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CICLO XXVIII

Biases in Visuo-Spatial Attention: from Assessment to Experimental Induction

Direttore della Scuola: Ch.ma Prof.ssa Francesca Peressotti

Supervisore :Ch.mo Prof. Marco Zorzi

Dottorando : Elvio A. Blini

To my father,

in loving memory.

“I was convinced that I understood her, and for this claim I gave myself a strange reason; this was that I understood my mother’s Singer sewing machine. At the age of ten I had dismantled the machine and put it together again. You pushed the wrought-iron treadle. This moved the smooth pulley, the needle went up and down. You pried up a smooth steel plate and there found small and intricate parts that gave off an odor of machine oil. To me the Señora was a person of intricate parts and smelled slightly of oil. It was on the whole a positive association. But certain bits were missing from her mind. The needle went up and down, there was thread on the bobbin, but the stitching failed to occur.”

Saul Bellow, *Humboldt’s gift*

ABSTRACT

In this work I present several studies, which might appear rather heterogeneous for both experimental questions and methodological approaches, and yet are linked by a common leitmotiv: spatial attention. I will address issues related to the assessment of attentional asymmetries, in the healthy individual as in patients with neurological disorders, their role in various aspects of human cognition, and their neural underpinning, driven by the deep belief that spatial attention plays an important role in various mental processes that are not necessarily confined to perception.

What follows is organized into two distinct sections. In the first I will focus on the evaluation of visuospatial asymmetries, starting from the description of a new paradigm particularly suitable for this purpose. In the first chapter I will describe the effects of multitasking in a spatial monitoring test; the main result shows a striking decreasing in detection performance as a function of the introduced memory load. In the second chapter I will apply the same paradigm to a clinical population characterized by a brain lesion affecting the left hemisphere. Despite a standard neuropsychological battery failed to highlight any lateralized attentional deficit, I will show that exploiting concurrent demands might lead to enhanced sensitivity of diagnostic tests and consequently positive effects on patients' diagnostic and therapeutic management. Finally, in the third chapter I will suggest, in light of preliminary data, that attentional asymmetries also occur along the sagittal axis; I will argue, in particular, that more attentional resources appear to be allocated around peripersonal space, the resulting benefits extending to various tasks (i.e., discrimination tasks).

Then, in the second section, I will follow a complementary approach: I will seek to induce attentional shifts in order to evaluate their role in different cognitive tasks. In the fourth and fifth chapters this will be pursued exploiting sensory stimulations: visual optokinetic stimulation and galvanic vestibular stimulation, respectively. In the fourth chapter I will show that spatial attention is highly involved in numerical cognition, this relationship being bidirectional. Specifically, I will show that optokinetic stimulation modulates the occurrence of procedural errors during mental arithmetics, and that calculation itself affects oculomotor behaviour in turn. In the fifth chapter I will examine the effects of galvanic vestibular stimulation, a particularly promising technique for the

rehabilitation of lateralized attention disorders, on spatial representations. I will discuss critically a recent account for unilateral spatial neglect, suggesting that vestibular stimulations or disorders might indeed affect the metric representation of space, but not necessarily resulting in spatial unawareness. Finally, in the sixth chapter I will describe an attentional capture phenomenon by intrinsically rewarding distracters. I will seek, in particular, to predict the degree of attentional capture from resting-state functional magnetic resonance imaging data and the related brain connectivity pattern; I will report preliminary data focused on the importance of the cingulate-opercular network, and discuss the results through a parallel with clinical populations characterized by behavioural addictions.

KEYWORDS

Unilateral Spatial Neglect; Visual Extinction; Spatial Attention; Multitasking; Attentional Load; Working Memory Load; Attentional Asymmetries; Psychological Refractory Period; Left Hemisphere Lesion; Neuropsychological Deficits; Stroke; Peripersonal Space; Virtual Reality; Optokinetic Stimulation; Mental Arithmetic; Eye Movements; Galvanic Vestibular Stimulation; Line Bisection; Subjective Straight Ahead; Subjective Visual Vertical; Vestibular Cortex; Spatial Representations; Reward; Attentional Capture; Value-driven Attentional Capture; Cingulate-Opercular Network; Clustering Coefficient; Resting-state fMRI; Brain Connectivity; Graph Analysis;

RIASSUNTO

In questo lavoro presenterò una serie di ricerche che possono sembrare piuttosto eterogenee per quesiti sperimentali e approcci metodologici, ma sono tuttavia legate da un filo conduttore comune: i costrutti di ragionamento e attenzione spaziale. Affronterò in particolare aspetti legati alla valutazione delle asimmetrie attenzionali, nell'individuo sano come nel paziente con disturbi neurologici, il loro ruolo in vari aspetti della cognizione umana, e i loro substrati neurali, guidato dalla convinzione che l'attenzione spaziale giochi un ruolo importante in svariati processi mentali non necessariamente limitati alla percezione.

