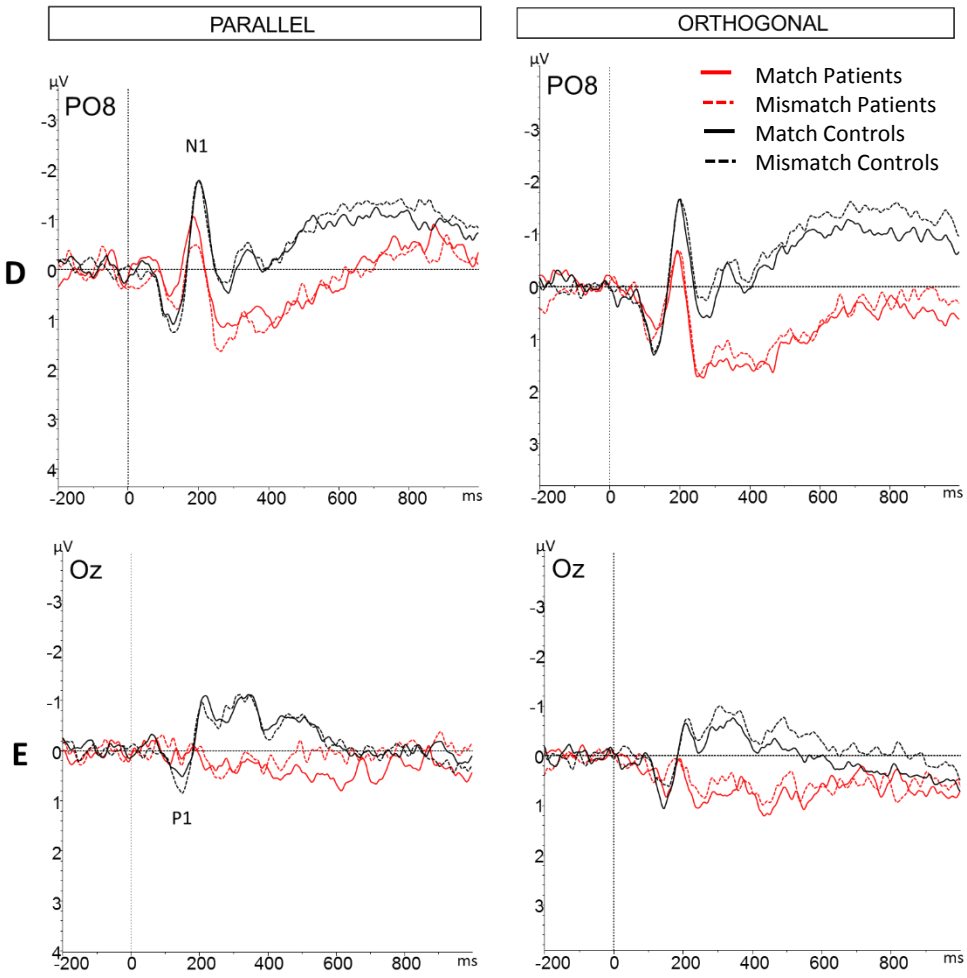


Figure 0.24. Grand Average ERPs of match (continuous line) and mismatch trials (dotted line) in response to the parallel (left) and orthogonal (right) gratings during retrieval for patients (red) and control participants (black). The x-axis represents time in milliseconds (ms) where 0 is stimulus onset. The y-axis represents voltage in microvolts (µV). At lateral occipital electrodes, P1 and N1 were observed (D). Similarly to experiment 1, in contrast with encoding, at central occipital electrodes, P1 was observed instead of C1 and P2 (E).

P1

P1 was observed at occipital electrodes (O1, O2, Oz) with a mean latency of 130ms (SD = 25) and 134ms (SD = 21) at match trials and with a mean latency of 128ms (SD = 23) and 134ms (SD = 22) at mismatch trials for patients and controls respectively.

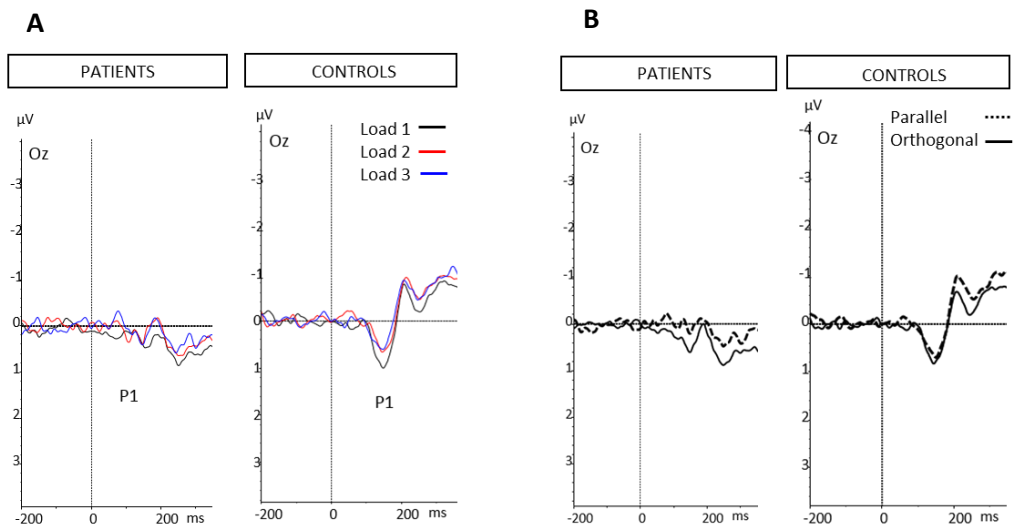


Figure 0.25. (A) Grand average ERP waveform representing P1 at electrode Oz in response to Load 1, 2 and 3 (averaged for parallel and orthogonal surround condition) for patients (left) and control participants (right). (B) Grand average ERP waveform representing P1 at electrode Oz in response to the parallel and orthogonal surround (averaged for Load 1, 2 and 3 conditions) for patients (left) and control participants (right). In both A and B, the x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in μV.

Latency

No group effect was found with P1 latencies. An interaction surround*load ($F(2,74) = 3$, $p = 0.05$, $p\eta^2 = 0.08$), a trend to an interaction match/mismatch*surround*group ($F(1,37) = 3.8$, $p = 0.06$, $p\eta^2 = 0.09$) and an interaction electrode*surround*load*group ($F(4,148) = 2.9$, $p = 0.03$, $p\eta^2 = 0.07$) were found. Analysis performed separately for the two groups revealed an interaction match/mismatch*surround for patients ($F(1,18) = 5$, $p = 0.04$, $p\eta^2 = 0.21$). Follow up analysis revealed that latencies were shorter for mismatch compared to match trials only for the orthogonal ($F(1,18) = 4.7$, $p = 0.04$, $p\eta^2 = 0.21$) but not for parallel surround. No further significant results were found for controls. Results for patients were not influenced by medication intake ($F(1,17) = 0$, $p = 0.99$, $p\eta^2 = 0$).

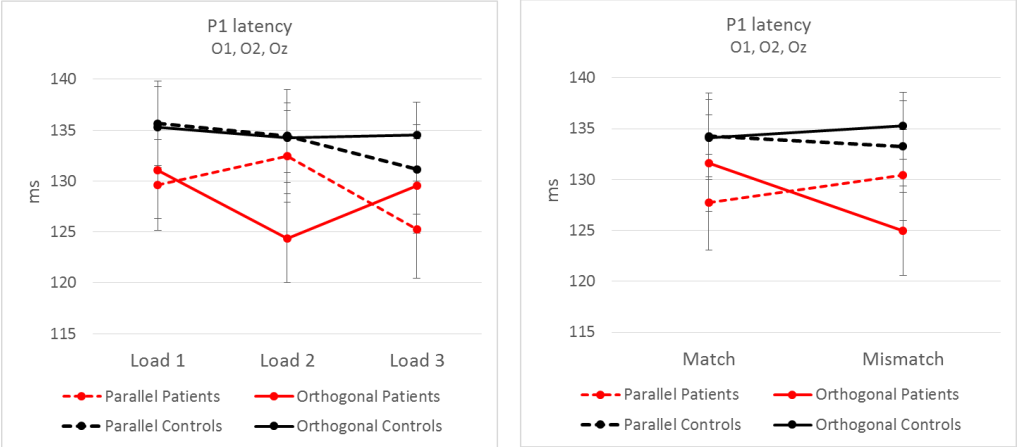


*Figure 0.26. Interaction surround*load (left) and interaction match/mismatch*surround (right) for P1 latency averaged for electrodes O1, O2 and Oz for patients (red) and control participants (black). The x-axis represents WM load 1, 2 and 3 conditions (left) and match and mismatch trials (right). The y-axis indicates time in ms. Error bars represent standard errors.*

Amplitudes

Overall, P1 amplitudes did not differ between the two groups. An interaction surround*group ($F(1,37) = 6.7$, $p = 0.014$, $p\eta^2 = 0.15$), an interaction surround*load*group ($F(2,74) = 6.1$, $p = 0.003$, $p\eta^2 = 0.14$) and a main effect of electrode ($F(1.7,61.7) = 12$, $p < 0.001$, $p\eta^2 = 0.24$) were found.

Further analysis performed separately for the two groups revealed a main effect of surround ($F(1,18) = 4.7$, $p = 0.04$, $p\eta^2 = 0.21$) and an interaction surround*load ($F(2,34) = 3.4$, $p = 0.04$, $p\eta^2 = 0.17$) for patients. Analysis performed at each load revealed that amplitudes for parallel surround were lower compared to orthogonal only in Load 1 condition (main effect of surround ($F(1,18) = 7$, $p = 0.02$, $p\eta^2 = 0.28$)). For controls, only an interaction electrode*surround ($F(2,38) = 4.8$, $p = 0.014$, $p\eta^2 = 0.20$) was found. Follow up analysis performed at each surround revealed a marginal main effect of load only for parallel ($F(2,38) = 3$, $p = 0.06$, $p\eta^2 = 0.14$) but not for the orthogonal surround. Medication did not seem to affect P1 amplitudes in patients ($F(1,17) = 2.7$, $p = 0.12$, $p\eta^2 = 0.14$).

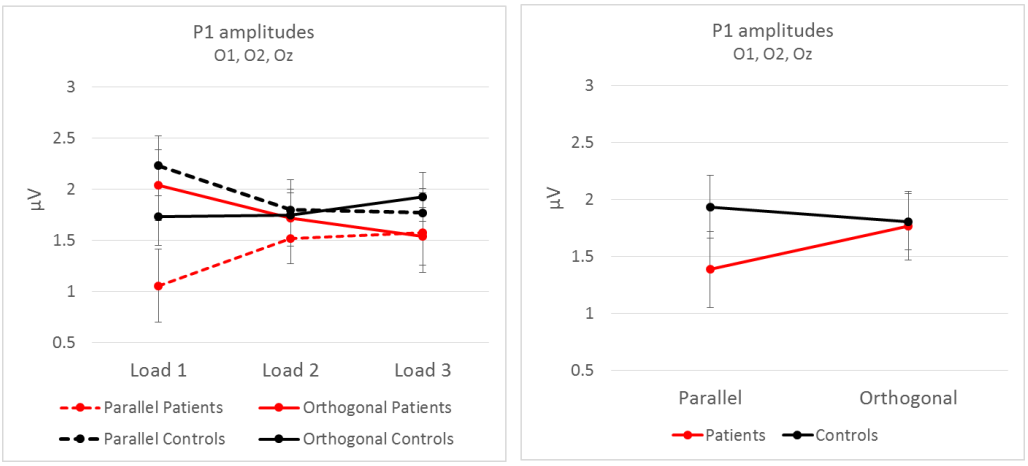


*Figure 0.27. Interaction surround*load (left) and main effect of surround (right) for P1 amplitudes averaged for electrodes O1, O2 and Oz for patients (red) and control participants (black). The x-axis represents WM load 1, 2 and 3 conditions (left) and parallel and orthogonal surrounds (right). The y-axis indicates voltage in μV. Error bars represent standard errors.*

N1

N1 was observed at lateral posterior electrodes (PO7, PO8, PO9, PO10) with a mean latency of 199ms (SD = 31) and 207ms (SD = 26) at match trials and with a mean latency of 200ms (SD = 30) and 208ms (SD = 26) at mismatch trials for patients and controls respectively. Significant effects were found only for N1 amplitudes, but not for latencies.

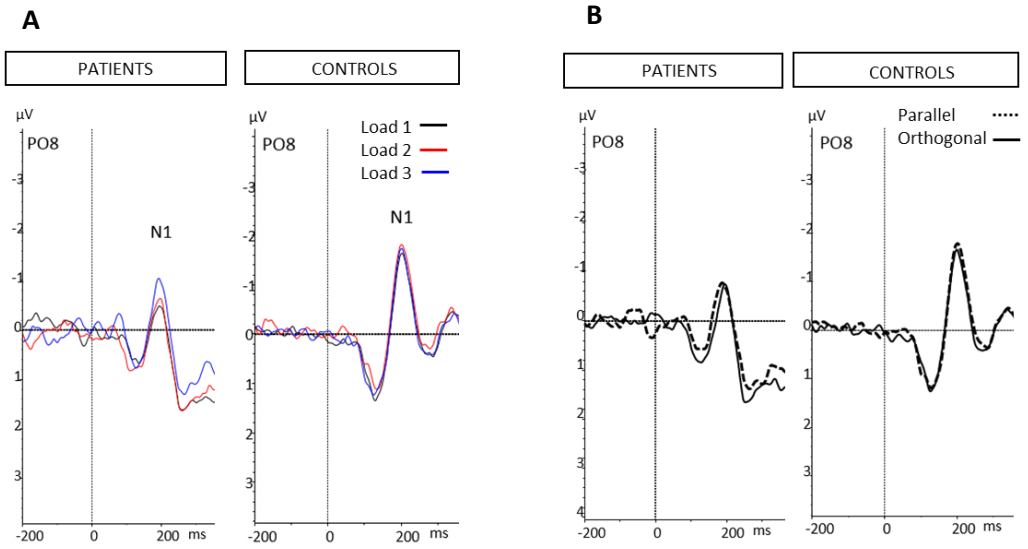


Figure 0.28. (A) Grand average ERP waveform representing N1 at electrode PO8 in response to Load 1, 2 and 3 (averaged for parallel and orthogonal surround condition) for patients (left) and control participants (right). (B) Grand average ERP waveform representing N1 at electrode PO8 in response to the parallel and orthogonal surround (averaged for Load 1, 2 and 3 conditions) for patients (left) and control participants (right). In both A and B, the x-axis represents time in ms where 0 is stimulus onset. The y-axis represents voltage in μV.

Amplitudes

N1 amplitudes did not significantly differ between the two groups. A main effect of surround ($F(1,37) = 4.4$, $p = 0.04$, $p\eta^2 = 0.11$) was found. N1 amplitudes were higher for parallel surround compared to orthogonal surround. As in experiment 1, a main effect of load ($F(1.6,57.8) = 7$, $p = 0.004$, $p\eta^2 = 0.16$) was found. N1 amplitudes increased with the increment of memory load. Since a trend to an interaction match/mismatch*electrode*load ($F(3.4,124) = 2.4$, $p = 0.06$, $p\eta^2 = 0.06$) was also found, match and mismatch trials were analysed separately. For match trials, a main effect of surround ($F(1,37) = 4.9$, $p = 0.03$, $p\eta^2 = 0.12$), a main effect of load ($F(1.6,60.1) = 6.4$, $p = 0.005$, $p\eta^2 = 0.15$) were found. N1 amplitudes were higher for parallel compared to orthogonal surround and they increased with the increment of memory load. An interaction electrode*surround*load ($F(4.4,164.3) = 2.8$, $p = 0.02$, $p\eta^2 = 0.07$) was also found. Follow-up analysis performed at each surround revealed that N1 amplitudes increased with load for orthogonal (main effect of load ($F(2,74) = 6.3$, $p = 0.003$, $p\eta^2 = 0.15$)) but not for parallel surround. For mismatch trials, there was only a trend to a main effect of load ($F(2,74) = 3$, $p = 0.06$, $p\eta^2 = 0.07$).

Patients results were not affected my medications ($F(1,17) = 0.62$, $p = 0.44$, $p\eta^2 = 0.04$).

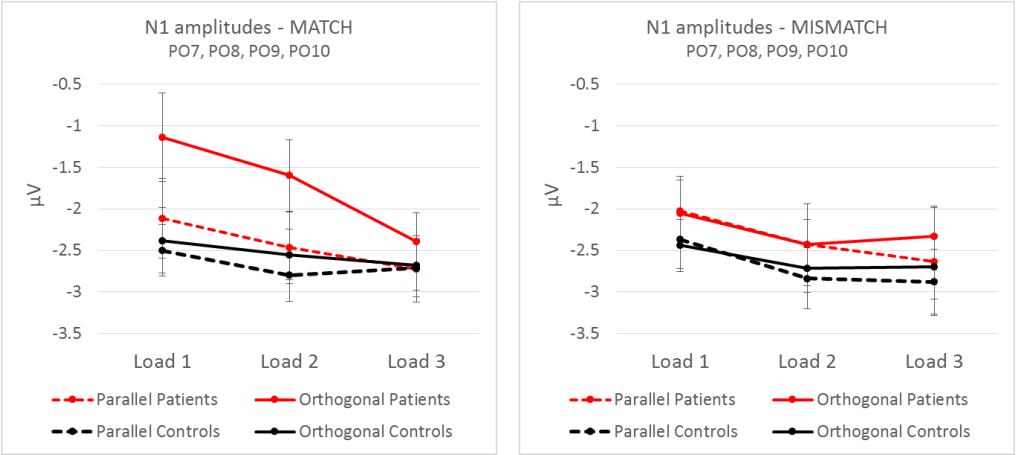


*Figure 0.29. Interactions surround*load for match (left) and mismatch trials (right) for N1 amplitudes averaged for electrodes PO7, PO8, PO9 and PO10 for patients (red) and control participants (black). The x-axis represents WM load 1, 2 and 3 conditions (left and right). The y-axis indicates voltage in µV. Error bars represent standard errors.*

Comparison between controls and participants from Study 1

For C1 amplitudes, an interaction load*group ($F(2,72) = 8.5$, $p < 0.001$, $p\eta^2 = 0.19$) was found. After controlling for age, gender and level of education the interaction load*group was still found ($F(2,66) = 10$, $p < 0.001$, $p\eta^2 = 0.23$). Although there were no main effects of covariates, an interaction surround*gender was found ($F(1,33) = 9.3$, $p = 0.004$, $p\eta^2 = 0.22$).