Quanto segue è stato dunque organizzato in due sezioni distinte. Nella prima mi soffermerò sulla valutazione delle asimmetrie visuospaziali, iniziando dalla descrizione di un nuovo paradigma particolarmente adatto a questo scopo. Nel primo capitolo descriverò gli effetti del doppio compito e del carico attenzionale su un test di monitoraggio spaziale; il risultato principale mostra un netto peggioramento nella prestazione al compito di detezione spaziale in funzione del carico di memoria introdotto. Nel secondo capitolo applicherò lo stesso paradigma ad una popolazione clinica contraddistinta da lesione cerebrale dell'emisfero sinistro. Nonostante una valutazione neuropsicologica standard non evidenziasse alcun deficit lateralizzato dell'attenzione, mostrerò che sfruttare un compito accessorio può portare ad una spiccata maggiore sensibilità dei test diagnostici, con evidenti ricadute benefiche sull'iter clinico e terapeutico dei pazienti. Infine, nel terzo capitolo suggerirò, tramite dati preliminari, che asimmetrie attenzionali possono essere individuate, nell'individuo sano, anche lungo l'asse sagittale; argomenterò, in particolare, che attorno allo spazio peripersonale sembrano essere generalmente concentrate più risorse attentive, e che i benefici conseguenti si estendono a compiti di varia natura (ad esempio compiti di discriminazione).

Passerò dunque alla seconda sezione, in cui, seguendo una logica inversa, indurrò degli spostamenti nel focus attentivo in modo da valutarne il ruolo in compiti di varia natura. Nei capitoli quarto e quinto sfrutterò delle stimolazioni sensoriali: la stimolazione visiva optocinetica e la stimolazione galvanico vestibolare, rispettivamente. Nel quarto capitolo mostrerò che l'attenzione spaziale è coinvolta nella cognizione numerica, con cui intrattiene rapporti bidirezionali. Nello

specifico mostrerò da un lato che la stimolazione optocinetica può modulare l’occorrenza di errori procedurali nel calcolo mentale, dall’altro che il calcolo stesso ha degli effetti sull’attenzione spaziale e in particolare sul comportamento oculomotorio. Nel quinto capitolo esaminerò gli effetti della stimolazione galvanica vestibolare, una tecnica particolarmente promettente per la riabilitazione dei disturbi attentivi lateralizzati, sulle rappresentazioni mentali dello spazio. Discuterò in modo critico un recente modello della negligenza spaziale unilaterale, suggerendo che stimolazioni e disturbi vestibolari possano sì avere ripercussioni sulle rappresentazioni metriche dello spazio, ma senza comportare necessariamente inattenzione per lo spazio stesso. Infine, nel sesto capitolo descriverò gli effetti di cattura dell’attenzione visuospaziale che stimoli distrattori intrinsecamente motivanti possono esercitare nell’adulto sano. Cercherò, in particolare, di predire l’entità di questa cattura attenzionale partendo da immagini di risonanza magnetica funzionale a riposo: riporterò dati preliminari focalizzati sull’importanza del circuito cingolo-opercolare, effettuando un parallelismo con popolazioni cliniche caratterizzate da comportamenti di dipendenza.

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During the last three years I've been through major – and to some extent abrupt – changes in my life. New city, new University, new lab, new career, new skills, new interests, new friends … I'm not good at inspirational speeches but I do want to thank all those who made this passage smoother.

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The present work, thought to represent a life-time achievement, is dedicated in loving memory of my father Valeriano, whom I miss deeply. I can't imagine a better life-time achievement than seeing you every day in the mirror.

To my grandmother Cecilia, and to all the tender childhood memories she left me. To my grandfather Francesco, to whom my efforts were promised.

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PREFACE

In this work I will present several studies of rather heterogeneous nature – for both topics and experimental approaches (that is, methods) – but all joined by a common *leitmotiv*: a genuine interest in spatial attention, its normal and pathological manifestations, its role in human cognition (also, and perhaps especially, when at first glance far from the attentional domain), and its neural underpinnings.

Spatial attention can be conceptualized either as the beam of a spotlight (Posner, Snyder, & Davidson, 1980), shedding light to different regions of the surrounding space, or as a zoom-lens, continuously narrowing or widening attentional focus (Eriksen & James, 1986). Regardless of which is the most appropriate metaphor, it's safe to say that spatial reasoning and spatial attention play a pervasive and pivotal role in a range of mental processes extending far beyond perception.

I will start with a section devoted to the assessment of visuospatial biases. This is probably the result of a long-lasting interest for the most dramatic manifestation of (lateralized) visuospatial disorder, namely Unilateral Spatial Neglect (USN). The reader will notice that USN is a constant reference throughout all this thesis, both because of pure scientific interest and desire to advance as possible its clinical and therapeutic management. In the first chapter I will therefore focus on a potentially useful approach to improve the process leading to the diagnosis of USN, described and tested with healthy participants; I will then move, in Chapter II, to its application in a clinical population with sustained left-hemispheric stroke. Chapter III will still be focused on the detection of attentional asymmetries in the healthy brain, as in Chapter I, but this time occurring in the sagittal (often neglected) axis.

The second section concerns experimental manipulations of spatial attention through sensory stimulations (i.e., visual, vestibular) or motivational cues, in order to explore its role in mental processes or neural underpinnings. As example of the ubiquitous nature of spatial attention, in Chapter IV I will describe its role in mental arithmetic. In Chapter V I will seek to critically discuss the recently proposed vestibular account for USN, and try to explore the effectiveness of a novel Galvanic Vestibular Stimulation protocol in inducing spatial biases in healthy persons. Finally, as token of my most recent research interest, in the final chapter I will present data concerning the capture of visuospatial attention by intrinsically rewarding distracters, together with preliminary data pointing to possible neural predictors.

This dissertation is submitted for the degree of Doctor in Philosophy at the University of Padova, Italy. The work is, to the best of my knowledge, original, except where references to previous work are made. Parts of this work will be presented elsewhere.

The research described herein has been carried as lead, independent author in collaboration with several precious colleagues, acknowledged at the end of each chapter, mostly within the Computational Cognitive Neuroscience Lab directed by Prof. Marco Zorzi. Research described in Chapter V has been carried within the Multisensory Space & Action team directed by Prof. Alessandro Farné.

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SECTION 1

Assessing the Distribution of Visuo-Spatial Attention

CHAPTER I

Effects of Multitasking over a Spatial Monitoring Task

ABSTRACT

Humans' ability to process information has limits and constraints; for example, paying attention to multiple tasks typically leads to a worse performance in at least one of them. We explored the detrimental effects of multitasking in a spatial monitoring task suited for highlighting even subtle attentional asymmetries. We wondered, specifically, whether very challenging attentional demands (introduced through n-back features for the concurrent tasks) could enhance the subtle leftward attentional bias described for healthy persons or rather induce transient visual neglect. Results, drawn from a sample of 40 healthy individuals, show that multitasking does hamper spatial monitoring in terms of both response accuracy and reaction times, the effect being increasingly evident the more secondary tasks are demanding, but without causing lateralized biases to emerge. We discuss the practical implications of this detrimental effect especially referring to the clinical and diagnostic assessment of spatial disorders (i.e., Unilateral Spatial Neglect).

1.0 INTRODUCTION

In everyday life multitasking is ubiquitous. Walking down a street while talking to a friend, cooking while listening to the news, driving while talking at the phone, are only a few common examples. From a cognitive scientist perspective, all these activities exploit divided attention: when we perform more than one task at the same time, and attention is required by all of them, attentional resources are necessarily shared. In these cases, given that humans have a limited capacity to process information (Marois & Ivanoff, 2005), performance in at least one of the tasks typically declines. For example, when two stimuli are presented in rapid succession, response times to the second one are generally slower (Psychological Refractory Period, PRP; Pashler, 1994; Welford, 1952), the source of delay being classically attributed to the limited capacity of attentional mechanisms necessary for response selection (Smith, 1967). A similar phenomenon, also believed to reflect central processing bottlenecks (Jolicœur, Dell'Acqua, & Crebolder, 2001), is the so-called Attentional Blink (AB; Shapiro & Raymond, 1994): when a sequence of visual stimuli is rapidly presented, the detection of a relevant target might be hampered if presented within a few hundred milliseconds after detection of a previous (also relevant) one. Dual-task interference on visual processing, indeed, appears a fruitful ground to study bidirectional links between perception and cognition; however, far from being restrained to theoretical implications, practical and clinical hints might be obtained as well.

For example, concurrent task demands have a detrimental effect in the detection of (Webster & Haslerud, 1964) or interference by (Lavie, Hirst, de Fockert, & Viding, 2004) peripheral stimuli, suggesting that visuo-spatial abilities might be particularly affected by attentional load. This is generally confirmed in PRP (Brisson & Jolicœur, 2007) and AB (Dell'Acqua, Sessa, Jolicœur, & Robitaille, 2006; Jolicœur, Sessa, Dell'Acqua, & Robitaille, 2005) paradigms modified as to introduce lateralized targets; a common finding, in these settings, is a modulation of N2pc electrophysiological activity (that is, posterior cortical sites contralateral to the attended target position generally show enhanced negativity), which is reduced or abolished the more concurrent tasks are demanding (Dell'Acqua et al., 2006). This is not only an observation bound to remain confined in a laboratory setting: if we go back to the examples of everyday life activities mentioned above, we might notice that one of the two tasks involved spatial monitoring (i.e., walking down a crowded street, trying not to hit someone, driving, or even cooking). It appears therefore appropriate to frame and quantify such detrimental effects over spatial attention.

Precious hints may be gathered when considering the most dramatic case of (lateralized) spatial attention disorder, which occurs in patients suffering for brain damage resulting in Unilateral Spatial Neglect (USN). USN is defined as the failure to report, respond to or orient towards stimuli in contralesional space, when this failure cannot be attributed to motor or sensory deficits (Driver & Vuilleumier, 2001; Heilman, Watson, & Valenstein, 1985). It is generally acknowledged that the severity of USN strongly depends on bottom-up task features (Aglioti, Smania, Barbieri, & Corbetta, 1997; Kaplan et al., 1991) and top-down attentional demands (Bonato, 2012; Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010; Robertson & Frasca, 1991; Sarri, Greenwood, Kalra, & Driver, 2009; but see Peers, Cusack, & Duncan, 2006). Both have been successfully employed to devise more sensitive tests (Bonato & Deouell, 2013; Kaplan et al., 1991). Vuilleumier et al. (2008) presented two USN patients with ipsi- or contra-lesional checkerboards in order to characterize their retinotopic mapping through fMRI while varying task demands at fixation: the main result was that the activation pattern of early visual cortices was roughly symmetrical in the low load condition, whereas a neat asymmetry emerged only under higher load, right-hemisphere structures being less activated by contralesional stimuli. Converging results have been obtained in studies on healthy participants with fMRI (Bahrami, Lavie, & Rees, 2007) and EEG (Bonato, Spironelli, Lisi, Priftis, & Zorzi, 2015; Handy, Soltani, & Mangun, 2001; Rauss, Pourtois, Vuilleumier, & Schwartz, 2009), supporting the notion that information filtering and selection occurs in earlier stages under high attentional demands (Lavie, 2005; Lavie & Tsal, 1994). A second common finding is a subsequent modulation of (mainly right-lateralized) parietal structures (Bonato et al., 2015; O'Connell, Schneider, Hester, Mattingley, & Bellgrove, 2011), especially located around the Temporo-Parietal Junction (TPJ; Todd, Fougnie, & Marois, 2005). TPJ is comparatively less activated during effortful visual search (Shulman et al., 2003) as well as under visual short term memory load (Todd et al., 2005) and heavy working memory (WM) encoding (Anticevic, Repovs, Shulman, & Barch, 2010), suggesting that the resulting inattentional blindness might also be explained in terms of suppression of the stimulus-driven ventral attentional network (Todd et al., 2005).