For N1 latencies, a main effect of group was found ($F(1,36) = 63$, $p < 0.001$, $p\eta^2 = 0.64$). N1 latency was shorter for participants from experiment 1 compared to controls. After controlling for age, gender and years of education, there was still a significant group effect ($F(1,33) = 48$, $p < 0.001$, $p\eta^2 = 0.60$). Although there were no main effects of covariates, an interaction load*age ($F(2,66) = 3.6$, $p = 0.03$, $p\eta^2 = 0.1$) was found. For N1 amplitudes, a load*group interaction ($F(2,72) = 5.2$, $p = 0.008$, $p\eta^2 = 0.13$) was found. After controlling for age, gender and years of education, the interaction load*group was still significant ($F(2,66) = 4.3$, $p = 0.02$, $p\eta^2 = 0.12$). In addition, the covariate years of education was marginally significant ($F(1,33) = 3.8$, $p = 0.06$, $p\eta^2 = 0.10$).

In addition, an interaction load*group ($F(2,72) = 3.2$, $p = 0.05$, $p\eta^2 = 0.08$) was found for P1 amplitudes, and an interaction surround*load*group ($F(2,72) = 3.7$, $p = 0.03$, $p\eta^2 = 0.09$) was found for slow waves at frontal electrodes. However, after controlling for age, gender and years of education, both interactions became not significant. Finally, for SW at visual electrodes no group differences were found.

CANTAB

Paired associate learning (PAL)

Independent paired sample t-tests revealed that patients made a significant higher number of errors compared to controls ($t(19.8) = 2.4$, $p = 0.024$). For patients, negative correlations were found between the number of errors in the PAL and overall WM accuracy ($r = -0.72$, $p = 0.002$).

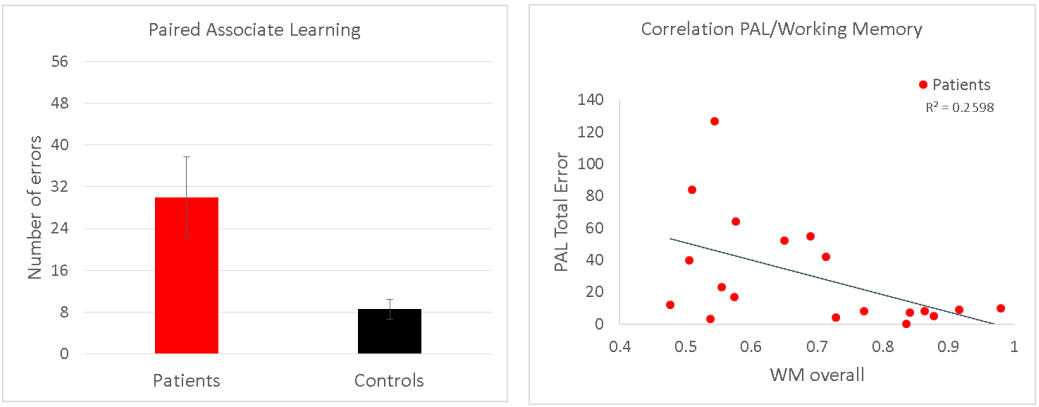


Figure 0.30. (Left) The number of errors in the Paired Associate Learning (PAL) task made by patients (red) and controls (black). Error bars represent standard errors. (Right) Correlation between patients' number of errors made in the PAL and overall WM performance. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

Spatial working memory (SWM)

Independent paired sample t-tests revealed that patients and controls performance did not differ both in terms of number of errors ($t(37) = 1.7$, $p = 0.1$) and in terms of strategy used ($t(37) = 1.3$, $p = 0.21$). For patients, negative correlations were found between overall WM accuracy number of errors in the ($r = -0.67$, $p = 0.007$) and strategy score ($r = -0.64$, $p = 0.01$).

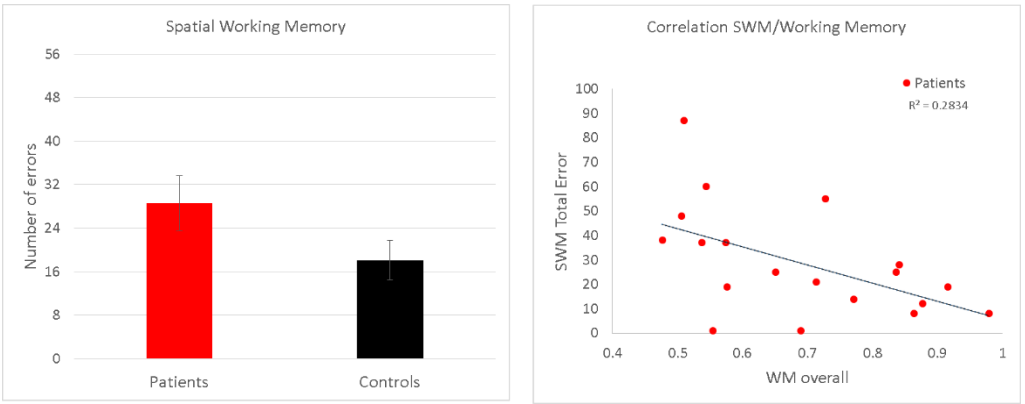
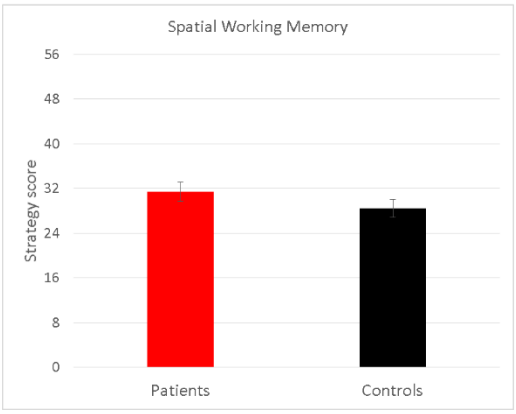


Figure 0.31. (Left) The number of errors in the Spatial Working Memory (SWM) task made by patients (red) and controls (black). Error bars represent standard errors. (Right) Correlation between patients' number of errors made in the SWM and overall WM performance. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.



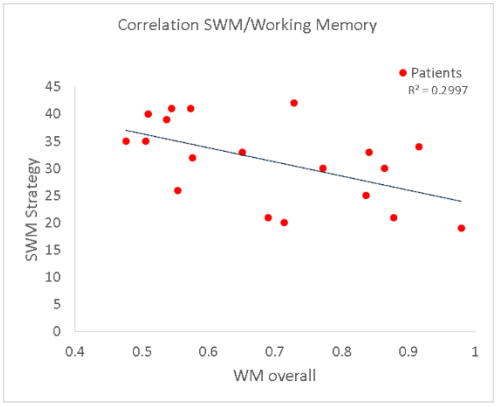


Figure 0.32. (Left) Strategy score in the Spatial Working Memory (SWM) task of patients (red) and controls (black). Higher strategy values are associated with poor strategy, whereas lower strategy values indicate good strategy (see methods section on page 129 for more details). Error bars represent standard errors. (Right) Correlation between patients' strategy score of the SWM and overall WM performance. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

MANSA

1. MANSA MEAN RATING SCORE	2. *"Do you have anyone you would call a close friend?"*	3. *"In the last week have you seen a friend?"*	4. *"In the past year have you been accused of a crime?"*	5. *"In the past year have you been victim of physical violence?"*
4.54 *(SD = 1.38)*	Yes = 12 No = 7	Yes = 6 No = 13	Yes = 0 No = 19	Yes = 0 No = 19

Table 0.4 Results from MANSA quality of life questionnaire. Column 1 represents the mean satisfaction rating score of the 12 Likert scale items. In columns 2, 3, 4 and 5, questions and the frequencies of answers for the four binomial items are reported (see methods section at page 130 for more details).

The mean score of all life satisfaction items was 4.54 (SD = 1.38). Thus, according to the satisfaction Likert scale, the overall life satisfaction of our patients' population was mixed (neither satisfied nor dissatisfied). Seven patients reported not to have a close friend, and 13 patients reported not to have visited or have been visited by a friend in the last week. None of the patients was accused or has been a victim of a crime in the past year. No correlations were found between MANSA and visual tasks or working memory accuracy.

Discussion

Behavioural

In experiment 2, it was tested the hypothesis that basic visual impairments in schizophrenia affect working memory performance. Specifically, it was examined whether visual lateral inhibitory mechanisms, known to be weakened in schizophrenia, could contribute to working memory deficits.

Firstly, LI impairments in schizophrenia (SZ) were addressed at a perceptual level with a contrast matching task and an orientation discrimination task. In both tasks, in order to induce LI, larger surrounds were placed outside the target which could be either parallel (stronger LI) or orthogonally oriented (weaker LI) to the central grating. Similarly to experiment 1, in the contrast matching task control participants showed a surround modulation on perceived contrast. Specifically, target contrast perception was significantly reduced in the parallel surround condition compared to both the orthogonal surround and to the grating presented in isolation. However, as expected, patients' contrast perception did not differ in the two surround conditions. This result replicates previous findings that have demonstrated a reduced surround suppression (SS) in patients with schizophrenia (Butler et al., 2008; Dakin et al., 2005; Javitt, 2009; Yoon et al., 2010; Yoon et al., 2009). Thus, it is assumed that while in control participants the parallel surround has induced a stronger LI compared to the orthogonal, the same effect was absent in the patients, probably reflecting a dysfunctional LI system.

In the orientation discrimination task, it was not observed a surround modulation in both populations. Orientation discrimination of the central grating embedded in the parallel surround did not differ from the orthogonal, either for controls or for patients. This seems to be in line with previous evidence that has also not found SS effects on orientation discrimination in SZ (Tibber et al., 2013). However, as in Tibber et al., (2013), it was found that patients' overall orientation discrimination threshold was significantly higher compared to controls. Patients, compared to controls, needed a larger tilt in order to discriminate between two subtle orientations. The magnitude of the effect was substantial since it was associated with a large effect size. In line with a large body of evidence that have demonstrated basic perceptual impairments in the disease (Butler et al., 2007, 2008; Javitt & Freedman, 2014; Silverstein, 2016; Silverstein & Keane, 2011a), this result highlights that patients with schizophrenia

seem to show diminished basic perceptual skills compared to healthy controls populations.

SS effects on WM performance were also tested. A delayed matching to sample working memory paradigm was used. Participants were asked to memorise the orientation of up to three circular gratings embedded in high contrast surrounds which were either vertically (parallel condition) or horizontally (orthogonal condition) oriented to the target. Overall, WM performance in patients with schizophrenia was significantly reduced and response time significantly lower compared with control participants. The magnitude of the differences between the two groups seemed to be substantial, as suggested by large effect sizes.

Although for both populations performance decreased with an increment of memory load, only for control participants performance was also modulated by the perceptual characteristics of the items. Specifically, only for controls, WM accuracy in Load 1 was lower in the parallel compared to the orthogonal surround condition. However, in Load 3 condition, accuracy, dPrime and correct rejections were higher in the parallel surround condition. Thus, in Load 1, when participants needed to encode a single item, controls made more errors in recognising the matching (or not matching) orientation of the probe when the encoded gratings were embedded in the parallel surround. As suggested for experiment 1, this result might reflect a simple perceptual interference which was more evident in the parallel surround condition.

However, in contrast to experiment 1, the opposite result was found when a higher number of items needed to be maintained. Specifically, in load 3 condition, control participants showed higher performance in the parallel compared to the orthogonal surround condition. Differently from Load 1, when a larger number of items needed to be encoded, LI mechanisms (which are stronger in the parallel surround condition) might have enhanced the formation of the memory representations, probably creating a more integrated representation of the target in its background. This seems to be in line with the functional role that has been proposed for SS. SS seems to minimise the redundancy of the visual scene by enhancing the perception of the visual items (Sachdev et al., 2012; Allman, Miezin, & McGuinness, 1985; Bakin, Nakayama, & Gilbert, 2000; Blakemore & Tobin, 1972). Thus, by making encoding mechanisms more efficient, stronger SS might have supported memory recall by facilitating the identification of the target among a set of encoded items. Note that, in experiment 1 no surround effect was found in load 3 condition. Although there were not significant

group effects between participants from experiment 1 and controls, the discrepancy in the accuracy result might be explained by the variability of age, gender or years of education of the controls and participants from experiment 1. This result might suggest that the SS effects on working memory performance are subject to inter-individual variability. Future studies will need to be designed in order to better address the potential causes of variability of SS effects on WM performance in different populations.

In the patients' cohort, WM performance did not differ between the two surrounds. However, it only decreased with an increment in the number of items to remember. Thus, patients' WM accuracy seemed not to be affected by SS mechanisms. However, patients' WM performance negatively correlated with the overall OD performance. This correlation seems to suggest that the patients showing a higher threshold at discriminating different orientations (lower performance), also performed worse in the WM task. Thus, patients with schizophrenia showed an overall higher OD threshold compared to controls, and the OD threshold also correlated with WM performance. This seems to support previous research that has proposed that basic sensory impairments found in SZ can contribute significantly to working memory deficits (Butler et al., 2008; Javitt, 2009; Javitt & Freedman, 2014). In fact, recent evidence is suggesting that WM deficits in schizophrenia might not be exclusively caused by high-level cognitive processing, but that basic perceptual processing play a major and active role in WM processing (Butler et al., 2008; Dias, Butler, Hoptman & Javitt, 2011; Haenschel & Linden, 2011; Javitt, 2009; Lee & Park, 2005).

Response times were significantly higher in patients compared to controls. This result is in line with previous studies that have found slower response times in patients with schizophrenia (Haenschel et al., 2007). However, contrarily to what it is typically found in WM literature (Haenschel et al., 2007), here response times became faster at higher memory loads both for patients and controls. Although the delayed matching to sample is a widely used paradigm in WM research, its combination with these specific stimuli and with various memory loads is quite new. However, since accuracy was above chance (over 50% of correct responses) both for patients and controls, it seems unlikely that this result is due to task design or to the inability of participants in performing the task. In chapter 6, potential future studies that could clarify this confound are discussed. In addition, a surround modulation of response times was

found both for patients and controls. Whereas for patients response times were faster for parallel surround both in load 1 and Load 3 conditions, for controls response times were slower for parallel surround only in Load 1. Thus, although patients' WM accuracy did not differ depending on the surround conditions, response times seem to be affected by the perceptual characteristics of the encoded items only in patients, but not in controls.

In sum, behavioural results of experiment 2 confirm that patients are not affected by SS mechanisms in the contrast perception. Moreover, whereas for controls WM accuracy differed depending both on load and on surround condition, patients' accuracy only decreased with the increment in memory load. However, the overall OD threshold was higher in patients compared to controls and negatively correlated with WM performance. This suggests that lower OD abilities were associated with lower WM accuracy in SZ patients.

ERPs RESULTS

Encoding

Overall, ERPs activity seemed not to be affected by medication intake, with an exception for P2 latency.

At encoding, no group differences were found with C1 at Oz electrode, P1 and N1 at lateral posterior electrodes. In the early phase of encoding, C1 amplitudes were modulated by memory load both for patients and controls. Past literature has suggested that C1 is not modulated by top-down attention but it seems to respond to purely visual events (Di Russo et al., 2003). However, here an increment of C1 amplitudes with increasing memory load was found, probably suggesting an increased attentional demand. This result seemed to be in contrast with past studies that have shown no attentional modulation of C1. Moreover, this result is also in contrast with experiment 1 in which there were not memory load effects on C1 amplitudes. Despite previous studies have shown that ERPs activity might change with demographic factors such as age (Kieffaber, Okhravi, Hershaw, & Cunningham, 2016) or gender (Melynyte, Wang, & Griskova-Bulanova, 2018), here C1 result was not explained by the variability of demographic factors between control participants and participants from

experiment 1. Future studies will need to address the potential factors that might determine the sensitiveness of C1 for memory load in different populations.

P1 and N1 amplitudes at occipital electrodes were modulated by WM load both for controls and patients. The magnitude of these effects seemed to be fairly solid since they were associated with large effect sizes. However, whereas P1 amplitudes decreased with the increment of memory load, N1 amplitudes increased. It is proposed these results might reflect different attentional mechanisms. Top-down attention operates both by enhancing task-relevant items and suppressing irrelevant information (Gazzaley & Nobre, 2012; Noonan et al., 2017). Although both P1 and N1 have been associated with attentional mechanisms, they seem to reflect different aspects of attentional processing (Hillyard et al., 1998; Kappenman & Luck, 2012a). For example, in studies testing spatial attention with valid and invalid cueing paradigms (Luck et al., 1994; Luck & Hillyard, 1995), P1 has been found to be enhanced in invalid-cue compared to neutral trials, whereas N1 was enhanced in valid compared to neutral trials. The authors suggested that whereas P1 reflects suppression of irrelevant information, N1 reflects enhanced attention and facilitation of item processing (Hillyard et al., 1998; Luck et al., 1994; Luck & Hillyard, 1995). Although these studies have tested spatial attention, the result of this study might be in line with this interpretation. In Load 2 and 3 conditions of the task, participants were required to encode an increasing number of items. However, since participants were aware that the surround was irrelevant for the subsequent recall, they also had to inhibit a larger number of irrelevant information (the surround). Thus, it is suggested that the P1-N1 result might reflect these parallel mechanisms. Specifically, the decrement of P1 amplitudes might reflect the suppression of an increasing number of irrelevant information, whereas N1 increment might be associated with increased attentional demand related to the encoding of an increasing number of relevant items. Alternatively, the decrement of P1 amplitudes might also reflect habituation. Habituation is an automatic process in which ERPs amplitudes tend to decrease with repeated presentation of similar stimuli (Ambrosini et al., 2016; Harris, 1943). Thus, alternatively, the P1 result might reflect decreased responses to an increasing number of sequentially presented stimuli.

N1 amplitudes were lower for the parallel compared to the orthogonal surround condition. As suggested for study 1, this result might reflect stimulus discriminatory processes or saliency effects (Machilsen et al., 2011; Vogel & Luck, 2000). Specifically,

N1 amplitudes were higher for stimuli that were presumably more perceptually salient (orthogonal surround stimuli). Alternatively, N1 decrement for parallel surround might also reflect more suppressive activity related to stronger LI mechanisms.

Thus, these results suggest that early visual ERPs activity changes according to an increased number of items to encode, probably reflecting attentional mechanisms. However, since no correlations were found between ERP activity at encoding and WM accuracy, it seems that encoding mechanisms did not directly influence the overall WM performance.