If the common result of high load in USN is the exacerbation of core lateralized biases, and if neural activity in healthy humans is markedly asymmetrical in the same conditions, one might wonder whether highly challenging task demands would induce spatial biases in healthy individuals, for whom subtle imbalances along the horizontal axis (leftward oriented) have been described (e.g., Jewell & McCourt, 2000). This is apparently the case of healthy subjects asked to perform recognition, but not detection, tasks under visual WM load (Emrich, Burianová, & Ferber, 2011). Emrich et al. (2011), however, found that recognition performance decreased under heavy concurrent task demands, but only for items presented in the left hemisphere; therefore their results do not support the enhancement of pre-existing biases, but rather the induction of a novel rightward bias perhaps following right-TPJ deactivation. Indeed, attentional load in healthy individuals either abolishes spatial biases (Bellgrove et al., 2004) or induces rightward ones (Pérez et al., 2009). Emrich et al. (2011) therefore suggested that this functional deactivation of right-TPJ under WM load might represent a fruitful working model to study visual USN in healthy populations (also see Gozli, Wilson, & Ferber, 2014). Following this suggestion, we sought to assess whether challenging concurrent task demands, once exceeding a critical threshold, might also hamper spatial monitoring (detection) and cause lateralized biases to emerge.

We capitalize on a dual-task paradigm recently proposed by Bonato and colleagues (2010) that, building on a purely top-down manipulation of tasks demands (that is, conserving invariance of physical stimulation) successfully highlights even subtle lateralized biases in patients with brain damage but no evidence of USN following a conventional neuropsychological assessment (Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2012). In the first part, shared across all our experimental manipulations, we asked to 40 healthy participants to rapidly report the side of presentation of a small dot appearing on the screen for a short (16.6 ms) time duration. Target(s) could appear on the left, right, or on both sides of the screen, hence mimicking a classic diagnostic test for USN and extinction (e.g., Làdavas, 1990). Concurrently to dot presentation, and in all conditions, both a sound and a visual shape were presented. In the first part of the experiment we kept the paradigm as similar as possible to Bonato et al. (2010), in order to study effects of attentional load in both auditory and visual domains (Crossmodal Load Task). In this part, after providing a response for the primary/monitoring task, participants were asked to either indicate the shape that was previously presented (dual-visual task), the sound (dual-auditory), or the picture with deviant perceptual features (single task). Note that the single task did not require active encoding of information in order to be successfully performed, and it was therefore included as baseline condition. Furthermore, we sought to manipulate parametrically attentional load by introducing n-back features to the paradigm (N-back Load Task). In a subsequent session, we used the previously introduced dual-visual condition as baseline (now called zero-back condition) to further add WM load in the visual modality: we therefore introduced the one and two-back conditions, in which participants had to indicate the shape that was presented at fixation two or three trials before, respectively.

We expected to observe an overall detrimental effect of secondary tasks across all conditions, perhaps with more demanding tasks inducing lateralized (rightward) biases.

2.0 METHODS

2.1 PARTICIPANTS

Forty undergraduate volunteers, twelve males and twenty-eight females, took part in the experiment after giving informed written consent. They were all undergraduate students at the University of Padua, recruited through web advertising and receiving small compensation for their participation. They were all native Italian speakers with no history of neurological or psychiatric disorders and normal or corrected-to-normal vision. The mean age of the sample was 23.45 years (SD= 1.94); seven individuals reported to be left-handed.

The study followed the Declaration of Helsinki standards and was approved by the referring Ethical Committee.

2.2 APPARATUS AND STIMULI

Participants were individually tested in a quiet room, sitting comfortably at a distance of about 50cm from a 17-inch computer monitor with embedded 60 Hz eye-tracking system. Their head was restrained by a chinrest and eye-movements recorded during the whole session. Responses were provided by means of a standard QWERTY keyboard using the S and K buttons with the left and right index fingers, respectively..

Crossmodal Load Task. There were three experimental conditions: the single-task condition and two dual-task conditions (visual vs. auditory). Each trial started with a white fixation cross (about 1cm wide) that was presented in the center of the screen for 800 ms. The fixation cross flickered for 200 ms before target presentation as a warning signal and to redirect covert attention to the screen center. The lateralized visuospatial target was a white disk (diameter: 8mm) presented against the black background for a duration of 16.6 ms (one screen refresh). The target could appear unilaterally, on the left or the right side of the display (lateral distance from fixation: 140mm), or bilaterally (both on the left- and on the right side). The three target locations (left, right, bilateral) were equiprobable and presented in random order. Simultaneously with the lateralized target(s), a visual shape (a picture chosen randomly among a set of six: triangle, square, circle, rhombus, hexagon, and pentagon) was shown at fixation and a sound (an environmental sound chosen randomly among: train whistle, doorbell, hammer, Japanese gong, bicycle bell, and telephone) were presented through binaural earphones (duration: 500 ms). Note that three figures and sounds were chosen for each participant randomly, and were the only relevant stimuli presented in this part (namely, the set of three non-chosen figures and sound were never presented in this first phase, and thus were always irrelevant). The fixation cross was presented once again starting from the end of auditory or centrally presented visual shapes and lasting for 1500 ms (that is, 2000 ms after target presentation, that was also the time limit given to participants in order to respond). During this whole period of time eye-movements were recorded: a region of interest – a 5x5 cm square – was created around the fixation cross; if more than two gaze samples fell outside this area the trial was flanked as containing deviant eye movements, and later discarded by the experimenter. A feedback text was also provided to participants in this case, at the end of the trial, suggesting to improve their fixation behaviour.

As soon as the lateralized target(s) were presented, subjects were asked to rapidly indicate their position in space with their left index finger in case of dots appearing to the left, with their right index finger in case of dots appearing to the right, and with both fingers simultaneously in case of a bilateral stimulation. Once 2000 ms elapsed, a selection mask was presented (see Fig. 1). In the dual-visual or dual-auditory conditions participants had to choose, among a choice of three, which image or sound (depicted as an image of the corresponding object, e.g., the picture of a telephone) was previously presented. In the single task condition, instead, we required a perceptual judgment: among a set of three irrelevant pictures we asked to indicate the one for which colors were reversed (e.g., with a white, and not black, background). Note, thus, that no encoding of previously presented stimuli was required for this task, whereas memory encoding of either visual or auditory stimuli was required for the dual tasks. However, sensory stimulation was identical across the three conditions. In other words, the manipulation was purely top-down, based on the presence/absence of concurrent task demands. Participants had a 3000 ms time-limit to comply with the secondary task. No stress on speed, but rather on accuracy, was used for the secondary task, differently from the first one, for which both speed and accuracy were stressed.