Group differences between patients and controls were found with P2 and slow waves (SW) activity. Specifically, P2 amplitudes seemed to respond to surround effects only in controls but not in patients. Specifically, in Load 2 condition, P2 amplitudes were lower for parallel compared to the orthogonal surround, only in controls, but not for patients. Moreover, as for experiment 1, P2 amplitudes positively correlated with the contrast matching task only in control population, suggesting that the higher contrast suppression in the visual task, the higher P2 peaks. Thus, both experiment 1 and experiment 2 seemed to highlight that P2 is particularly sensitive to surrounds suppression effects. However, in patients, P2 amplitudes did not differ between the two surrounds. In a perceptual discrimination task, Wang et al (2012) found that P2 amplitudes in healthy controls were higher compared to patients. Moreover, P2 amplitudes correlated with higher perceptual discrimination performance only in controls. In contrast, for patients, P2 was not modulated by the different perceptual characteristics of the items. The authors interpreted this finding as reflecting poor perceptual discriminatory abilities in patients with SZ (Wang et al., 2012). Since here P2 amplitudes responded differently to the parallel and orthogonal surround in healthy population but not in patients, it is suggested that perceptual discriminatory processes at encoding seem to be decreased in SZ.

Group differences were also found during late encoding, with SW activity both at frontal and visual electrodes. Surround*load*group interactions were found both at frontal and at visual electrodes. However, it is noted that the magnitude of the effect (effect size) was large only at frontal electrodes, whereas it was medium at visual electrodes. This might suggest that the effect was more powerful at frontal compared to visual electrodes.

SW activity for patients was higher for parallel compared to orthogonal surround, specifically in Load 1 condition. In contrast, for controls, SW activity only decreased with the increment in memory load. Thus, it seems that in the SW time window (450-900ms) when the stimulus was no more physically present, patients still show a surround modulation with a very similar trend in the frontal and visual electrodes. This effect seems to emerge more clearly only in Load 1 condition probably because the representation of the item was isolated, and not overlaid with other stimuli (as in Load 2 and 3). Although for controls SS mechanisms are observed until the stimulus is physically displayed on the screen (with P2), for patients perceptual processing are observed during a later phase. Likewise, Wang et al. (2012) found that, compared to controls, perceptual discrimination processes in patients appeared with a later ERP component (N2 instead of P2). The authors suggested that slowed perceptual mechanisms seemed to be compensated with delayed processing (Wang et al., 2012). Further WM studies have proposed that encoding mechanisms in schizophrenia are sluggish compared to healthy populations (Hartman et al., 2002). In light of this previous evidence, it is proposed that encoding in SZ seems to be slower compared to control and probably compensated with delayed processes.

Alternatively, the SW result might be interpreted as reflecting hyperfocusing of attention (Gray et al., 2014; Kreither et al., 2017; Leonard et al., 2013a). Previous evidence has found that, compared to controls, SW activity (specifically CDA) in patients with schizophrenia was higher at load 1 and lower at load 3 (Leonard et al., 2013b). The authors suggested that patients lack in distributing attention broadly since they tend to hyperfocus only on a subset of information (Leonard et al., 2013b). The result of this study seems to be also in line with this interpretation. However, since this decrement was only found in the parallel but not in the orthogonal surround, this result further suggests that difficulties in sustained attention in SZ might be also influenced by the perceptual features of the items, and not only by the number of items to retain. However, these ERPs results did not correlate with WM behavioural performance. Thus, it seemed that the delayed encoding processes observed in patients with SZ did not directly affect WM performance.

In sum, ERPs results at encoding showed that both for patients and controls, P1 and N1 amplitudes seem to be modulated both by memory load and SS effects, likely reflecting attentional mechanism. However, P2 amplitudes were decreased with the

parallel surround stimuli only in controls, but not in patients. Moreover, whereas SW activity during late encoding for controls only decreased with the increment in memory load, for patients surround effects were still observed in Load 1 condition, probably reflecting slowed encoding mechanisms.

Retrieval

At retrieval, P1 and N1 components were observed at occipital electrodes. Here, it was also explored whether ERPs activity differed depending on whether the orientation of the probe match or did not match the orientation of the target stimulus at encoding. Overall, both P1 and N1 activity was not influenced by medication intake.

Group interactions were found with P1 latency and amplitudes. Specifically, P1 latency was shorter for match compared to mismatch trials for the orthogonal surround only for patients but not in controls. Moreover, P1 amplitudes for orthogonal surround were higher compared to the parallel surround only in Load 1 condition. Previous studies investigating P1 activity in SZ have suggested that patients with SZ show a narrow focus of attention, i.e. they tend to recruit more attentional resources only on a subset of internal representations (Gray et al., 2014; Kreither et al., 2017; Leonard et al., 2013a). For example, in a spatial attention task, Kreither and colleagues (2017) showed to patients with SZ and healthy controls one coloured square which, in different blocks of trials, could appear either in the centre of the screen or in one of four peripheral locations. In different trials, participants had to attend either centrally or peripherally and had to indicate the stimulus onset. They found that, in contrast to control, P1 amplitudes of patients with SZ in relation to centrally presented stimuli did not differ when participants had to attend centrally compared to when they had to attend to the periphery of the screen. The authors suggested that patients' attention was biased toward centrally presented items even when they were task-irrelevant. Although in this experiment it was not tested spatial attention and the stimuli were always presented centrally, this P1 result in patients might relate to these findings. Specifically, since P1 amplitudes were higher for the orthogonal surround, patients might have focused their attention on a subset of internal representation. However, since this effect was more pronounced only at Load 1 condition, the decrement of P1 amplitudes with parallel surround stimuli might also simply reflect a more suppressive activity exerted by the parallel surround.

No group effects were found for N1. Specifically, for both populations, N1 amplitudes were higher for parallel compared to orthogonal surround and increased with the increment in memory load. However, it is noted that the effect size was large only for the load effect, but it was medium for the surround effect. This might suggest a more substantial memory load modulation on N1 amplitudes compared to surround.
As suggested for experiment 1, it is proposed that these results reflect a larger deploy of attentional demand in relation to higher memory loads. Moreover, this result also suggests that N1 is involved in perceptual discriminatory processes between the presented probe and the internal memory representation (Hillyard et al., 1998; Pinal et al., 2014; Vogel & Luck, 2000).

In sum, ERPs results at retrieval suggest that attentional resources are distributed differently between patients and controls. Specifically, differently from controls, patients tend to hyperfocus only on a subset of internal memory representations which are probably more perceptually salient (Gray et al., 2014; Kreither et al., 2017; Leonard et al., 2013a). However, at the stage of N1 processing, patients and controls activity was relatively similar.

CANTAB, clinical symptoms and quality of life

It was also explored whether our WM behavioural results are associated with a standardised assessment of WM measures in SZ. Specifically, two tests (Paired Associate Learning and Spatial Working Memory) taken from the CANTAB schizophrenia battery were performed. It has been demonstrated that the tests comprising the CANTAB schizophrenia battery are of clinical relevance for the development of novel drug treatments that target cognitive dysfunctions in the disease (Barnett et al., 2010).
Both Paired Associate Learning and Spatial Working Memory performance negatively correlated with the overall WM accuracy of this experiment's task. These correlations show that lower WM performance was associated with lower performance in the CANTAB tests. Thus, this result suggests that in this sample, patients' performance of this experiment's WM task is associated with performance in standardised memory tests for schizophrenia. However, whereas in the Paired Associate Learning task, people with schizophrenia made a larger number of errors than controls, the two

groups did not differ in the spatial working memory task, neither in terms of error nor in terms of strategy. This result seems to be in contrast with the current literature which has highlighted diffuse WM deficits in patients independently of WM modality (Lee & Park, 2005). However, Elliott, McKenna, Robbins, & Sahakian (1998) also found that, compared to healthy controls, patients in the CANTAB SWM test were not severely impaired compared to healthy controls. Moreover, a meta-analysis carried out on studies that used CANTAB tests on SZ populations showed that, compared to first-episode SZ, long-term patients performance tend to be more heterogeneous in the SWM, suggesting that performance in this test might change during illness (Stip, Lecardeur, & Sepehry, 2008). Note that the patients in this sample were outpatients with clinical symptoms that ranged between absent to minimal (according to the PANSS results). Studies that have compared inpatients with clinically stable outpatients have suggested that, compared to inpatients, outpatients tend to show better neurocognitive functions particularly for speed of processing, visual attention and working memory (Comparelli et al., 2012; Kurebayashi & Otaki, 2018; Trampush et al., 2015). Thus, despite patients in the current sample were clinically stable, patients' WM performance of this experiment's task, which was specifically aimed to target the influence of visual dysfunctions on WM, was decreased compared to controls.

Moreover, patients' did not report a negative evaluation of their quality of life. According to the MANSA questionnaire, patients appeared to be neither satisfied nor dissatisfied with their quality of life. However, correlations between MANSA results and our WM task were not found. Previous studies have found significant associations between WM performance and work/education status (Shamsi et al., 2011). However, work/education status is considered as an objective evaluation of the quality of life factors (Priebe & Fakhoury, 2008). Here, with the MANSA questionnaire, it was tested a more subjective evaluation of the quality of life factors (Priebe & Fakhoury, 2008; Priebe et al., 2010, 2011). Thus, it seems that WM decreased performance might not negatively affect the way in which patients evaluate their everyday living.

Summary

In sum, confirming past evidence, in experiment 2 it has been shown that in patients with SZ contrast perception is not affected by the SS effect. Overall, WM accuracy for

patients was lower and reaction times were slower compared to controls. For patients, WM accuracy only decreased with the increment of memory load, but it did not differ depending on surround condition. Moreover, OD threshold for the patients was significantly higher compared to controls and negatively correlated with WM performance. This suggests that patients with higher OD abilities also performed better in the WM task.

At a neural level, P2 amplitudes in load 2 condition were modulated by the two surrounds and correlated with the contrast matching task only in controls but not in patients. However, for patients surround effects seem to be delayed since they were observed during late encoding in the SW activity. This result probably reflects sluggish and unprecise stimulus discrimination processes (Hartman et al., 2002; Wang et al., 2012). At retrieval, in Load 1 condition, P1 amplitudes for the orthogonal surround were higher compared to the parallel only for patients but not for controls, suggesting that patients tend to hyperfocus only on a subset of memory representations (Gray et al., 2014; Kreither et al., 2017; Leonard et al., 2013a).

Patients WM accuracy of this experiment's task was related to performance in standardised cognitive tests aimed to assess cognitive deficits in SZ. Overall, the patients in this sample did not show severe clinical symptoms and were neither satisfied nor dissatisfied with their quality of life. However, subjective measures of quality of life did not correlate with WM performance.

To conclude, in experiment 2 it has been shown that in patients with SZ, contrast perception is not affected by the SS effect. This confirms past evidence that has demonstrated impaired LI activity in SZ. WM performance was significantly lower in patients compared to controls. Moreover, patients that showed a higher OD threshold also showed lower WM accuracy, suggesting that lower perceptual abilities are associated with lower WM performance. In conclusion, these results seem to support the idea that decreased basic perceptual skills observed in SZ are related to WM processing.

Chapter 5 - Working Memory and attention

Rationale of the experiment

In experiment 1 it was found that when only one item needs to be encoded, stronger LI seems to reduce WM performance. Moreover, experiment 1 and 2 have shown that LI effects seem to be more visible in ERP components typically related to stimulus discrimination (N1), saliency (P2) and attention (P1). The results of Experiment 1 lead to a further question about whether LI can interfere with attentional processes. This chapter is aimed to clarify whether basic perceptual processes, such as LI, can interfere with attention during WM processing.

Introduction

In natural vision, attention is of crucial importance. One of the main functions of attention is to bring into focus a relevant feature of the visual scene and ignore irrelevant elements, even when they are more visually salient (Gazzaley & Nobre, 2012; Griffin & Nobre, 2003).

It is believed that attention selects the relevant information to perform a given task through top-down mechanisms in which activity of posterior sensory regions (such as the visual cortex) is regulated by signals sent from anterior areas (such as the PFC or parietal cortex) (Braver et al., 2012; Duncan, 2001; Fuster, 2008; Miller & Cohen, 2001; Shallice, 1982). A large body of evidence has shown that the same attentional selection of relevant information can be directed not only to external goals, but also to internal representations and, as such, this would benefit WM performance (Gazzaley & Nobre, 2012; Griffin & Nobre, 2003). Since successful WM performance may also depend on the enhancement of relevant information and inhibition of distractors, several authors support the idea that attention and WM are strictly interconnected (if not overlapping) mechanisms (Awh, Vogel, & Oh, 2006; Awh & Jonides, 2001; Chun, 2011; Cowan, 1988; Gazzaley & Nobre, 2012; Noonan et al., 2017; Postle, 2006).

The crucial importance of attention for WM processing is demonstrated by a series of studies showing that attentional processes are present throughout all the WM phases with the goal of optimising accuracy (Bollinger et al., 2010; Dell'Acqua, Sessa, Toffanin,

Luria, & Jolicœur, 2010; Eimer & Kiss, 2010; Gazzaley & Nobre, 2012; Griffin & Nobre, 2003; Mayer et al., 2007; Murray, Nobre, & Stokes, 2011; Nobre, 2008). One of the methods typically used to test attention involves the modulation of expectations with the use of predictive cues, task signals appearing before (or after) the presentation of memory items that have the goal of orienting the focus of attention on a particular stimulus or location. In this kind of paradigms, since participants are deliberately instructed about which items (or locations) have to be ignored, attention has a direct inhibitory function (Noonan et al., 2017). Indeed, the use of cues seems to be extremely beneficial for WM performance (Bollinger et al., 2010; Griffin & Nobre, 2003; Hawkins et al., 1990; Jonides, 1981; Müller & Findlay, 1987; Müller & Rabbitt, 1989; Palmer, 1990; Posner, 1980b). For example, Griffin and Nobre (2003) used a delayed match to sample WM task in which four crosses of different colours were presented on the screen and after a delay participants had to judge whether a probe cross appearing in the middle of the screen was present or not in the encoded array. Crucially, during the task, a cue was presented either before (pre-cue) or after (retro-cue) the memory array. The cue consisted of an arrow indicating the position of the cross that was about to be probed (validly for 80% of trials and invalidly for the remaining trials). In a third condition, a neutral cue was presented consisting in a square (instead of an arrow) which consequently did not highlight any location. They found that WM performance was higher in valid-cue trials (both for pre-cue and retro-cue) compared with invalid and neutral cue conditions. Moreover, in a follow-up experiment in which the authors collected EEG data along with the same WM paradigm, they found that visual N1 was elicited in the contralateral hemifield to the attended location, both for pre and retro-cue trials (Griffin & Nobre, 2003).

More recently, Bollinger and colleagues (2010) have provided neural evidence that top-down signals linking fronto-parietal and visual areas reflect preparatory activity in service to an upcoming WM goal to accomplish. In an fMRI study, the authors used an object-delayed response WM task in which participants had to match either a probe face or scene to a previously encoded stimulus. In half of the trials, a pre-cue indicated whether a face or a scene was about to appear, while in the other half a neutral cue was not informative about the following category of stimuli. The authors found an increment in connectivity between fronto-parietal areas and the fusiform face area (FFA), an area in the visual cortex associated with face processing, arising after the appearance of the pre-cue for faces but before the onset of the actual stimulus. In

addition, this increment in connectivity was also predictive of WM performance. The authors interpreted these findings as a reflection of preparatory top-down activity that is eventually beneficial for WM accuracy (Bollinger et al., 2010).

Nevertheless, top-down attentional mechanisms are not entirely immune to perceptual interferences. Recently, Hitch, Hu, Allen, & Baddeley (2018) have demonstrated that although the focus of attention is heightened, it is still susceptible to perceptual interference from irrelevant items. They set out a WM task in which participants saw four coloured shapes sequentially displayed at four corners of an invisible square. During the delay period, a to-be-ignored shape, which may or may not appear, was used as a distractor only in some of the trials. After the delay, participants saw in the middle of the screen either a colour or a shape and they had to name the corresponding shape (or colour) of the previously encoded memory test set. Crucially, the authors prioritised the item in the second position in order to engage the internal focus of attention. Specifically, participants were told that they would have received additional points if items in the second position were correctly recalled (compared to the other positions). They found that the item prioritised (in the second position), was better recalled compared to the others, even when the distractor was presented during the delay. However, the items in the other positions were worse recalled when the distractor was present. Moreover, the authors found a strong recency effect in the no-distractor condition. When the item in the last position was probed, it was better recalled than the items in the other positions. According to the authors, these results suggest that the focus of attention is not stable and it is highly susceptible to perceptual interference. More specifically, if the focus of attention is oriented to one specific item, it can still be accessed by an irrelevant but perceptually salient stimulus (the distractor), thus lowering the recall of the target item. However, this effect can be partially compensated by prioritising a specific target item. Moreover, they proposed that the recency effect is an automatic process which entails the focus of attention to be dominated by recently perceived stimuli (Hitch et al., 2018).

Therefore, although evidence has shown a tight link between attention and WM, the underlying mechanisms by which heightened attention is beneficial for WM performance are still debated. Noonan and colleagues (2017) have suggested that the functional role of top-down mechanism could be related both to the enhancement of target representation and to the suppression of distractors. However, it's still not clear how enhanced target representations are retained in early visual areas and protected

from distractors. In an fMRI study, Lewis-Peacock and colleagues (2012) found that only relevant items could be successfully decoded from BOLD signals, while non-target items could not, suggesting that only items that fall into a particular attentional state are also turned into memory representations (Lewis-Peacock et al., 2012). To test how selected WM items are retained in visual areas in a privileged state compared to non-target items Zokaei and colleagues (Zokaei et al., 2014) used Transcranial Magnetic Stimulation (TMS) over MT+, an area in the visual cortex associated with motion processing (Bisley & Pasternak, 2000; Pasternak & Greenlee, 2005). In their task, two groups of either green or red moving dots were presented above and below a fixation cross. During the retention delay, before TMS pulses were applied with an ineffective or effective intensity, a cue appeared on the screen consisting of the colour green or red flashed in the fixation cross. At retrieval, a green or red arrow appeared and participants had to adjust it to the movement direction of the dots with the same colour. Crucially, the colour of the cue could match or not the colour of the probe arrow, therefore being informative or not. The authors found that in the ineffective TMS condition participants remembered the matching cued direction with greater precision compared to the non-matching cued direction. However, with effective high-intensity TMS, thus temporarily impairing visual cortex activity, this advantageous effect of the cue disappeared, since behavioural performance did not differ anymore between the valid and invalid cue trials. The authors concluded that early visual areas, driven by top-down mechanisms, contributed to the maintenance of selected internal representations over non-target items (Zokaei et al., 2014). This study suggests that visual areas are able to enhance the representation of a particular WM content, presumably through top-down influences, and to protect it from potential distractors. To describe how top-down signals are reflected in the visual cortex, Hopf and colleagues (2006) have suggested that the focus of attention is organised in a center-surround fashion with a centre region, where the focus of attention is at a maximum, and a surrounding region, where attention signals are at a minimum. This mechanism allows to enhance some stimuli while suppressing others, and it is particularly useful in crowded visual scenes when isolating relevant information over a series of distractors might be more challenging (Luck, Girelli, McDermott, & Ford, 1997; Treisman, 1996). Tsotsos and colleagues (1995) have designed a selective tuning computational model which shows that a zone of enhanced activity for the relevant target areas is surrounded by an area of suppressed activity. In the model, as in an

inverse pyramid, irrelevant representations are hierarchically suppressed from one level to the other, in order to increasingly narrow down the focus of attention (Figure 5.1). Thus, according to this model, top-down inputs that propagate through the visual cortex suppress the activations related to irrelevant target areas (Hopf et al., 2006; Tsotsos et al., 1995).

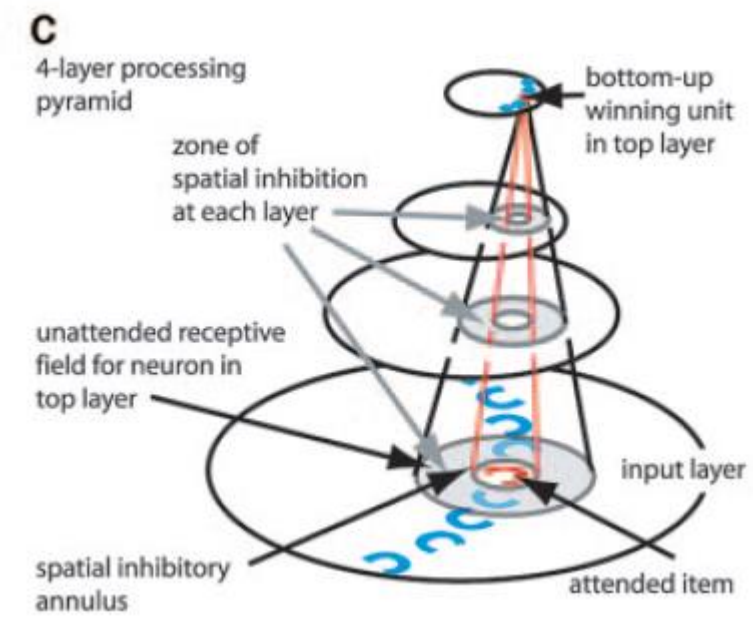


Figure 0.1. Adapted from Hopf et al. (2006). Top-down selection according to Tsotsos et al. (1995) model. Grey circle areas represent activity inhibited by top-down signals. Red areas represent the focus of attention which highlights relevant items. From one layer to the other, the inhibition area constantly adapts in order to narrow down the focus of attention on the selected target item.

To test this hypothesis, Hopf and colleagues (2006) designed a magnetoencephalography (MEG) experiment with a visual search paradigm in which participant had to search for a target (a red letter "C") within a line of eight distractors (blue letters "C") while always fixating in the middle of the screen. The target randomly appeared in any of the eight locations that were either close or far from the fixation centre and participants had to indicate the orientation of a gap placed on the left or on the right side of the target. In half of the trials a probe circle, that had to be ignored, was showed around the fixation point (Figure 5.2). In the trials in which the probe was present, they found that MEG responses to the target were highest when the target was shown in the central fixation point. However, the responses were lowest when

the target was presented next to the fixation point and increased as the target appeared further from the centre. The authors suggested that the brain responses were suppressed the most when a non-target item fell next to the focus of attention, whereas responses were less suppressed as the distractors moved away from the focus of attention (Hopf et al., 2006). The authors concluded that their results support the biased competition theory of attention by Desimone and Duncan (Desimone & Duncan, 1995) according to which attention operates in order to select a target stimulus among a series of distractors. If a distractor falls within the receptive field of a target it gets suppressed. This mechanism would be functionally relevant as it prevents the distractors to confuse the representation of the target (Desimone & Duncan, 1995).

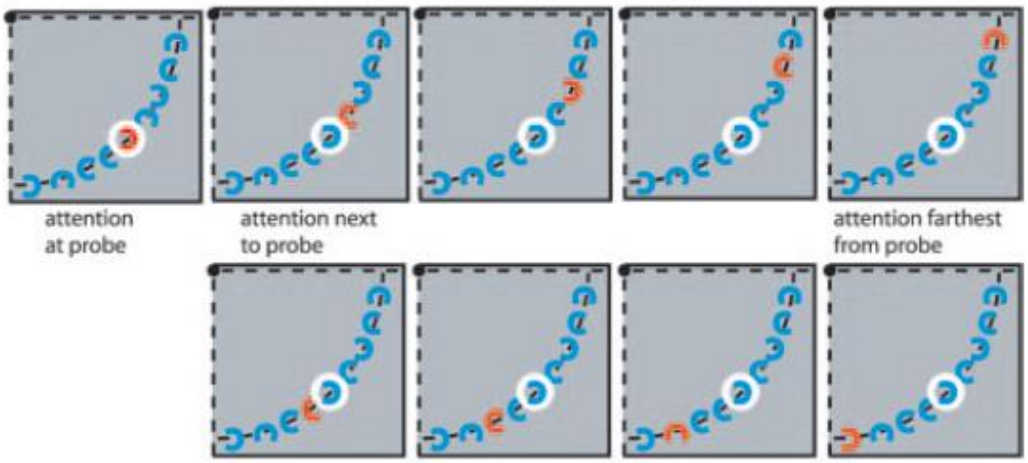


Figure 0.2. Experiment design by Hopf et al., (2006). Participants had to search for the red "C" while always fixating the centre. A ringed white probe was showed around the fixation in half of the trials that acted as a distractor to suppress. Suppression was maximal in "attention next to probe" condition, whereas it was minimal in "attention farthest from probe" condition.

To sum up, this evidence suggests that attention has a crucial role in the selection of relevant WM contents in visual areas through top-down controls from higher cortical areas. According to Hopf and colleagues, this mechanism would work in a center-surround fashion in which the target representation is enhanced while its surrounding area gets suppressed (Hopf et al., 2006).

Kiyonaga & Egner (2016) demonstrated that these center-surround selection mechanisms do not only operate with visual attention but they are also exerted towards internal WM representations. Participants saw two circles of different colours presented over two consecutive intervals. After a delay, a number appeared indicating

which one of the two circles participants were about to be probed. After the cue, a probe circle appeared and participants had to judge whether the colour of the probe circle match or did not match the colour of the cued item. Crucially, the colour of the probe could gradually range from a perfect match to the test to a completely dissimilar colour. They found that response times were fastest when the colour of the probe was a perfect match or when it was completely dissimilar to the test item. However, reaction times were significantly slower when the colour of the probe was different but more similar to the colour of the test item. However, they found this effect only in response times, as accuracy did not differ when the colours were similar or very dissimilar. The authors interpreted this result as reflecting a center-surround attentional organisation for WM representations. Top-down attentional mechanisms allow to focus on limited, but task-relevant information. In a similar way, this inhibitory function would operate also on WM internal representations in order to suppress distracting information. These results support the idea that both attention and WM operate to highlight relevant information while suppressing the irrelevant ones. Whereas attention is exerted toward external and physically present stimuli, WM would operate on internally maintained information (Awh et al., 2006; Awh & Jonides, 2001; Chun, 2011; Cowan, 1988; Gazzaley & Nobre, 2012; Harrison & Tong, 2009; Kiyonaga & Egner, 2016; Noonan et al., 2017; Postle, 2006).

This description of a center-surround organisation of attention and WM proposed by Hopf and colleagues (2006) and Kiyonaga & Egner (2016) echoes the one related to LI, a physiological mechanism defined as the suppression exerted by visual cells towards neuron in their proximal distance (Butler et al., 2008; Carandini & Heeger, 2012; Sachdev et al., 2012). LI seems to increase when a surround is placed outside the receptive field of a neuron. Moreover, LI seems to be maximal when the surround is parallel oriented to the target, compared to when it is horizontally oriented. LI can be at the basis of perceptual distortions such as the surround suppression effect, in which contrast or orientation perception of a central target can be altered by the presence of a larger surround (Blakemore & Tobin, 1972; Dakin et al., 2005; Xing & Heeger, 2001; Zenger-Landolt & Heeger, 2003).

Although it has been proposed that LI has the function to improve the precision of the internal representations (Arnsten, 2013; Butler et al., 2008; Sachdev et al., 2012), it is not clear whether LI effects are regulated by the focus of attention. Moreover, to my knowledge, it has not yet been explored to what extent attentional top-down

mechanisms enable to protect from distractors WM internal representations regulated by LI mechanisms.

Experiment 3: aims and predictions

Although it has been proposed that LI enhances the precision of the internal representations (Arnsten, 2013; Butler et al., 2008; Sachdev et al., 2012), results from Experiment 1 seems to be in contrast with this claim. In fact, the encoding of a single stimulus (load 1) that induced stronger LI mechanisms, reduced WM performance. Presumably, in Load 1 condition the focus of attention was heightened since it was oriented on a single item and it was not distributed among different stimuli (as in Load 2 and 3 conditions). Thus, the result from experiment 1 left unclear whether the observed LI effect at load 1 was attributable to a purely perceptual effect or whether LI interfered with the focus of attention.

Thus, the aim of Experiment 3 was to clarify whether the relationship between LI effects on WM performance observed in Experiment 1 (Chapter 3) can be attributed to top-down attentional selection mechanisms. Specifically, here it was tested whether LI effects on memory representation can be heightened by increasing the focus of attention.

Similarly to experiment 1 and 2, items that induced two different levels of Surround Suppression (SS) were used (see methods section for a detailed description). The same stimuli were used in a contrast matching task and an orientation discrimination task in order to explore LI effects at a perceptual level, and also during a delayed matching to sample WM task, in order to test LI effects on working memory performance. Differently from Experiments 1 and 2, attention was specifically modulated in the working memory task. Specifically, in half of the trials, a pre-cue was introduced in order to prepare participants to place the focus of attention of one specific item of the memory array. Here, only behavioural data were collected.

In light of the current literature and in light of the results from Experiment 1, it was predicted:

- WM performance to be higher when items are cued compared to when all the items need to be remembered.
- Since in experiment 1 it was observed lower WM accuracy for parallel surround items in Load 1 condition, here it was expected items embedded in the parallel surround to be harder to remember compared to orthogonal surround independently from cue position (main effect of surround)
- Contrast matching to be higher for parallel compared to orthogonal surround.

Methods

Participants

Twenty-one right-handed participants (14 females and 7 males, mean age = 23.81 years, SD = 5.8) took part in the study. According to self-report, all participants had normal or corrected to normal vision and were free of neurological and psychiatric disorders. The study was approved by the ethics committee at City, University of London and all participants signed an informed consent before participation.

One outlier female participant was removed from all the analysis since her behavioural performance in the orientation discrimination task could not be calculated as it exceeded several standard deviations from the mean. Therefore, the final sample consisted of 20 participants (13 females and 7 males, mean age = 24.05 years, SD = 5.9).

Stimuli and design

For all four tasks, circular grating items embedded in larger surrounds were generated using Matlab software and Psychtoolbox 3.0.12 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) and presented centrally on a grey background CRT monitor with a gamma correction of 2.2 at a viewing distance of 58cm.

Throughout all the tasks the circular gratings were presented either in isolation or embedded in a larger, 100% contrast surround. In the "parallel" condition the orientation of the surround relative to the centre was 0° degrees and in the "orthogonal" condition the orientation relative to the centre was 90° deg. Participants

were not informed about these two stimulus conditions. Trials were randomised among conditions and among participants in all the tasks.
A more detailed description about stimulus and parameters is outlined in chapter 2.

Tasks

Participants sat in a dark and soundproof Faraday cage. Participants performed the same contrast matching task (CM) and orientation discrimination (OD) task of experiment 1 and 2 and a delayed matching to sample working memory task with a pre-cue added at encoding (see below for detailed description). As in experiment 1 and 2, a two Intervals Forced Choice Detection (2IFCD) task was performed before the WM task, in order to establish each participant visual supra-threshold.
A detailed description of the contrast matching, orientation discrimination and 2IFCD tasks are outlined in Chapter 2.

Working Memory task

Before the WM task, participants performed a 2IFCD task with the aim of determining the contrast supra-threshold for perceptibility of the target in the two surround conditions (Parallel and Orthogonal) for each participant.
A delayed matching to sample task was used to measure working memory. However, the task for this experiment was slightly modified. At the beginning of each trial, a cue was presented for 300ms in a randomised order. The cue was in the form of a number (either 1, 2 or 3) which indicated which one of the following items participants had to remember. After the cue, always three gratings with different orientations were presented for 300ms each (interstimulus interval = 500ms). Therefore, in every trial participants saw one target item to memorize, plus two distractors (Figure 5.3A). The gratings were presented embedded within either a “parallel” or “orthogonal” surround. After a delay period (1000ms), participants saw a single Gabor (with no surround) for 1000ms and they had to indicate whether the orientation of the latter matched or not the orientation of the previously cued grating. Therefore, the task employed a 3x2 design with “cue-position" as the first within-participants factor with three levels (position one, two and three) and "surround" as the second within-participants factor with two levels (parallel and orthogonal). Participants performed

180 trials, 90 of which with the parallel and 90 with the orthogonal surround. Participants performed 60 trials per each cue.

As a control condition, we also designed a "NoCue" version of the same task in which no cue was showed but participants always had to memorise three gratings. Delay and retrieval period were identical to the Cue condition (Figure 5.3B).
Task design employed a 2x2 with "cue" as the first within-participants factor with two levels (Cue and NoCue condition) and "surround" as the second within-participants factor with two levels (parallel and orthogonal).
For this condition, participants performed 180 trials, 90 of which with the parallel and 90 with the orthogonal surround. Participants performed 360 trials in total (Cue and NoCue condition). Accuracy, Response Times, dPrime, Hits and Correct Rejections were calculated as described in chapter 2.

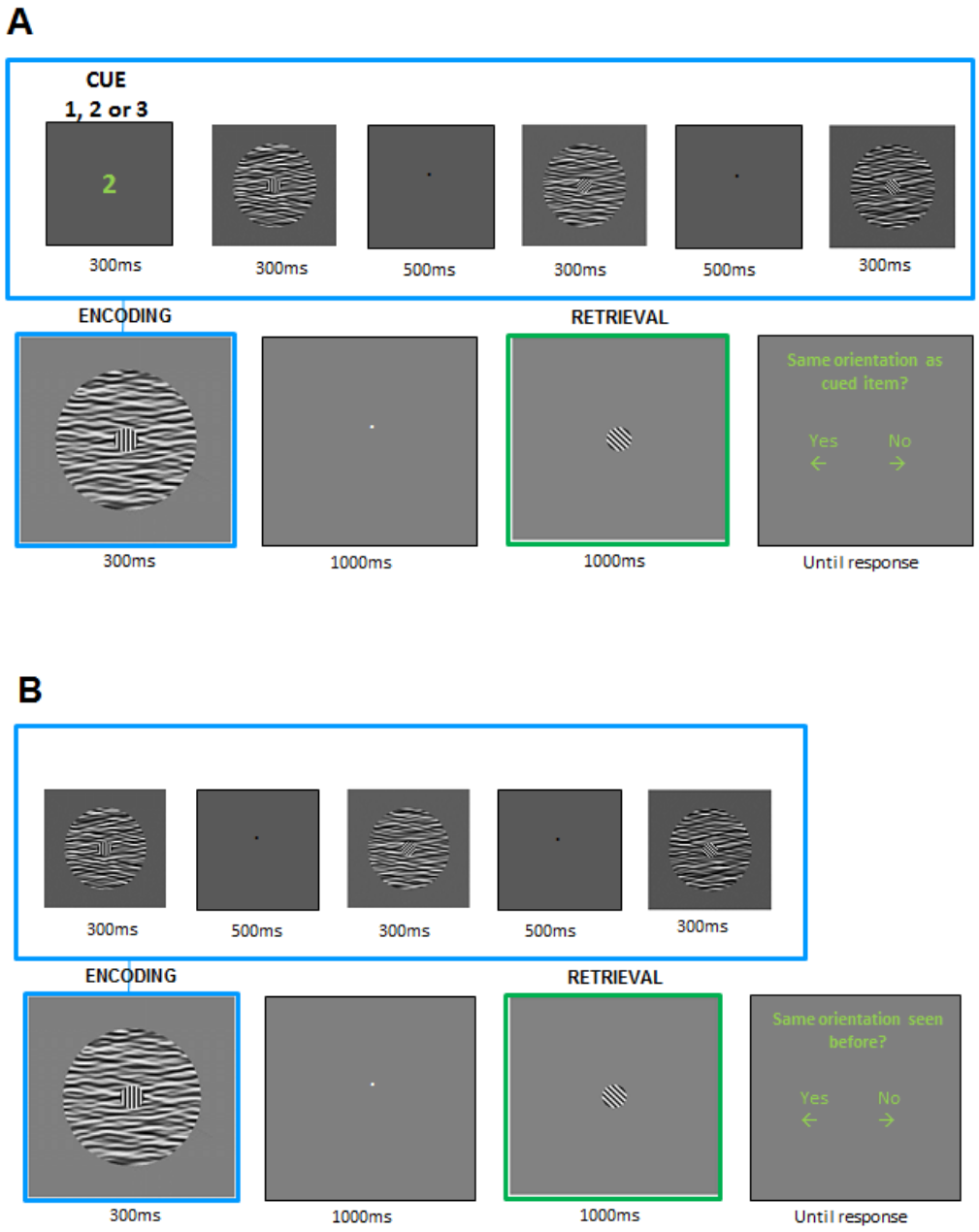


Figure 0.3 Design of the WM task. (A) Cue condition: Participants viewed always three gratings embedded in parallel or orthogonal surround throughout the trials (encoding). Before the gratings, either number 1, 2 or 3 was presented (cue) to indicate which one of the following orientations participants had to remember. After a retention interval of 1000ms in which a white dot was presented, participants viewed a probe-target with no surround which either matches or did not match the orientation of the item that was cued during the encoding phase (retrieval). Participants had then to decide if the probe orientation was the same or different to the orientation cued in the previously encoded test set. (B) NoCue condition: Same design as A but no cue was presented. Therefore, participants had to always memorise three gratings. The contrast of the items has been increased only for presentation purposes.

Statistical analysis

Orientation discrimination

Paired sample t-tests were performed to assess differences in orientation discrimination between the parallel and orthogonal surround. Since orientation discrimination results in this experiment differed from the results of experiment 1, an ANOVA was conducted to verify whether group differences occurred. Specifically, a 2x2 repeated measure ANOVA with surround condition as the two levels within-participants and group as the between-participants factor (experiment 1 and experiment 3) was performed.

Contrast Matching

Paired sample t-test was performed to assess differences in contrast matching between the parallel and orthogonal surround, and also between the reference contrast value (30% Michelson contrast) and contrast matching for parallel and orthogonal surround.