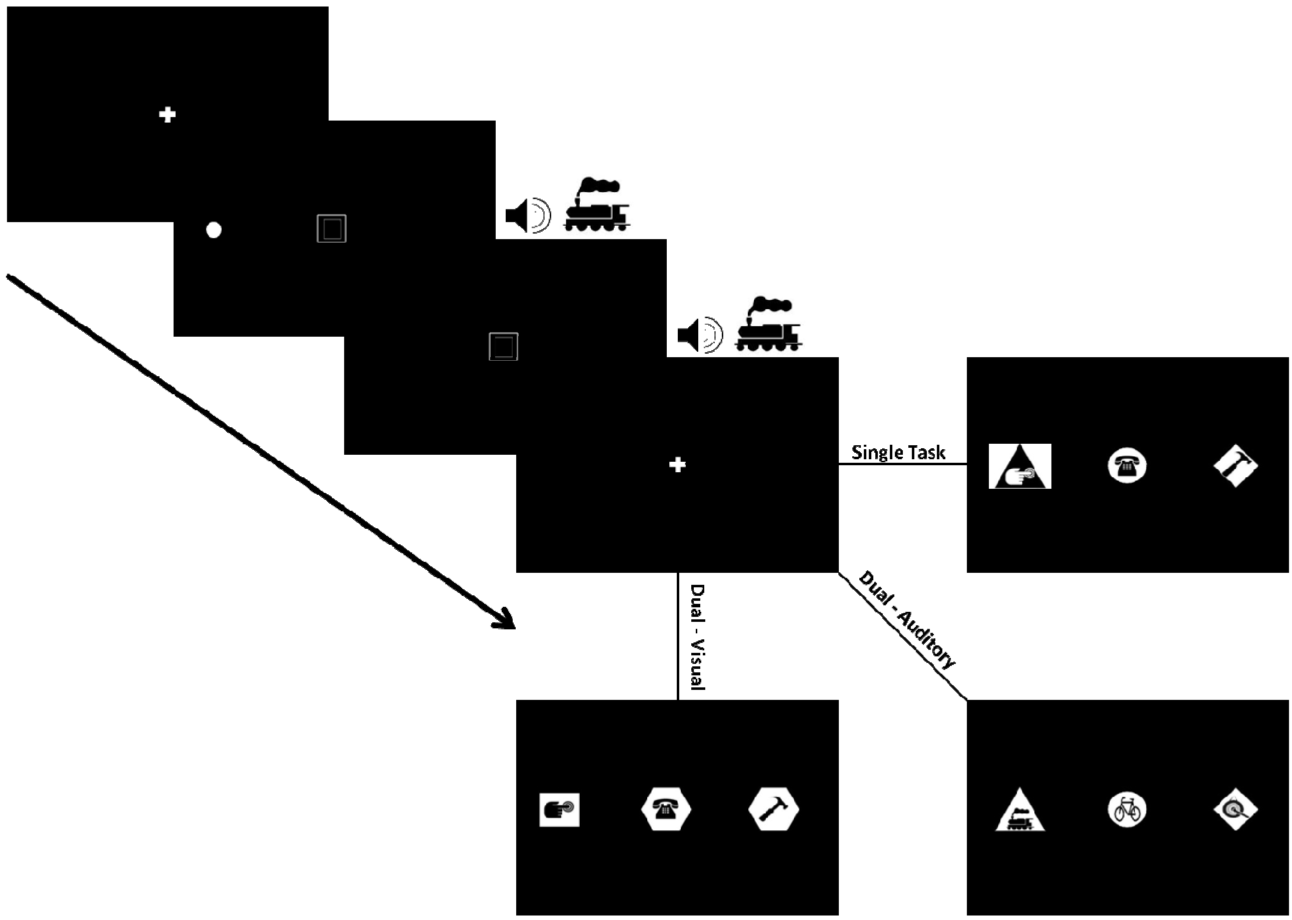

Fig. 1. Experimental design. After the presentation of a fixation cross for 1000 ms a dot was briefly presented in the left, right, or in both sides of the computer screen. An auditory ecological sound (e.g., train whistle) and a geometrical shape (e.g., square) were also concurrently presented for a total duration of 500 ms. Participants had to firstly report the side of target presentation by means of keypresses. Once this request was accomplished, one selection menu was presented: according to the task at play, participants were asked to either select the shape that was previously presented (dual-visual task), the sound (dual-auditory), or the picture with deviant perceptual features (single task). Note that, despite physical stimulation being the same, the single task does not require active encoding of information other than the peripheral target location.

N-back Load Task. Core features of this task are shared with the cross modal paradigm (Fig. 1). Participants were still required to perform the spatial monitoring task first, but the type of task was changed. While one condition, called here Zero-back, is identical to the dual-visual condition of the previous paradigm, we further manipulated parametrically working memory load by adding n-back features to the secondary tasks. That is, beside the Zero-back condition we introduced the One-back and Two-back conditions, in which participants had to indicate the shape that was presented at fixation two or three trials before, respectively. This is therefore an intra-modality (visual) manipulation of pure working memory load. Given that we expected the secondary tasks to be more challenging in this paradigm, we extended the time limit for the secondary task to 10000 ms. In addition, feedbacks were provided, at the end of the trial, concerning both accuracy to the primary/monitoring and secondary tasks, beside the feedback over eye movements.

2.3 PROCEDURE

Participants performed the two tasks in two different days. They always performed the Crossmodal task in the first session and the N-back one in the second. A 9-point calibration for the eye-tracker was performed before each task to begin.

Crossmodal Load Task. The experiment was divided in 4 blocks, each condition (Single, Auditory, or Visual) being repeated three times for block, in a pseudo-randomized order (i.e., without repetitions), and each target type (Left, Right, or Bilateral) being repeated 24 times in a random order, balanced within Load conditions. In other words, each block was composed of 9 brief runs composed of 8 trials. Each block consisted, in fact, of 72 trials, after which breaks were provided. A practice phase, consisting of 24 trials (8 for each Load condition), was carried out before starting the experiment to allow familiarizing with the primary and secondary tasks. During this phase the experimenter ensured that participants fully understood task requirements. The occurrence of the different shapes or sounds (3 x 3) was fully randomized on a trial basis. Overall, the experiment consisted of 288 trials (3 Load conditions x 3 Types of target x 32 trials per cell).

N-back Load Task. The experiment was divided in 6 blocks, each condition (Zero-, One-, or Two-back) being repeated two times in the whole experiment; tasks order was counterbalanced across participant *via* automatic permutation at the beginning of the experiment, the sequence so created being repeated two times. Each block consisted of 27 trials (9 trials for each target Type condition, randomly selected among Left, Right, or Bilateral) – this number does not take into account dummy trials (one or two more) introduced to allow n-back conditions. Breaks were provided after each block. A practice phase consisting of 30 trials (10 for each condition) was carried out before starting the experiment to allow familiarizing with the novel secondary tasks. During this phase the experimenter ensured that participants fully understood task requirements. The occurrence of the different shapes or sounds (3 x 3) was randomized on a trial basis. Overall, the experiment consisted of 162 trials (3 n-back Load conditions x 3 Types of target x 18 trials per cell).

3.0 RESULTS

Data were analyzed with the open-source software R (R Core Team, 2015). Data obtained from the practice phase were dismissed. Trials invalidated by eye movements (Crossmodal Load: 6.06 %; N-back Load: 5.33 %) were discarded as well.

Accuracy to the monitoring and secondary tasks was analyzed through *mixed-effects multiple regression models* (Baayen, Davidson, & Bates, 2008) using the lme4 package for R (Bates, Maechler, Bolker, & Walker, 2014). A great advantage of mixed models is that they are based on single trial data (rather than on averaged data), they do not assume independence amongst observations, and the model fitting procedure takes into account the covariance structure of the data, including random effects (i.e., individual variability). All models, furthermore, had a logistic link-function, which is appropriate for a dependent variable with binary distribution (i.e., accuracy). As a first step we defined a model containing the most appropriate random effects justified by experimental design: specifically, we added random intercepts for Subject and target Type (Left, Right, and Bilateral), hence allowing different baseline levels for these factors; furthermore, a random slope for attentional Load (Single, Auditory, and Visual for the Crossmodal Task; Zero, One, and Two-back for the N-back one) was included, allowing different performances across Subjects related to this manipulation. The model with the final random effects structure was then used to introduce the evaluate the role of fixed effects. We used a stepwise approach, adding main effects before interactions, and used log-likelihood tests to assess whether the improvements in the model fit were statistically significant.