Working Memory

To test whether performance improved with the presence of the cue, a 2x2 repeated measure ANOVA was performed with Cue/NoCue and surround as within-participants factors. To test whether the position of the item to remember influenced performance and whether position effects can interact with the two different surrounds, only the Cue trials were analysed with a 3x2 repeated measure ANOVA with position and surround as within-participants factors. Moreover, correlations were performed between accuracy and contrast matching and orientation discrimination.

Measures of effect size are reported in terms of partial eta squared ($p\eta^2$) (Cohen, 1988; Cohen, 1973). The magnitude of the effect size will be interpreted as small with $p\eta^2$ = 0.01 circa, medium with $p\eta^2$ = 0.06 circa and large with $p\eta^2$ = 0.14 circa (Cohen, 1988; Levine & Hullett, 2002; Norouzian & Plonsky, 2018).

Results

Orientation discrimination

OD threshold for the parallel surround was significantly higher than threshold for orthogonal surround ($t(19) = 2.7$, $p = 0.013$). Repeated measure ANOVA performed with participants from experiment 1 revealed a main effect of group ($F(1,36) = 9.1$, $p = 0.005$, $p\eta^2 = 0.20$). OD threshold for participants from experiment 3 was higher than OD threshold for participants from experiment 1. An interaction OD*group was also found ($F(1,36) = 9.1$, $p = 0.005$, $p\eta^2 = 0.20$). OD threshold for the parallel surround was significantly higher than threshold for orthogonal surround only for participants from experiment 3 ($t(19) = 2.7$, $p = 0.013$), but not for participants from experiment 1 ($t(17) = 1.5$, $p = 0.15$).

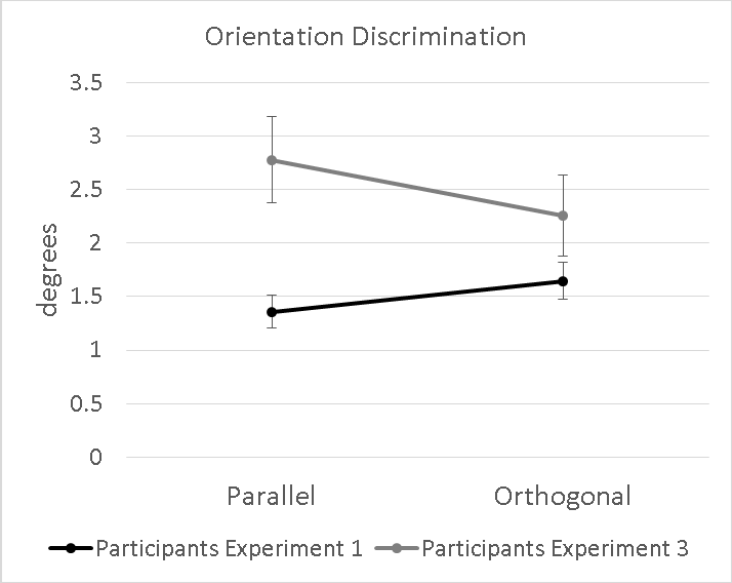


Figure 0.4. Orientation discrimination results for participants from experiment 3 (grey line) and participants from experiment 1 – Chapter 3 (black line). The x-axis represents the parallel and orthogonal surround conditions. The y-axis indicates the orientation discrimination threshold. Error bars represent standard errors.

Contrast matching

As in study 1 and 2, paired sample t-test revealed that the contrast matching for the parallel surround was significantly higher than orthogonal surround ($t(19) = 3.8$, $p = 0.001$). Moreover, contrast matching for the parallel surround differed from the reference contrast ($t(19) = 3.6$, $p = 0.002$) but this was not the case for the orthogonal surround ($t(19) = 1.6$, $p = 0.13$).

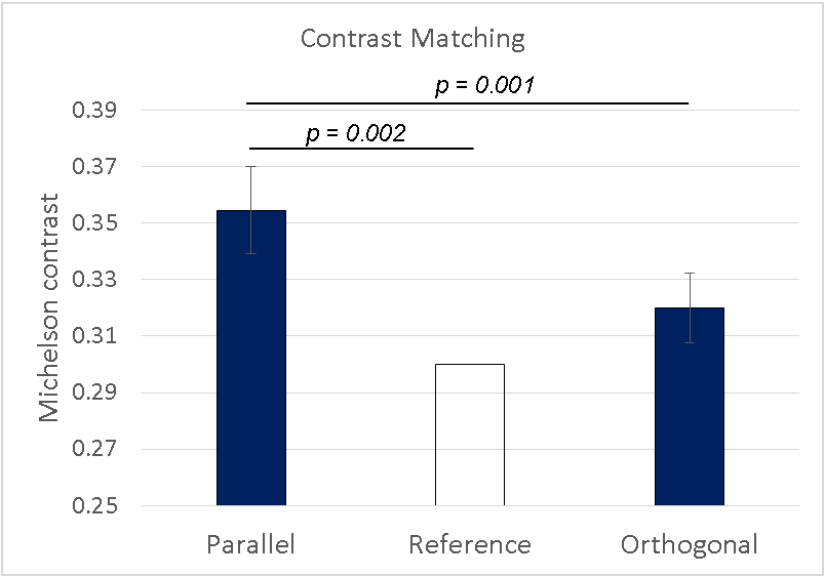


Figure 0.5. Contrast matching results for the parallel and orthogonal surround condition. The x-axis represents the parallel and orthogonal surround conditions. The white bar represents the reference contrast of the isolated patch which was constant throughout the task (30% Michelson contrast). Values on the y-axis represent contrast matching expressed in Michelson contrast. Horizontal black lines represent significant differences found between the parallel and orthogonal surround and between the parallel surround condition and the reference. Error bars indicate standard errors.

Working memory

Cue/No-Cue trials

	Cue Parallel	No-Cue Parallel	Cue Orthogonal	No-Cue Orthogonal
Accuracy Mean *(SD)*	0.88 *(0.03)*	0.70 *(0.03)*	0.89 *(0.02)*	0.71 *(0.03)*
dPrime Mean *(SD)*	2.47 *(0.20)*	1.25 *(0.22)*	2.58 *(0.16)*	1.26 *(0.23)*
Hits Mean *(SD)*	0.90 *(0.04)*	0.73 *(0.04)*	0.91 *(0.03)*	0.74 *(0.04)*
Correct Rejections Mean *(SD)*	0.86 *(0.02)*	0.69 *(0.04)*	0.87 *(0.02)*	0.67 *(0.02)*
Response Times Mean (seconds) *(SD)*	0.42 *(0.02)*	0.46 *(0.03)*	0.41 *(0.02)*	0.47 *(0.03)*

Table 0.1. Working Memory behavioural results for the parallel and orthogonal surround in the cue (cue 1, 2 and 3 trials averaged) and no-cue conditions. Mean and standard deviations (in brackets) are displayed for accuracy, dPrime, hits, correct rejections, and response times. For response times, means and standard deviations are expressed in seconds.

Mean and standard deviations for working memory behavioural results in the cue and No-cue trials are reported in Table 5.1.

A main effect of cue was found for accuracy ($F(1,19) = 65$, $p < 0.001$, $p\eta^2 = 0.78$), dPrime ($F(1,19) = 80.5$, $p < 0.001$, $p\eta^2 = 0.81$), hit rate ($F(1,19) = 40$, $p < 0.001$, $p\eta^2 = 0.68$), correct rejections rate ($F(1,19) = 38$, $p < 0.001$, $p\eta^2 = 0.67$) and response times ($F(1,19) = 4.7$, $p = 0.04$, $p\eta^2 = 0.20$). Performance in the cue condition was significantly higher compared to the No-Cue condition. Response times in the cue condition were significantly lower compared to the No-Cue condition. However, no surround effects were found.

Cue trials

A main effect of position was found for accuracy ($F(2,38) = 3.2$, $p = 0.05$, $p\eta^2 = 0.14$). Performance related to the item cued in the last position was higher than performance related to the item in the first position.

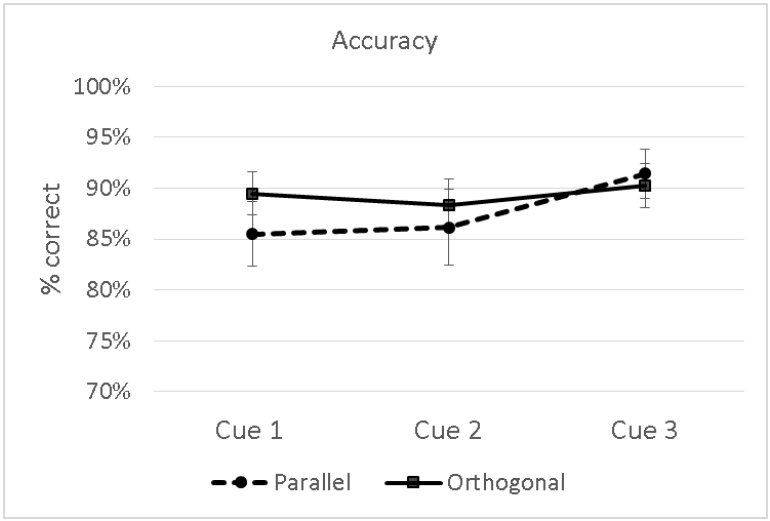


Figure 0.6. Main effect of position for WM accuracy for the parallel and orthogonal surround conditions. The x-axis represents cue 1, 2 and 3 conditions. The y-axis indicates the percentage of correct responses. Error bars represent standard errors.

For hit rate, an interaction surround*position ($F(1.5,27.6) = 4.6$, $p = 0.028$, $p\eta^2 = 0.20$) was found. Further analysis performed for each surround revealed a main effect of position only for the parallel ($F(1.5,28.8) = 3.7$, $p = 0.048$, $p\eta^2 = 0.16$), but not for the orthogonal surround. However, pairwise comparisons only revealed that hit rate for cue 3 was marginally higher than hit rate for cue 2 (MD = 0.08, SE = 0.03, $p = 0.07$).

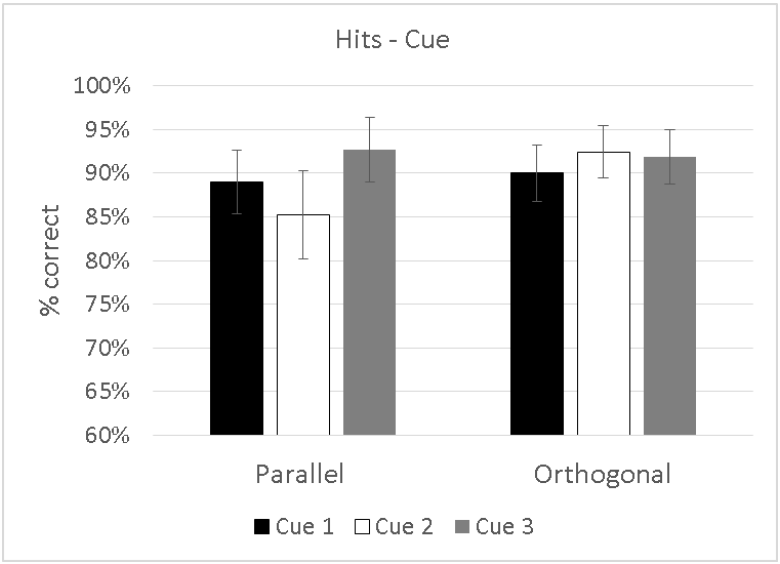


*Figure 0.7. Interaction surround*position for Hit rate for parallel (left) and orthogonal (right) surround conditions. The x-axis represents the parallel and orthogonal surround conditions. The y-axis indicates the percentage of correct responses. Error bars represent standard errors.*

In addition, a main effect of surround ($F(1,19) = 5.2$, $p = 0.035$, $p\eta^2 = 0.21$) was found for response times. Response times of parallel surround trials were higher compared to response times of orthogonal surround trials.

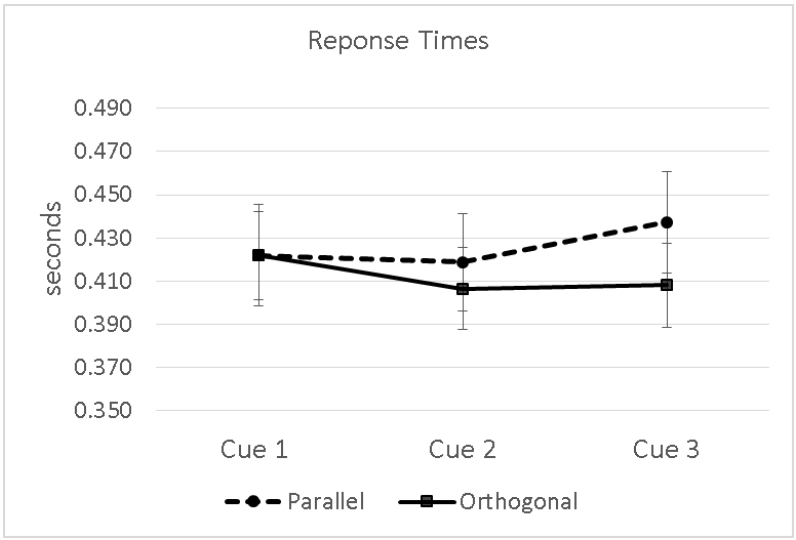


Figure 0.8. Main effect of surround for WM response times for the parallel and orthogonal surround conditions. The x-axis represents cue 1, 2 and 3 conditions. The y-axis indicates time in seconds. Error bars represent standard errors.

No significant effects were found for correct rejections.

Correlations

Orientation Discrimination and Contrast Matching

As for experiment 1, a trend to a negative correlation was found between CM and OD in the parallel condition (r = -0.42, p = 0.06) but not for the orthogonal surround (r = -0.38, p = 0.1).

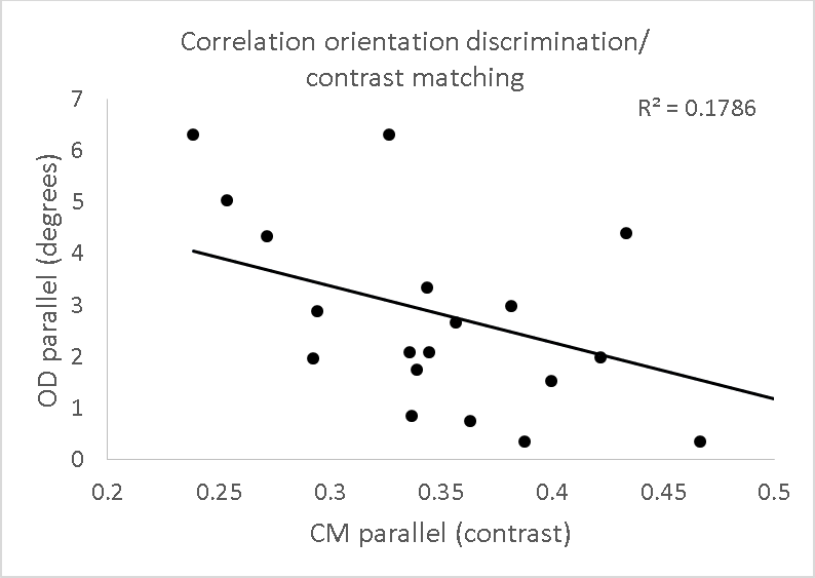


Figure 0.9. Correlation between contrast matching (x-axis) and orientation discrimination (y-axis) for the parallel surround condition. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

Orientation Discrimination and Working Memory

Negative correlations were found between OD and WM accuracy in the NoCue condition both for parallel (r = -0.70, p = 0.001) and orthogonal surround (r = -0.74, p < 0.001).

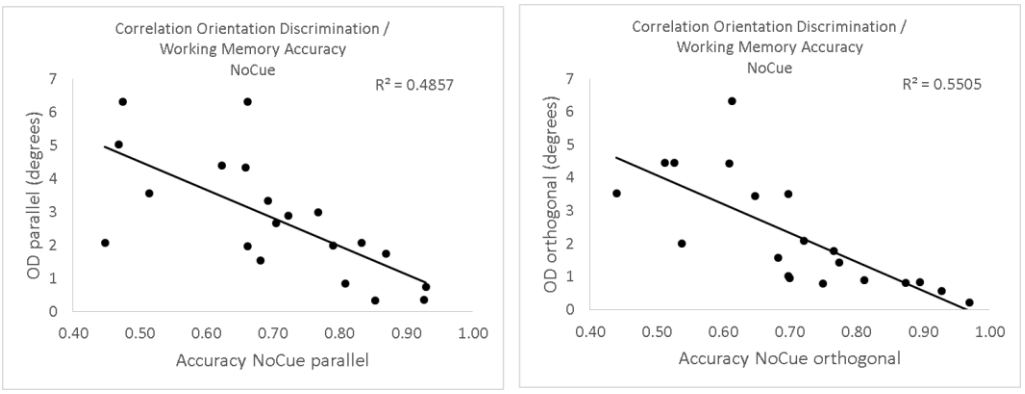


Figure 0.10 Correlations between WM accuracy in the NoCue condition (x-axis) and orientation discrimination (y-axis) in the parallel (left) and orthogonal surround (right) conditions. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

However, hit rate in the No-Cue condition negatively correlated with OD only for orthogonal surround (r = -0.50, p = 0.024).

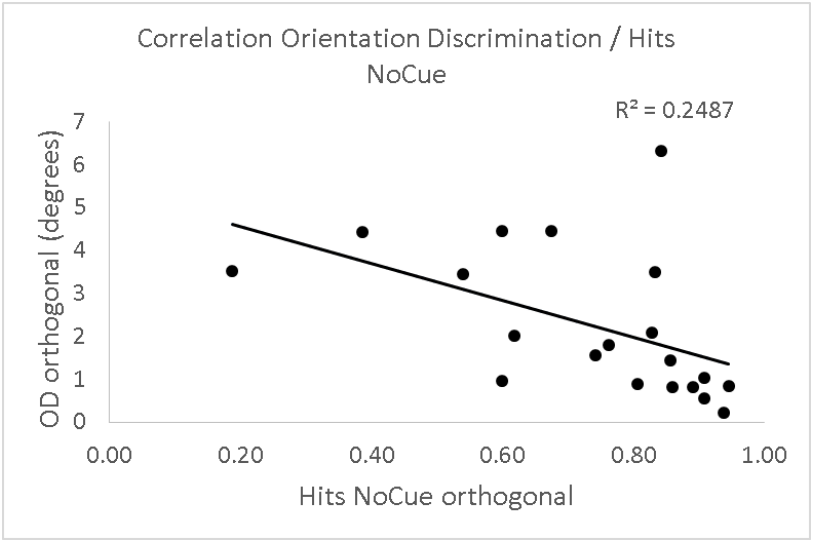


Figure 0.11. Correlations between Hit rate in the NoCue condition (x-axis) and orientation discrimination (y-axis) in the orthogonal surround condition. R^2 is the correlation coefficient squared, representing the strength of the linear relationship between the two variables.

Discussion

The aim of this study was to explore the relationship between LI effects on WM performance and top-down attentional mechanisms. Specifically, here it was tested whether LI effects on memory representation can be heightened by increasing the focus of attention.

As for experiment 1 and 2, LI effects on visual perception were preliminarily assessed with a contrast matching and an orientation discrimination task. Consistently with the previous experiments, it was found that, in the contrast matching task, contrast perception was significantly reduced in the parallel compared to both the orthogonal surround condition and to the reference contrast item. Thus, in line with the current literature, it seems that the parallel surround induced stronger LI mechanisms compared to the orthogonal (Dakin et al., 2005; Vanegas et al., 2015; Xing & Heeger, 2001; Yoon et al., 2009; Zenger-Landolt & Heeger, 2003).

However, in contrast to experiment 1 and 2, here a surround suppression effect was also found on orientation discrimination (OD). Specifically, participants needed a larger tilt in order to discriminate between two subtle orientations when the gratings were embedded in parallel, compared to the orthogonal surround. Thus, in this cohort, stronger LI mechanisms seemed to alter orientation perception. Surround suppression effects on orientation discrimination are known from past studies (Clifford, 2014; Howard, 1982; Solomon & Morgan, 2009). However, it is believed these effects can be extremely variable among participants (Clifford, 2014). Moreover, previous studies have shown that participants with a higher orientation discrimination threshold, are also more likely to show the SS effect on orientation discrimination (Song et al., 2013b). This finding from Song and colleagues (2013b) was confirmed by comparing participant from this experiment with the participants from experiment 1. It was found that participants from experiment 3 showed a higher orientation discrimination threshold compared to participants from experiment 1. This result was associated with a large effect size, indicating a solid magnitude. Moreover, only participants from experiment 3 showed a SS effect in the orientation discrimination task. Thus, this result seems to be in line with previous literature suggesting that the SS effect on orientation discrimination tend to emerge more clearly with participants with a higher orientation discrimination threshold (Song et al., 2013b). In line with experiment 1, a negative correlation was also found between contrast matching and orientation discrimination for the parallel, but not for the orthogonal surround. Participants that showed a higher

contrast matching also showed a lower orientation discrimination threshold (better performance). Since this correlation was specific for the parallel surround condition, it seemed to suggest that LI mechanisms in contrast perception are related to LI mechanisms in orientation discrimination.

In this study, it was also explored whether LI mechanisms can interfere with the focus of attention. A delayed matching to sample WM paradigm was used. Participants were asked to match the orientation of a probe circular grating to either an array of three gratings previously encoded (NoCue condition) or to one specific circular grating while ignoring two distractors (Cue condition). In the latter condition, the target grating was highlighted by a pre-cue shown at the beginning of each trial, so that participants knew which item to attend (and the ones to ignore) before their actual appearance. During encoding, gratings were embedded either in a parallel or orthogonal surround both in Cue and in No-Cue trials. As past evidence has suggested (Gazzaley & Nobre, 2012; Griffin & Nobre, 2003), it was found that the presence of the cue was beneficial for WM performance. When participants were cued towards a specific item, their accuracy was significantly higher compared to when none of the items was cued. Moreover, the performance was modulated by the position of the item to remember. Within the cue trials, WM accuracy was higher when participants were asked to memorise the last item appearing in the memory array compared to when they had to remember the first one. This result might reflect a recency effect. Past evidence has suggested that recency seems to be an automatic process in which recently perceived items tend to occupy the focus of attention to a greater extent compared to the other items (Allen, Baddeley, & Hitch, 2006; Hay, Smyth, Hitch, & Horton, 2007; Hitch et al., 2018; Phillips & Christie, 1977).

In No-Cue trials, no surround effects were found. Similarly to experiment 1, this seems to suggest that, when the internal memory representations are overlaid on top of each other, LI effects on memory recollection seem to be weaker or not visible. Moreover, OD negatively correlated with WM accuracy both for the parallel and the orthogonal surround. Specifically, participants that needed a larger tilt threshold in the orientation discrimination, showed lower performance in the WM task. However, these correlations were found for both surround conditions and not specifically for the parallel surround. Thus, in line with experiment 1, it seems that higher WM performance is associated with higher orientation discrimination abilities. As suggested for experiment 1, this result seems to highlight that basic perceptual

abilities can support WM performance, especially at higher memory loads. Specifically, the process of memorising a set of different orientations might be facilitated by higher OD skills.

Nevertheless, only for hit rate, lower OD threshold was associated with higher hit rate only in the orthogonal but not in the parallel surround. Thus, it seemed that OD with stronger LI was not related to a higher hit rate. Hit rate appeared to be more sensitive to surround effects since an interaction surround*position was found. This result was associated with a large effect size, suggesting a relatively high magnitude. In hit rate, the position of the cued item influenced performance in the parallel, but not in the orthogonal surround condition. Although marginally, only when a parallel surround was shown, the last item was better remembered than the second. This seems not to be the case for the orthogonal surround, where performance was not significantly affected by the position of the item to remember. This result could reflect a recency effect. The last item encoded tend to dominate the focus of attention and, therefore, it is also better recalled (Allen et al., 2006; Hay et al., 2007; Hitch et al., 2018; Phillips & Christie, 1977). However, since this effect was found only in the parallel but not in the orthogonal surround, it might suggest a moderate interference of LI on attentional mechanisms. For example Hitch, Hu, Allen, & Baddeley (2018) have shown that the focus of attention is not stable and can suffer from the interference of perceptually salient distractors. Here, although the focus of attention was heightened by the cue both in the parallel and in the orthogonal surround condition, in hit rate a position effect was found only in the parallel surround. This might indicate that stronger LI mechanisms might render memory representations more fragile and vulnerable to the interference of the distractors. More specifically, stronger LI might interact with the focus of attention and facilitate inter-stimulus interference mechanisms.

Finally, LI seems to influence WM performance also in terms of response times. Independently from the position, when target items were embedded in the parallel surround participants were slower at indicating whether the probe's orientation matched (or did not matched) the orientation of the test item. This seems to be in line with previous evidence that has investigated SS effects on WM. In a WM task testing center-surround mechanisms of attention, Kiyonaga & Egner (2016) found that response times were slower when probe stimuli were closely similar to the encoded items. However, response times were faster when probe stimuli were more dissimilar. The authors suggested that attention operates on WM contents in a center-surround

organisation, i.e. by enhancing relevant information and suppressing irrelevant information (Kiyonaga & Egner, 2016). Likewise, response times finding of this study seems to be in line with these results. With stronger LI (parallel surround condition) response times were slower, probably reflecting a center-surround modulation of attention during WM performance. In sum, these results suggest that a stronger LI (induced by the parallel surround) might interfere with the fidelity of working memory traces. Specifically, stronger LI might have enhanced the interference of the distractors towards the target item.

Some of these results seem to support the biased competition theory of attention by Desimone and Duncan (Desimone & Duncan, 1995) which suggests that attention operates in order to select a target stimulus among a series of distractors. Participant showed a better performance in cue trials, where attention allowed heightening the target item in a more efficient way compared to NoCue trials, in which attention had to be distributed among the target and the distractors.
However, it was also shown that the focus of attention might still be vulnerable to perceptual interference exerted from the distractors (Hitch et al., 2018). Here position effects were found on Hit rate only in the parallel, but not in the orthogonal surround condition. Thus, stronger LI might probably render memory items more susceptible to the interference of distractors.

To conclude, these results seem to indicate that lateral inhibition interferes with the internal representations of the items. The surround effects found only in the cue condition (but not in the NoCue) seem to suggest that selective attention could be modulated by lateral inhibition. Specifically, the study has highlighted that, in hit rate, position effects were more enhanced only in the parallel, but not in the orthogonal surround, suggesting that with stronger LI mechanisms memory internal representations might be more exposed to the interference of the distractors.

Chapter 6 - General Discussion

The current project investigated how lateral inhibitory (LI) activity affect working memory (WM) performance, both in the general population and in schizophrenia (SZ). In addition, this project also explored to what extent LI interact with attention during WM processing.

Brief summary of the literature background and aim of the project

WM is defined as the ability to temporarily hold memory information over a short period of time (Baddeley, 2003). WM supports many everyday activities, such as mental calculation, learning and reasoning, and as such, it is considered as a fundamental cognitive skill (Baddeley, 2003; Baddeley & Hitch, 1974; D'Esposito & Postle, 2015; Goldman-Rakic, 1996). WM impairments have been consistently found in clinical conditions such as schizophrenia (Barch, 2006; Lee & Park, 2005). Moreover, WM deficits seem also to have a negative impact on the quality of life of these patients (Shamsi et al., 2011). Traditionally, WM research has mainly focussed on maintenance and retrieval abilities (Barch, 2006; Hartman, Steketee, Silva, Lanning, & McCann, 2002; Lee & Park, 2005; Courtney, Ungerleider, Keil, & Haxby, 1997; Zarahn, Aguirre, & D'Esposito, 1997). Nevertheless, recent evidence has highlighted that mechanism occurring during the encoding phase can have a significant impact on the overall WM performance both in healthy and in SZ populations (D'Esposito & Postle, 2015; Javitt, 2009; Javitt & Freedman, 2014). However, it is still not clear to what extent perceptual mechanisms affect WM performance.

LI refers to an inhibitory activity exerted from visual cortex neurons towards their neighbouring cells (Blakemore & Tobin, 1972; Butler et al., 2008; Carandini & Heeger, 2012; Xing & Heeger, 2001; Zenger-Landolt & Heeger, 2003). LI is believed to be at the basis of perceptual phenomena such as the surround suppression effect (Butler et al., 2008). In the surround suppression (SS) effect, the perception of a central target is altered by the presence of a bigger surround (Colin Blakemore & Tobin, 1972; Xing & Heeger, 2001). Moreover, this effect seems to be larger when the surround has similar characteristics to the target. For example, SS seems to be stronger when the orientation difference between the surround and the target is lower (Vanegas et al., 2015; Zenger-Landolt & Heeger, 2003). However, it has been demonstrated that the

SS effect is abnormal in SZ. Specifically, in patients with SZ, the perception of a central target seems not to be affected by the presence of a larger surround (Dakin et al., 2005; Yoon et al., 2009).

Thus, even though the SS effect has been repeatedly found at a perceptual level, it has not yet been explored whether SS and LI also affect visual WM. Moreover, although attentional top-down mechanisms regulate WM processing (Gazzaley & Nobre, 2012; Noonan et al., 2017), it has been shown that attention can be vulnerable to perceptual interference (Hitch et al., 2018). Thus, it is not clear to what extent LI activity interferes with attention.

In light of this research, two EEG experiments and one behavioural experiment have been set out in order to explore whether LI mechanisms affect visual WM performance in the general population (Experiment 1) and in patients with SZ (Experiment 2). Moreover, it has been explored whether LI can interfere with a heightened focus of attention (Experiment 3).

The main findings were that:

- LI mechanisms affect contrast perception only in healthy controls but not in patients.
- LI seems to decrease WM performance in Load 1 condition (in Experiment 1 and 2), but it seems to increase it in Load 3 condition (in Experiment 2), only in controls but not in patients with schizophrenia.
- Overall OD threshold negatively correlated with WM accuracy both in healthy population and in patients with schizophrenia, suggesting that a higher OD threshold is associated with lower WM accuracy.
- At encoding, posterior P2 showed lower amplitudes in response to the parallel surround stimulus only in healthy population, but not in patients.
- During late encoding, slow wave activity was higher in response to the parallel surround stimulus load 1 condition only for patients, but not for controls.
- At retrieval, for both controls and patients, N1 amplitudes were higher for parallel compared to orthogonal surround and they increased with the increment in memory load, specifically for match trials.
- However, only for patients, P1 amplitudes were lower for the parallel compared to the orthogonal surround at retrieval.

- LI seems to interfere with a heightened focus of attention. The Hit rate for the item cued in the last position was higher than the item cued in the second position only for the parallel, but not for the orthogonal surround stimuli. Thus, the parallel surround enhanced inter-stimulus interference.

Each of these findings is discussed more in detail below. In addition, methodological issues and directions for future research are outlined in the chapter.

Summary of main findings

Behavioural results

LI at perception

Throughout all the three experiments LI mechanisms at a perceptual level were assessed at first. Specifically, a contrast matching and an orientation discrimination task were used to analyse the surround suppression effects on perceived contrast and orientation. A circular Gabor grating was showed either in isolation or embedded in a larger high contrast surround. Since the surround effects on the target seem to be orientation specific (Xing & Heeger, 2001; Yoon et al., 2009), the surround was designed either with a parallel or orthogonal orientation to the target, in order to respectively induce a stronger or weaker SS. Indeed, in experiment 1, in the control population of experiment 2 and in experiment 3, larger suppression in the parallel surround condition in the contrast matching task was consistently found. Specifically, with the parallel surround, the perceived contrast of the target was decreased both compared to the orthogonal surround and to the target seen in isolation. This result is a replication of several studies that have demonstrated that LI mechanisms induce a decrement in contrast perception of a central target that is also orientation specific. In fact, decreased contrast perception seems to be larger when the orientation difference between the surround and the target is lower, as in the parallel surround condition (Vanegas et al., 2015; Xing & Heeger, 2001; Yoon et al., 2010; Yoon et al., 2009; Zenger-Landolt & Heeger, 2003). Thus, contrast matching results of this study seem to suggest that the parallel surround condition has induced stronger LI mechanisms on perceived contrast.

However, schizophrenia patients did not show the same surround modulation. Contrast matching performance in the patients' cohort did not differ depending on the

parallel or orthogonal surround, or compared to the isolated target. This result also replicated previous findings that have shown weakened LI functioning in SZ. Specifically, previous studies have demonstrated that patients with SZ are immune to the SS effect. In a contrast matching task, Dakin and colleagues (2005) have found that, contrary to healthy controls, contrast perception in patients with SZ is not affected by the presence of the surround. Yoon and colleagues (2009) further demonstrated that the SS abnormalities in SZ are also observed when varying the orientation of the surround towards the target. Patients with SZ seem not to show decreased contrast perception when target items are embedded in a parallel compared to an orthogonal surround. Thus, our result in contrast matching task seems to be in line with the current literature. Contrary to controls, the parallel surround did not induce decreased contrast perception in our SZ sample.

Surround suppression effects on orientation perception were also explored with an orientation discrimination task. Over two consecutive intervals two target gratings, embedded either in a parallel or in an orthogonal surround, were shown with different orientations and participants had to judge whether the orientation of the target in the second interval was rotated in a clockwise or anti-clockwise direction compared to the first interval. Results in this task did not show a consistent pattern. Specifically, in healthy populations of experiment 1 and 2, orientation discrimination did not differ depending on the parallel and orthogonal surround condition. In contrast, the healthy cohort of experiment 3 showed a surround effect. Specifically, in the parallel surround condition, compared to the orthogonal, participants needed a larger tilt in order to discriminate between two orientations. Thus, in this cohort, consistently with the contrast matching results, the parallel surround seems to have altered orientation perception of the central target to a greater extent compared to the orthogonal surround. The surround suppression effect on orientation discrimination seems to be susceptible to large inter-individual variability (Clifford, 2014; Howard, 1982; Solomon & Morgan, 2009). Moreover, it has been demonstrated that participants that have a lower orientation discrimination threshold are also less likely to be affected by the SS effect (Song, Schwarzkopf, & Rees, 2013). This claim was confirmed by comparing participants from experiment 1 with participants from experiment 3. Specifically, participants from experiment 3 showed a significant higher OD threshold compared to participants from experiment 1. Indeed, only participants from experiment 3 showed a SS effect on perceived orientation, but not participants from experiment 1.

In experiment 2, both patients and controls did not show a SS effect on OD threshold. This is in line with previous studies showing that SS effects on OD threshold seem not to differ between patients and controls (Tibber et al., 2013). However, independently from the SS conditions, patients with SZ showed an overall higher OD threshold compared to controls indicating that, both in the parallel and in the orthogonal condition, patients needed a larger tilt in order to discriminate between two subtle orientations.

In sum, as suggested by the current literature, SS affects perceived contrast only in healthy controls, but not in patients. Inter-individual variability was found in the OD task. Specifically, participants that showed a lower overall OD threshold also did not show the SS effect. Although it was found no SS modulation on OD in schizophrenia, patients' overall OD threshold was significantly higher compared to healthy controls.

LI effects on working memory

The main aim of this project was to test whether LI can affect WM performance, both in healthy controls and in SZ patients. For experiment 1 and 2 a delayed matching to sample WM task was developed in which participants were asked to memorise the orientation of up to three gratings embedded either in a parallel or in an orthogonal surround. After a short delay, a probe gabor (without the surround) was presented and participants were asked to indicate whether the orientation of the probe matched or did not match the orientation of one of the items in the test set. For experiment 3, the paradigm was slightly adjusted in order to meet the experimental question. The results of this task will be discussed later in the chapter.

As expected, both for participants in experiment 1 and for controls in experiment 2, WM performance decreased with the increment in load. In addition, both in experiment 1 and 2, for healthy participants SS effects on WM performance depended on memory load. Specifically, in experiment 1 and in control population of experiment 2, in Load 1 condition accuracy for parallel surround was lower compared to the orthogonal surround. Given the low load condition, this result might be attributed to a perceptual effect induced by the surround, which is probably not related to WM processing. However, in the healthy controls cohort in experiment 2, accuracy was higher for parallel compared to the orthogonal surround in Load 3 condition. It is believed that LI contributes to the precision of sensory representation by, for example,

heightening differences in orientation discontinuity or by enhancing the identification of the targets (Bakin et al., 2000; Colin Blakemore & Tobin, 1972; Calford & Semple, 1995; Carandini & Heeger, 2012; Coen-Cagli et al., 2015; Knierim & van Essen, 1992; Laskin & Spencer, 1979; Mountcastle, 1975; Nelson & Frost, 1978; Sutter & Loftus, 2003; Von Békésy, 1967; Walker et al., 1999). For example, Coen-Cagli et al. (2015) recorded single unit spike activity from three monkeys visual cortex during the display of natural images. They found stronger suppression in V1 for homogeneous compared to heterogeneous images. The authors concluded that SS is needed to efficiently encode images that present homogeneous characteristics (Coen-Cagli et al., 2015). Differently from the current experiments, in this study the authors tested SS effects on natural images. Nevertheless, the parallel surround condition was still intended to induce stronger LI mechanisms since the orientation of the target was closer to the orientation of the surround. Thus, since in Load 3 condition of this experiment's task more than one item had to be encoded, LI might have facilitated the identification of the target orientation, probably by heightening the memory internal representations. However, SS effects on high WM load were not consistent, since they were found only in the control population of experiment 2. Control participants of experiment 2 had to be matched with the patients' population. Therefore, compared to experiment 1, the recruitment for this population was controlled for age, gender and years of education. Despite performance from control participants of experiment 2 and participants of experiment 1 was not statistically different, it is suggested that the demographic factors might have somewhat influenced this discrepancy in the results. For example, evidence has shown that the surround suppression effects might change in different age ranges. While some studies have found increased suppression effects in older adults compared to a younger cohort (Karas & McKendrick, 2015; Wang, Yu, Fu, Tzvetanov, & Zhou, 2018), other experiments have found opposite results with surround suppression being reduced with older compared to younger adults (Betts, Sekuler, & Bennett, 2009; Nguyen & McKendrick, 2016). Nevertheless, evidence suggests that surround suppression effects can change throughout the lifespan in healthy populations. Therefore, given the large age variability between the populations of experiment 1 and 2, it is suggested that age might have influenced the results.