The effect of Target Type (Left, Right, and Bilateral) and Load (Single, Auditory, and Visual for the Crossmodal Task; Zero, One, and Two-back for the N-back one) on RTs for accurate responses, instead, was assessed by means of ANOVA; a Bayesian ANOVA and t-tests (Rouder, Speckman, Sun, Morey, & Iverson, 2009) were also performed through the BayesFactor package for R (Morey & Rouder, 2015) to further complement analysis and obtain a straightforward index (i.e., Bayes Factor, BF) to quantify the strength of evidence for each model and combination of factors (Kass & Raftery, 1995). Note that this approach exploit objective (default) priors (Rouder, Morey, Speckman, & Province, 2012), proposed as to decrease researchers' degrees of freedom, given that BFs partly depend on priors choice. Besides, a Bayesian perspective allows to quantify the strength of evidence for a null hypothesis, whereas a frequentist one is unable to do so (that is, lack of evidence is not evidence for a null effect, Kass & Raftery, 1995).

Bayesian t-tests were also employed for a fine-grained analysis of error patterns in the monitoring task. Indeed, beside evaluating overall accuracy it is crucial to explore the presence of lateralized errors (that is, right- vs. left-sided extinctions, or an asymmetrical pattern of omissions to unilateral stimuli). For Bilateral trials we therefore computed Asymmetry Indices (AI): they were obtained by subtracting the individual proportion of "left" responses from the proportion of "right" responses. A negative AI indexes that "left" responses prevailed among errors while positive AI reveals prevalence of "right" responses. For unilateral trials, AIs were obtained by subtracting the proportion of omissions for right-sided targets from the proportion of omissions for left sided targets. The resulting index is similar to the previous one, with negative values representing a leftward bias and positive values representing a rightward bias. Note that all AI values express the asymmetry in terms of proportion of errors. That is, a value of -1 indicates that all of the right targets but none of the left targets were missed, whereas a value of 0 indicates that an equal number of left and right targets were missed (or that no targets were missed). For each AI, we first assessed whether it significantly differed from 0 (thereby indexing spatial bias) by means of a one-sample t-test (across all Load conditions), and then proceeded with assessing the modulatory effect of attentional Load.

3.1 Crossmodal Load Task

Spatial Monitoring: accuracy. We first assessed whether accuracy in the spatial monitoring task was modulated by the Load condition (i.e., Single Task, Visual Dual Task, Auditory Dual Task), and whether it was different across target Types (Left, Right, Bilateral, Catch). Accuracy was therefore entered as dependent variable in the mixed model analysis.

Both the fixed main effects (Load: $\chi^2 = 12.09$, $p = 0.002$; Target type: $\chi^2 = 9.84$, $p = 0.007$) yielded significant improvement of the model fit. We then assessed the two-way interaction (against a model containing only the relative main effects) and found no further improvements in model fit ($\chi^2 = 7.97$, $p = 0.093$).

The main effect of Type refers to the Bilateral condition being less accurate (94.9 %) than Left (97.4 %; $\beta = 0.92$, Wald= 6.77, $p < 0.001$) and Right (96.79 %; $\beta = 0.52$, Wald= 4.3, $p < 0.001$); the difference among Left and Right was also significant ($\beta = 0.4$, Wald= 2.74, $p = 0.006$). Accuracy was also different across Load conditions (Auditory: 97.03 %; Single: 96.63 %; Visual: 95.87%): the Auditory one achieved a better performance than Single and Visual ($\beta \geq 0.53$, Wald≥ 2.72, $p \leq 0.006$) but the latter two did not differ ($\beta = 0.13$, Wald= 0.78, $p = 0.44$). Results are depicted in Fig. 2.

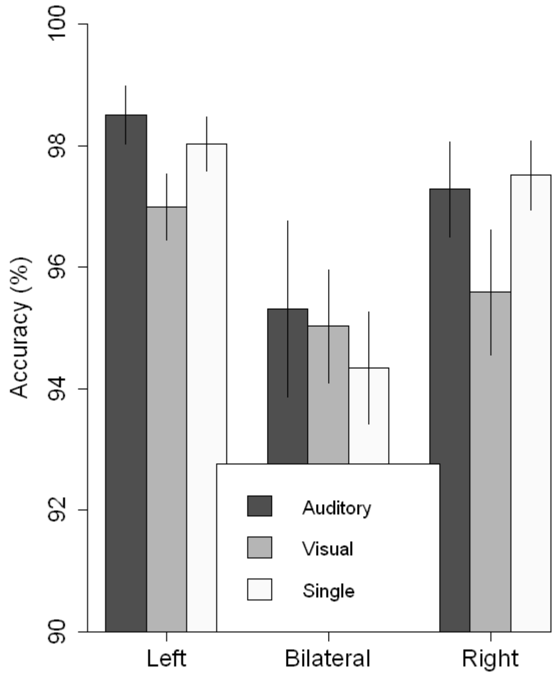

Fig. 2. Accuracy to the primary monitoring task is depicted as a function of target Type (x-axis) and attentional Load. Targets presented to the left side of space were detected better than right-sided and bilateral ones, and right sided were better detected than bilateral ones. Performance, was better under Auditory load with respect to the Single and Visual conditions. However, these two main effects did not interact. Error bars depict SEM.