Moreover, only in experiment 1, a negative correlation between the overall OD performance and accuracy in Load 3 condition was found. This correlation seems to

suggest that in Load 3 condition, when memory demand was presumably higher, better WM accuracy was associated with lower OD threshold (i.e. higher OD skills). Recent evidence has highlighted the important contribution of low-level processing to higher-order cognition. Specifically, WM studies supporting the sensorimotor recruitment models have suggested that basic perceptual mechanisms are active also during WM processing and, as such, can influence the overall performance (Albers et al., 2013; D'Esposito & Postle, 2015; Harrison & Tong, 2009; Magnussen, 2000; Magnussen & Greenlee, 1999; Pasternak & Greenlee, 2005; Zaksas et al., 2001). In line with these studies, this result seems to suggest that basic sensory abilities, such as OD skills, can support WM performance.

In experiment 2, SS effects on WM accuracy in SZ were not observed. Overall, patients showed significantly lower performance and higher response times compared to controls. Similarly to controls, patients' performance decreased with the increment in memory load. However, in contrast with controls, WM accuracy did not differ depending on the parallel or orthogonal surround. Similarly to the contrast matching task, WM accuracy in patients was not affected by SS. In addition, it was found that the overall OD threshold for patients was significantly higher compared to healthy controls. Moreover, patients' WM performance negatively correlated with overall OD threshold, indicating that patients that showed lower OD skills, also showed lower performance in the WM task. This also seems to be in line with a body of evidence that has proposed that WM deficits observed in SZ might not be exclusively related to dysfunctional top-down mechanisms. In fact, encoding processes, during which basic sensory perceptual activity is involved, can actively contribute to WM deficits observed in the disease (Butler et al., 2008; Dias, Butler, Hoptman & Javitt, 2011; Haenschel et al., 2007; Haenschel & Linden, 2011; Javitt, 2009; Javitt & Freedman, 2014; Lee & Park, 2005).

Nevertheless, a surround modulation of response times in patients was found. Specifically, in the patients' cohort, response times were faster for parallel surround both in Load 1 and Load 3 conditions. Moreover, whereas in experiment 1 response times did not differ with load, in experiment 2 response times became faster with the increment of memory load in both groups. This is in contrast with what it is typically found in WM studies (Haenschel et al. 2007). Nevertheless, since accuracy was above 50% correct for all participants, it seems unlikely that this result is due to the

inadequacy of the paradigm. Specifically, since accuracy was above chance, it seems implausible that participants were not able to perform the task, or misunderstood the instructions. In the limitation section of this chapter, potential explanations for this result are discussed.

In sum, WM results from experiment 1 and 2 highlighted that SS effects do not directly affect WM performance, both in healthy populations and in patients with SZ. However, overall higher OD skills were associated with better WM both in healthy populations and in patients with SZ, suggesting the importance of basic perceptual abilities during WM processing.

ERPs results.

In experiment 1 and experiment 2, EEG data were also collected. For this project, the analysis of the ERPs has been particularly useful since it allowed to explore surround suppression and memory load effects during the encoding and retrieval phases of WM. In the next section, ERPs results found in experiment 1 and 2 at encoding and retrieval will be summarised.

Encoding

During encoding, both for experiment 1 and 2, C1 was observed at Oz electrode. C1 is typically elicited by items with very basic visual perceptual features (Luck, 2005). Moreover, C1 polarity can be positive or negative depending on the location in which the stimulus is presented (Hansen et al., 2016; Luck, 2005). However, it has been found that when stimuli are displayed in the fovea C1 has a negative polarity (Hansen et al., 2016). Likewise, since the stimuli were displayed in the centre of the screen, C1 was observed with a negative polarity. Moreover, only in experiment 2, C1 amplitudes increased with the increment of memory load. This effect was not explained by demographical differences in the samples. Although this result might suggest increasing attentional processing, this interpretation is in contrast with previous evidence that has related C1 to purely perceptual, but not attentive processing (Di Russo et al., 2003). Di Russo, Martinez, & Hillyard (2003) showed participants a circular checkerboard displayed in four different locations. An arrow indicated to participants which one of the four locations they had to attend to. They found that C1 amplitudes

for the attended location did not differ from the amplitudes for the unattended location. Thus, they concluded that C1 is not modulated by attention. However, this study has tested spatial attention but not in the context of WM processing. Future studies will need to account for the variability of C1 amplitudes in different populations in response to an increasing number of items during WM encoding.

At lateral posterior electrodes, P1 and N1 were elicited. In Experiment 2, P1 and N1 were modulated by memory load for both controls and patients. In contrast with previous evidence that has found an increment of P1 amplitudes associated with memory load (Haenschel et al., 2007), here P1 amplitudes decreased with the increment of memory load. Despite Haenschel and colleagues (2007) also used a delayed matching to sample WM task, they presented abstract shapes with a presentation time of 600ms. The difference in the nature of the stimuli might explain the discrepancy in the memory load result. However, in experiment 2 it was found that whereas P1 decreased with memory load, N1 amplitudes increased with a higher number of items to encode. It is proposed that these opposite effects might reflect different attentional modulation. Top-down attention operates both by enhancing task-relevant items and suppressing irrelevant information (Gazzaley & Nobre, 2012; Noonan et al., 2017). Both P1 and N1 have been associated with attentional mechanisms. For example, in studies testing spatial attention, P1 has been found to be enhanced in invalid compared to neutral trials which required higher inhibition of irrelevant information. In contrast, N1 was enhanced in valid compared to neutral trials, which required enhancement of relevant information (Hillyard et al., 1998; Luck et al., 1994; Luck & Hillyard, 1995). Although these studies have tested spatial attention but not WM, it is suggested that this P1-N1 result might be in line with this interpretation. Specifically, in the higher load conditions of this experiment's task (Load 2 and 3), participants needed both to encode a larger number of items but also to suppress a larger number of surrounds, since participants knew that the surround was irrelevant for the subsequent recall. Thus, it is proposed that the P1-N1 result might reflect these parallel mechanisms. The decrement of P1 amplitudes might reflect the suppression of an increasing number of irrelevant information, whereas N1 increment might reflect a larger deploy of attentional resources associated with an increasing number of items to encode.

Surround effects at encoding were found with posterior P2. For participants in experiment 1, P2 amplitudes were lower for the parallel compared to the orthogonal

surround. This effect was marginally found also for control participants in experiment 2. In addition, both in experiment 1 and 2, P2 amplitudes positively correlated with the contrast matching only for parallel but not for the orthogonal surround. Thus, P2 seemed to respond to LI mechanisms in healthy population. Previous evidence has associated P2 with stimulus saliency (Machilsen et al., 2011; Straube & Fahle, 2010). Instead of specifically addressing SS effects, these studies have tested contour integration in the context of an iso-oriented compared to a randomly oriented background. They showed that P2 amplitudes were lower with highly salient stimuli (Machilsen et al., 2011; Straube & Fahle, 2010). In both papers, the authors suggested that differences in the allocation of attentional resources might explain P2 amplitudes differences. Here P2 was lower for the parallel surround. It has been proposed that highly salient stimuli are the ones that need less attentional demand since the perceived difference between the target and the background is larger (Itti & Koch, 2001). Thus, in this experiment, the orthogonal surround items might be considered as more salient since the orientation difference between the target and the surround is larger. However, here P2 amplitudes were lower for the less salient stimuli (parallel surround condition). Thus, it is suggested that the P2 amplitudes decrement with the parallel surround might reflect a perceptual effect associated with the more suppressive activity exerted from the parallel surround.

In contrast, P2 amplitudes in SZ patients were not modulated by the two different surrounds, suggesting poor perceptual discrimination processing. Wang, Dobkins, Mcdowell, & Clementz (2012) have found decreased P2 in SZ during perceptual discrimination task. They tested a group of chronic SZ patients and a group of healthy controls on a speed discrimination EEG task in which two vertical sinusoidal gratings, showed over two intervals, moved away from fixation in a horizontal direction. Participants had to indicate which of the two gratings was the fastest. The authors found that, in relation to the second stimulus, P2 amplitudes were significantly reduced in patients compared to controls. In contrast, patients showed an enhanced later component (specifically, N2) which also correlated with their behavioural performance. The authors suggested that perceptual discriminatory processes in SZ are delayed since they occurred at a later time (with N2 instead of P2) compared to controls. A similar effect was also observed in the ERPs results of this study. Specifically, in patients, surround effects were found not with P2 but during late

encoding with SW activity. SW activity, both at frontal and at visual electrodes, was higher for parallel compared to orthogonal surround specifically in Load 1 condition. Even though in the SW time window the stimuli were no more physically present on the screen, only patients but not controls, still showed a SS modulation. It is suggested that this result might reflect slowed encoding processes in SZ (Hartman et al., 2002; Tek et al., 2002; Wang et al., 2012). However, Wang and colleagues (2012) found delayed processing during a speed discrimination task, but not in the context of WM processing. Moreover, surround effects on SW activity were found only in Load 1 condition. Thus, this SW result in SZ is open to alternative interpretations. Previous studies have found that, compared to controls, SW activity (specifically CDA) in patients with schizophrenia decreased with the increment of memory load (Leonard et al., 2013b). In a change detection WM paradigm, patients with SZ and healthy controls saw groups of one, three or five coloured shapes. The groups of shapes appeared both on the right and on the left side of the screen, but participants were required to memorise the colours of the objects only one of the two sides. After a delay, the shapes re-appeared on the screen and participants had to judge whether the colour of the shapes in the target side had changed or not. They found that CDA activity was higher at Load 1 and lower at Load 3, only in patients. The authors suggested that patients lack in distributing attention broadly (Leonard et al., 2013b). In fact, evidence has suggested that patients with SZ tend to hyperfocus only on a subset of information (Gray et al., 2014; Kreither et al., 2017). In the current study it has been found that, in SZ patients, SW decreased with the increment of memory load in the parallel surround condition. Thus, this SW result might also reflect hyperfocusing on a subset of internal representations. However, since this decrement was found only in the parallel but not in the orthogonal surround, this result further suggests that difficulties in sustained attention in SZ might be also influenced by the perceptual features of the items.

In sum, ERPs results at encoding suggest that P2 component seems to respond to LI effects in healthy population, but not in patients. In contrast, in patients with SZ, SS effects are not observed with P2 components but during late encoding with SW activity, suggesting that perceptual discrimination processes are poor in SZ.

Retrieval

At retrieval, a single gabor (without the surround) was presented. Instead of C1 and P2, P1 and N1 were observed at occipital electrodes in response to the probe.

In experiment 1, P1 amplitudes decreased with memory load. As suggested for encoding, this result might be related to inhibitory mechanisms (Hillyard et al., 1998; Luck et al., 1994; Luck & Hillyard, 1995). Specifically, at higher WM load a larger number of irrelevant items needed to be suppressed. Similarly to encoding, in experiment 1 and 2 (both for patients and controls) it was found that N1 amplitudes increased with the increment of memory load. As proposed for encoding this result might instead reflect increased attentional demand (Hillyard et al., 1998; Luck et al., 1994; Luck & Hillyard, 1995). However, previous studies have also found an increased activity with memory load at retrieval, but with N2 instead of N1 amplitudes. In a delayed matching to sample WM task, Pinal et al. (2014) showed to participants a white rectangular domino tiles filled with up to six black dots. After a delay, another domino tile was presented as a probe and participants had to judge whether the dots matched or did not match with the previously encoded one. Memory load was manipulated by varying the number of the black dots on the domino tiles. They found that, at retrieval, N2 amplitudes increased with memory load. The authors suggested that this result was associated with comparison processes between the presented probe and the internal memory trace. Moreover, the authors also interpreted this result as reflecting a larger attentional demand required in higher loads conditions (Pinal et al., 2014). N1 result of this study might also be in line with this interpretation. Although Pinal et al., (2014) results are related to N2 instead of N1, the very different nature of stimuli used might account for the discrepancy in the findings. Thus it is suggested that N1 increment with memory load at retrieval might be associated with comparison processes between the probe and the internal memory representations. This seems to be further confirmed by the surround effect found with N1 amplitudes at retrieval, both in experiment 1 and 2 (both for patients and controls).

Although at retrieval the surround was not physically present, N1 amplitudes were higher for parallel compared to the orthogonal surround. N1 component has been previously associated with stimulus discrimination (Vogel & Luck, 2000). Vogel and Luck (2000) found that N1 amplitudes were larger when participants had to identify a specific stimulus over a set of items, compared to when they just had to detect the simple appearance of any item. The authors suggested that N1 is associated with some

sort of stimulus discrimination processes (Vogel & Luck, 2000). Thus, the modulation of N1 amplitudes depending on the two surrounds might be interpreted as reflecting stimulus discrimination processes. Additionally, in studies testing contour integration, N1 amplitudes have been found to be increased with items embedded in a more coherent background, a condition considered more salient and therefore easier to perceive (Machilsen et al., 2011). Thus, alternatively, N1 result at retrieval might also be interpreted as reflecting higher perceptual saliency of the orthogonal surround stimulus.

In experiment 2, only P1 activity in patients with SZ differed from controls. Specifically, P1 amplitudes for parallel surround were lower compared to orthogonal only in Load 1 condition. P1 has been previously associated with attentional mechanisms (Kappenman & Luck, 2012b; Luck, 2005; Luck, Woodman, & Vogel, 2000). In SZ, P1 has been associated with hyperfocusing of attention (Gray et al., 2014; Kreither et al., 2017; Leonard et al., 2013b). For example, in a double oddball paradigm, Kreither and colleagues (2017) showed to patients with SZ and healthy controls one coloured square which, in different blocks of trials, could appear either in the centre of the screen or in one of four peripheral locations. Participants were instructed to attend either to the centre of the screen or to the four peripheral locations and to signal the presence of the square. They found that when participants had to attend centrally, in patients with SZ P1 amplitudes were higher for stimuli appearing in the periphery. However, for stimuli appearing centrally, P1 amplitudes did not differ within conditions, suggesting that patients were not able to filter out stimuli presented centrally when they needed to be ignored. The authors suggested that patients showed a hyperfocus of attention towards stimuli that were presented centrally, even when they were task-irrelevant (Kreither et al., 2017). This study somewhat relates to our P1 result at retrieval. Although spatial attention was not specifically tested and although all of the stimuli were presented centrally, patients showed higher P1 amplitudes in relation to a subset of representation (the orthogonal surround stimuli). Thus, it is proposed that this result might reflect a hyperfocus of attention towards stimuli that were probably easier to perceive. Alternatively, since this surround modulation was more pronounced only in Load 1 condition, this P1 result might also be interpreted as a simple suppressive effect induced by the previously displayed parallel surround.

In sum, ERPs results at retrieval showed that, although the surround was not physically present, N1 amplitudes were lower for the parallel compared to the orthogonal surround condition. This might be indicative of comparison processes between the probe and the internal memory trace. However, N1 activity did not differ between patients and controls, suggesting that during the retrieval phase, patients' ERP activity was similar to controls.

The relationship between WM and clinical symptoms and quality of life

In experiment 2, it was also explored whether the WM results observed in this experiment's task for patients were related to standardised measures of WM in SZ and with clinical symptoms and quality of life. Participants in experiment 2 performed the Paired Associate Learning (PAL) and the Spatial Working Memory (SWM) tests from the CANTAB battery for schizophrenia (Barnett et al., 2010). The error rate for patients was higher compared to controls only in the PAL, but the two populations did not differ in the SWM. This seems to be in contrast with previous studies that have found diffuse WM deficits in SZ independently from modality (Lee & Park, 2005). However, a meta-analysis that specifically addressed CANTAB tests findings in schizophrenia revealed that, compared to first-episode SZ, long-term patients performance tend to be more heterogeneous in the SWM test (Stip et al., 2008). For example, Elliott, McKenna, Robbins, & Sahakian (1998) tested outpatients with SZ with relatively preserved intellectual functions (measured with the National Adult Reading Test – NART). They found that, compared to healthy controls, patients with SZ were not severely impaired in the CANTAB SWM test. This evidence suggests that spatial WM deficits in SZ might change over the course of illness (Stip et al., 2008).

In this experiment, outpatients were recruited that, according to the PANSS results, were stable and did not show clinical symptoms at the time of the test. Evidence has suggested that, compared to inpatients, outpatients tend to show better neurocognitive functions particularly for speed of processing, visual attention and working memory (Comparelli et al., 2012; Kurebayashi & Otaki, 2018; Trampush et al., 2015). Thus, their clinical status might account for the lack of impairment in the SWM CANTAB test. Nevertheless, it has been still found that performance in the CANTAB test was associated with the performance of this experiment's WM task. Patients that

made more errors in the CANTAB tests also performed worse in the WM task. Moreover, despite patients were clinically stable, their performance was still significantly lower compared to a healthy population in our WM task, which specifically targeted basic visual dysfunctions in WM. This supports the view that WM deficits are persistent in SZ also when patients are not experiencing clinical symptoms (Barch, 2006; Butler et al., 2008; Haenschel & Linden, 2011; Javitt, 2009; Javitt & Freedman, 2014; Lee & Park, 2005). Moreover, this result also highlights that even when patients are clinically stable, they might still show impairments in WM tasks in which specific basic perceptual processes are involved.

Finally, in experiment 2 the quality of life for the patients' cohort was also measured with the MANSA questionnaire. Patients were neither satisfied nor dissatisfied with their quality of life. In addition, MANSA results did not correlate with our WM task. Previous studies have associated WM performance in SZ with objective measures of quality of life, such as work/education status (Shamsi et al., 2011). However, the MANSA questionnaire assessed a more subjective evaluation reported by the patients regarding their quality of life status (Priebe & Fakhoury, 2008; Priebe et al., 2010, 2011). Thus, it might be concluded that in patients that reported an average quality of life status, WM decreased abilities did not interfere with everyday living.

LI and attention

The results from experiment 1 and 2 left unclear whether LI effects observed in WM performance in Load 1 condition are related to attention. Specifically, it has been proposed that LI enhances the representation of visual items (Arnsten, 2013; Butler et al., 2008; Sachdev et al., 2012). However, in experiment 1 and 2 it was found that in Load 1 condition, in which attentional resources were presumably focused on a single representation, stronger LI decreased WM performance. Thus, it was hypothesised that when attention is heightened, LI mechanisms might interfere more heavily with the recollection of memory information.

This hypothesis was tested in a behavioural experiment (Experiment 3) which was aimed to explore whether enhanced LI mechanisms interfere with a heightened focus of attention. For experiment 3, in addition to the contrast matching and orientation discrimination tasks which results have been commented above in this chapter, a modified version of the working memory task was used in order to specifically

modulate attention. The task was a delayed matching to sample in which participants were asked to memorise the orientation of three gratings embedded either in a parallel or orthogonal surround. After a delay, a probe grating without the surround was shown and participants had to judge whether the orientation matched or did not match one of the orientations previously shown (NoCue condition). Crucially, in half of the trials, a pre-cue appearing before the memory test set indicated which of the three gratings had to be memorised (Cue condition). With this design, participants were required to focus their attention on one specific item while ignoring the others. In line with previous literature (Gazzaley & Nobre, 2012; Griffin & Nobre, 2003), it was found that WM performance was higher when the cue was present compared to the NoCue condition, suggesting that WM performance benefits from a heightened focus of attention. This result seems to be in line the biased competition theory of attention by Desimone and Duncan (Desimone & Duncan, 1995) which suggests that attention operates in order to select a target stimulus among a series of distractors.

Moreover, position effects were also observed. The items that were cued in the first position were less remembered than items cued in the last position. This result might be attributed to recency effects in which the last encoded item tend to be better recalled compared to the others. This effect has been repeatedly found in WM literature and it has been explained as a tendency of the focus of attention to be easily dominated by the most recently perceived item (Allen et al., 2006; Hay et al., 2007; Hitch et al., 2018; Phillips & Christie, 1977).

Surround effects were found in Cue trials for response times and hit rate. Specifically, response times for the parallel surround were slower compared to the orthogonal surround. This seems to be in line with previous evidence that has investigated SS effects on WM (Kiyonaga & Egner, 2016). Kiyonaga & Egner (2016) showed participants two circles of different colours presented over two consecutive intervals. After a delay, a cue indicated which of the two circles had to be matched with a subsequent probe. After the cue, a probe circle appeared whose colour could gradually range from a perfect match to the hue of the test to a completely dissimilar colour. They found that response times were slower when the colour of the probe was more closely similar to the colour of the test. However, response times were faster when the colour of the probe was either identical or more dissimilar to the colour of the test. The authors interpreted the result as a reflection of attentional mechanisms on WM. Specifically, they suggested that attention operates on WM contents in a center-surround

organisation, i.e. by enhancing relevant information and suppressing irrelevant information (Kiyonaga & Egner, 2016). This response times finding seems to be in line with these results. When the center-surround inhibition was stronger (parallel surround condition) response times were slower, probably reflecting attentional effects on WM performance.

In addition, a position effect was also observed for the hit rate in the parallel surround condition. Participants showed a higher percentage of hit rate for the last item cued compared to the second, only in the parallel surround condition. For the orthogonal surround, hit rate was not affected by the position of the encoded item. Recent studies have demonstrated that the focus of attention can be vulnerable to the presence to a perceptually salient, although irrelevant, item (Hitch et al., 2018). Hitch, Hu, Allen, & Baddeley (2018) tested participants on a WM task in which four coloured shapes were presented at four corners of an invisible square. During the delay, a distracting stimulus appeared in half of the trials. At retrieval, participants saw either a colour or a shape and they had to verbally name the corresponding shape (or colour) previously encoded. Crucially, they prioritised the item in the second position in order to heighten the focus of attention. They found that the prioritised item was better recalled compared to the others, even when the distractor was presented during the delay. However, the items in the other positions were worse recalled when the distractor was present. The authors concluded that the focus of attention can still be accessed by a perceptually distracting item, even though it is irrelevant for task purposes (Hitch et al., 2018). It is proposed that this result in experiment 3 is in line with this claim. With a heightened focus of attention, WM traces may be more susceptible to the interference of SS effects. Specifically, SS might have rendered the memory trace more fragile, thus facilitating inter-stimulus interference mechanisms.

In sum, it is suggested that LI activity interferes with a heightened focus of attention. Specifically, stronger center-surround suppression might have facilitated inter-stimulus interference mechanisms.

Limitations and future directions

Overall, this project shed lights on the impact of basic sensory processes on WM performance both in healthy and in patients with schizophrenia. Although the

experiments were designed attempting to avoid all the potential confounds, a number of limitations were, of course, encountered.

Firstly, as far as it is known, this is the first study that applies stimuli that specifically target SS in a WM task both in healthy and in a population of patients with schizophrenia. Thus, despite most of the results were associated with relatively large effect sizes, these findings need to be interpreted with caution. In order to rely on the results, this paradigm with these specific stimuli needs to be further tested on additional populations. Moreover, sample sizes in the experiments of this project were relatively small. Small sample sizes might inflate effect sizes and this might decrease confidence in the reliability of the data (Button et al., 2013). Therefore, future studies might attempt to re-test this paradigm with larger sample sizes in order to ensure reproducibility.

Secondly, although previous literature has proposed that LI enhances stimuli perception by facilitating the perception of orientation discontinuity, contours or by favouring the identifications of targets via pop-out mechanisms (Allman et al., 1985; Bakin et al., 2000; Blakemore & Tobin, 1972; Calford & Semple, 1995; Coen-Cagli et al., 2015; Gilbert & Wiesel, 1990; Knierim & van Essen, 1992; Laskin & Spencer, 1979; Levitt & Lund, 1997; Mountcastle, 1975; Nelson & Frost, 1978; Sutter & Loftus, 2003; Von Békésy, 1967; Walker et al., 1999), some of our results seem to be in contrast with this claim. For example, in experiments 1 and 2 it was observed that when only one item needed to be encoded, LI actually decreased WM performance. However, in experiment 2, in Load 3 condition LI increases WM performance. Future studies will need to better clarify whether LI facilitates or hinder the formation of memory representations. For example, future experiments might attempt to strengthen the SS effect by decreasing even more the orientation difference between the target and the surround. In addition, future studies might also investigate overall SS effects on WM. Specifically, in the current task, the orthogonal surround was considered as a “control” condition in which SS mechanisms were weakened. However, the simple presence of the surround still triggers SS. Thus, future studies might attempt to include also a “no-surround” condition. This would allow clarifying whether the presence of the surround (independently from the parallel or orthogonal condition) impact WM performance compared to trials that do not trigger LI effects.

A further limitation encountered in experiment 2 concerns the response times (RT). In contrast to the expectations, RT became faster with the increment of memory load, especially for the patients' population. Since accuracy was above 50% for all participants, it is unlikely that this result suggests that participants were not able to perform the task. Nevertheless, this RT effect needs further investigation. Future studies might attempt to adjust some parameters in order to limit this effect. For example, although the upcoming appearance of the probe was signalled (by presenting a white fixation dot during the delay period), it might have been unexpected for some participants, especially for Load 1 and 2 conditions. This might have affected their reaction times. Thus, future studies might attempt to signal the display of the probe more distinctively in order to ensure that participants have a clear expectation of the upcoming stimulus.

In this experiment, a multiple of the individual supra-threshold contrast level, to apply in the WM task, was calculated. However, it was observed that OD (and not CM) correlated with WM performance, suggesting a relationship between OD and the WM task. Future studies might attempt to adjust the individual threshold for orientation discriminability, instead of contrast. This would allow testing more precisely whether SS mechanisms have an impact on the subjective OD threshold during WM processing. Moreover, it was also observed that the OD threshold was decreased in SZ and that OD performance was associated with WM. Thus, future studies might attempt to develop OD visual training in order to verify whether increasing OD skills in SZ also improve WM performance.

A further limitation of the study concerns the different ERPs result observed between participants from experiment 1 and controls from experiment 2. As outlined in Chapter 4, it seems that for most of the ERPs these differences might be attributed to a cumulative effect of demographic factors such as age, gender and years of education. However, these factors did not clearly explain all the discrepancies (for example for C1 and N1). Thus, in order to be able to generalise the results, future experiments might need to recruit more homogeneous samples in terms of demographic characteristics. Moreover, further WM experiments might need to account for the potential sensitiveness of C1 to memory load.

Patients of the current sample were relatively clinically stable and reported an average quality of life. Future studies might attempt to apply this experimental design to a population of first episode SZ or to patients with more severe symptoms. This would allow exploring whether LI effects on WM might differ in SZ populations with different degrees of clinical symptoms, or whether these effects are independent of symptomatology.

Finally, here a relationship between WM performance and quality of life was not found. Future studies might attempt to further investigate the quality of life in patients with SZ and its relationship with cognitive functions. Previous studies have found that WM performance was associated with work status (Shamsi et al., 2011). However, since the patients in this sample were mostly unemployed, there was not enough variability to verify whether the work status was related to WM performance in our task. Future studies might attempt to recruit patients' samples that are more heterogeneous in terms of quality of life factors.

Conclusions

Overall, this project aimed to explore LI effects on WM performance both in healthy populations and in patients with schizophrenia. Moreover, we also explored whether LI activity interferes with attention during WM processing.

In line with previous studies, it was confirmed that the SS effect altered contrast perception only in controls but not in patients. Moreover, patients' WM performance was lower compared to controls, and it did not differ depending on the two surround conditions. In addition, it was found that higher OD skills were associated with better WM performance both in healthy and in SZ patients, suggesting that basic perceptual abilities support WM.

Posterior P2 amplitudes were decreased with stronger LI only in healthy controls, but not in patients. However, during late encoding, SW activity was higher with stronger LI, only for patients but not for controls. It has been proposed that this result might suggest slowed and unprecise encoding processes. At retrieval, N1 increased with memory load and it was higher with stronger LI mechanisms both for healthy controls

and for patients. However, only for patients surround effects were observed earlier in time with P1. These findings at retrieval might indicate that attentional and stimulus discriminatory mechanisms are distributed differently between patients and healthy controls. Patients might tend to hyperfocus on a subset of internal representations. Finally, in experiment 3 it was found that stronger LI mechanisms interfere with the focus of attention by heightening inter-stimulus interference mechanisms.

Overall, this project has showed that SS mechanisms seem not to influence WM performance. However, the overall OD threshold was significantly decreased in SZ and negatively correlated with WM performance. This suggests that decreased basic perceptual abilities might affect WM performance in SZ. Future studies might attempt to test whether training OD abilities can also improve WM performance in schizophrenia.

Appendices

Appendix 1: Positive and Negative Syndrome Scale (PANSS)

(Chapter 4 – Experiment 2, page 121)

The Positive and Negative Syndrome Scale (PANSS) is a highly validated scale to assess clinical symptoms in schizophrenia (Kay et al., 1987). The scale consists of a Positive Scales of seven items, a Negative Scale of seven items and a General Psychopathology Scale of 16 questions. All items are assessed on a seven points Likert scale representing increasing levels of psychopathology where:

1 = absent; 2 = minimal; 3 = mild; 4 = moderate; 5 = moderate severe; 6 = severe; 7 = extreme

Here below we report a brief description of what each item assesses, as stated in the original PANSS.

Positive Scale

P1. Delusions. Beliefs which are unfounded, unrealistic and idiosyncratic.

P2. Conceptual disorganisation. Disorganised process of thinking characterised by disruption of goal directed sequencing (e.g. circumstantiality, loose associations, tangentiality, gross illogicality or thought block.

P3. Hallucinatory behaviour. Verbal report or behaviour indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory or somatic realms.

P4. Excitement. Hyperactivity as reflected in accelerated motor behaviour, heightened responsivity to stimuli, hypervigilance and excessive mood lability.

P5. Grandiosity. Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power and moral righteousness.

P6. Suspiciousness/Persecution. Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, distrustful attitude, suspicious hypervigilance or frank delusions that others mean harm.

P7. Hostility. Verbal and non-verbal expressions of anger and resentment, including sarcasm, passive-aggressive behaviour, verbal abuse and assualtiveness.

Negative Scale

N1. Blunted affect. Diminished emotional responsiveness as characterised by a reduction in facial expression, modulation of feelings and communicative gestures.

N2. Emotional withdrawal. Lack of interest in, involvement with, and affective commitment to life events.

N3. Poor rapport. Lack of interpersonal empathy, openness in conversation and sense of closeness, interest or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and non-verbal communication.

N4. Passive/apathetic social withdrawal. Diminished interest and initiative in social interactions due to passivity, apathy, anergy or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living.

N5. Difficulty in abstract thinking. Impairment in the use of abstract symbolic mode of thinking, as evidenced by difficulty in classification, forming generalisations and proceeding beyond concrete and egocentric thinking in problem solving tasks.

N6. Lack of spontaneity and flow of conversation. Reduction in the normal flow of communication associated with apathy, avolition, defensiveness or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal interactional process.

N7. Stereotyped thinking. Decreased fluidity, spontaneity and flexibility of thinking, as evidenced in rigid, repetitious or barren thought content.

General Psychopathology Scale

G1. Somatic concern. Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease.

G2. Anxiety. Subjective experience of nervousness, worry or apprehension ranging from excessive concern about the present or future to feelings of panic.

G3. Guilt feelings. Sense of remorse or self-blame for real or imagined misdeeds in the past.

G4. Tension. Overt physical manifestation of fear, anxiety and agitation, such as stiffness, tremor, profuse sweating and restlessness.

G5. Mannerisms and posturing. Unnatural movements or posture as characterised be an awkward, stilted, disorganised, or bizarre appearance.

G6. Depression. Feeling of sadness, discouragement, helplessness and pessimism.

G7. Motor retardation. Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness of stimuli, and reduced body tone.

G8. Uncooperativeness. Active refusal to comply with the will of significant others, including the interviewer, hospital staff or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility or belligerence.

G9. Unusual thought content. Thinking characterised by strange, fantastic or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical and patently absurd.

G10. Disorientation. Lack of awareness of one's relationship to the milieu, including persons, place and time, which may be due to confusion or withdrawal.

G11. Poor attention. Failure in focused alertness manifested by poor concentration, distractibility from external and internal stimuli, and difficulty in harnessing, sustaining or shifting focus to new stimuli.

G12. Lack of judgement and insight. Impaired awareness and understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognise past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalisation or treatment, decision characterised by poor anticipation or consequences, and unrealistic short-term and long-range planning.

G13. Disturbance of volition. Disturbance in the wilful initiation, sustenance and control of one's thoughts, behaviour, movements and speech.

G14. Poor impulse control. Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary or misdirected discharge of tension and emotions without concern about consequences.

G15. Preoccupation. Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behaviour.

G16. Active social avoidance. Diminished social involvement associated with unwarranted fear, hostility, or distrust.

Appendix 2: The Manchester Short Assessment of Quality of Life (MANSA)

(Chapter 4 – Experiment 2, page 125)

Section 1

Date of birth

Gender 1=Male, 2=Female

Ethnic origin 1=White,

2=Black Caribbean

3=Black African

4=Black Other

5=Indian

6=Pakistani

7=Bangladeshi

8=Chinese

9=Other

Diagnosis Use ICD 10, DSM-IV or any other coding system that is in place in your service

Section 2

In a first interview, ask all questions 1 to 9. In a repeat interview, ask first, whether there have been any changes in the respondent's circumstances as assessed in section 2. If the answer is yes, complete questions 1 to 9. If the answer is no, go straight to section 3 (question 10).

1. Age at leaving full time education

2. Employment status 1=In Paid employment

2=In sheltered employment

3=Training / education is main occupation

4=Unemployed

5=Retired

6=Other

If employed, ask questions 3 and 4, otherwise go straight to question 5

3. What is your occupation?

4. How many hours a week do you work?

5. What is your total monthly income after tax?

6. Which if any state benefits do you receive?

7. How many children (if any) do you have?

8. Who else (if anybody) do you live with?

1=Live alone

2=With partner

3=With parents

4=With child/children under 18

5=With child / children over 18

6=Other (please specify)

9. In which type of residence do you currently live?

01=House /flat (owner occupied)

02=House / Flat (Housing association)

03=House / flat (private rent)

04=Boarding Out (incl B&B)

05=Hostel, supported / group home

06=Sheltered housing,

07=Residential home

09=Hospital ward

10=No fixed abode

Section 3

All questions in this section are to be asked every time the instrument is applied.

10. How satisfied are you with your life as a whole today?*

11. How satisfied are you with your job (or sheltered employment, or training/education as your main occupation)?*

or if unemployed or retired

How satisfied are you with being unemployed / retired?*

12. How satisfied are you with your financial situation?*

13. Do you have anyone who you would call a "close friend"? 1=YES, 2=NO

14. In the last week have you seen a friend? (visited a friend, been visited by a friend, or met a friend outside both your home and work) 1=YES, 2=NO

15. How satisfied are you with the number and quality of your friendships?*

16. How satisfied are you with your leisure activities?*

17. How satisfied are you with your accommodation?*

18. In the past year have you been accused of a crime? 1=YES, 2=NO

19. In the past year have you been a victim of physical violence? 1=YES, 2=NO

20. How satisfied are you with your personal safety?*

21. How satisfied are you with the people that you live with?*

or if you live alone

How satisfied are you with living alone?*

22. How satisfied are you with your sex life?*

23. How satisfied are you with your relationship with your family?*

24. How satisfied are you with your physical health?*

25. How satisfied are you with your mental health?*

***Satisfaction Scale**

1	2	3	4	5	6	7
Couldn't be worse	***Displeased***	***Mostly Dissatisfied***	***Mixed***	***Mostly satisfied***	***Pleased***	***Couldn't be better***

Appendix 3: Edinburgh Handedness Inventory Questionnaire

(Chapter 4 – Experiment 2, page 122)

Handedness questionnaire

Instructions

For each of the activities below, please indicate:
Which hand do you prefer for that activity?
Do you ever use the other hand for the activity?

Which hand do you prefer to use when: Please tick the boxes.

Activity	left	No preference	right	Do you ever use the other hand? Yes/ No
Writing				
Drawing				
Throwing				
Using scissors				
Using a toothbrush				
Using a knife (without a fork)				
Using a spoon				
Using a broom (upper hand)				
Striking a match				
Opening a box (holding the lid)				
Holding a computer mouse				
Using a key to unlock a door				
Holding a hammer				
Holding a brush or comb				
Holding a cup while drinking				

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