Spatial Monitoring: asymmetry indices. We then analyzed, within Bilateral and Unilateral trials, the proportion of right vs. left responses occurring in each Load condition through series of Bayesian t-tests on AIs. All BFs reported in this section are base 1 BFs. Differently from base 10 BFs, BF_{01} reflects the strength of evidence in favor of the null hypothesis (in our case, that no difference exists among the examined means).

Bilateral targets. AIs, across Load conditions, were not different from 0 (that is, they were not spatially lateralized; BF_{01}= 3.78). There was no different prevalence of right vs. left sided extinction within the Single (BF_{01}= 4.39), Auditory (BF_{01}= 2.2) or Visual (BF_{01}= 5.75) tasks.

Unilateral targets. Similarly to AIs for Bilateral trials, responses to Unilateral trials were not spatially lateralized (BF_{01}= 4.88, across Load conditions). There was no asymmetry in right vs. left sided omissions within the Single (BF_{01}= 5.67), Auditory (BF_{01}= 5.74) or Visual (BF_{01}= 4.29) tasks.

Altogether, therefore, results bring evidence in favour of the lack of lateralized asymmetries in healthy subjects tested with our paradigm, regardless of Load condition.

Spatial Monitoring: reaction times. We then assessed whether reaction times (RTs) in the spatial monitoring task were modulated by the Load condition (i.e., Single Task, Visual Dual Task, Auditory Dual Task), and whether it was different across target Types (Left, Right, Bilateral).

RTs markedly differed across Load conditions ($F_{(2,78)}$= 30.54, p< 0.001, η_p^2= 0.44), participants being faster in detection without concurrent task demands (Single task: M= 574.63 ms, SD= 150.33) and slower with Auditory (M= 593.25 ms, SD= 154.33) and Visual Load (M= 627.38 ms, SD= 155.36). All Bonferroni corrected post-hoc t-tests reached significance ($t_{(39)}\geq$ 4.22, p<0.001). In addition, RTs differed across Target Type ($F_{(2,78)}$= 7.61, p< 0.001, η_p^2= 0.163). Participants were slower in Bilateral trials (M= 615 ms, SD= 157.2) and faster in Left (M= 595.68 ms, SD= 150.97) and Right trials (M= 584.52 ms, SD= 153.9). Post-hoc comparisons showed a significant difference only across Bilateral and Unilateral trials ($t_{(39)}\geq$ 2.97, p≤0.006, Bonferroni corrected), but not across Left vs. Right ($t_{(39)}$= 1.4, p=0.49).

Finally, the Load by Type interaction was not significant ($F_{(4,156)}$= 0.48, p= 0.75) showing that RTs for different target Types were not modulated by attentional Load in either modality. A Bayesian analysis yielded, coherently, a BF= $2.59e^{15}$ in favor of the model containing the two main effects (and the random effect of Subject); it was therefore by far the most informative model, followed by the model also containing the two-way interaction (BF= $5.6e^{13}$). The fact that the Bayes Factor dropped by a factor of 46.13 when adding the interaction means that our data strongly support the absence of such effect. Results are depicted in Fig. 3.

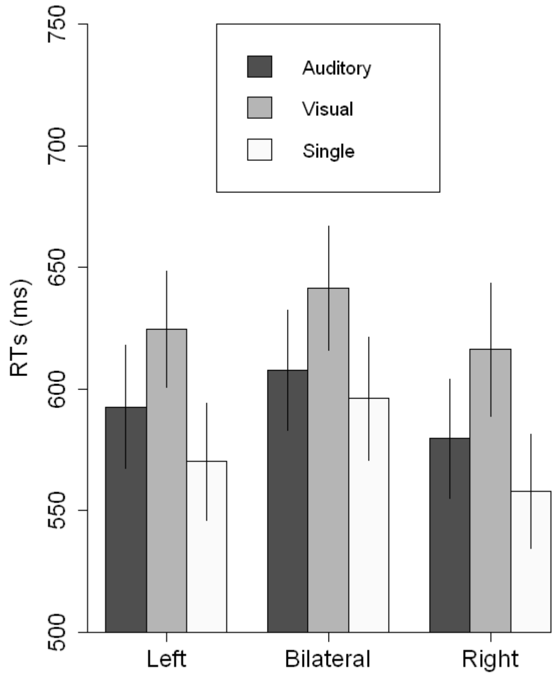

Fig. 3. Reaction times to the primary monitoring task are depicted as a function of target Type (x-axis) and attentional Load. Participants were faster in absence of concurrent task demands (Single task) and slower in dual task conditions (especially the Visual one). They were also faster in responding to unilateral as opposed to Bilateral trials. However, there was no interaction. Error bars depict SEM.

Concurrent Task: accuracy. We finally assessed whether accuracy in the secondary task was modulated by Load condition (i.e., Single Task, Visual Dual Task, Auditory Dual Task), and whether it was different across target Types (Left, Right, Bilateral). Accuracy was entered as dependent variable in the mixed model analysis.

The only significant fixed effect was the main effect of Load (χ^2= 15.2, p< 0.001), whereas neither target Type nor the Load by Type interaction reached significance (χ^2≤ 7.51, p≥ 0.11). Performance in the Auditory task (93.16 %) was better than Visual (89.28 %; β= 0.52, Wald= 3.84, p< 0.001) but not Single (90.65 %; β= 0.14, Wald= 0.54, p= 0.59) tasks. Single and Visual tasks also differed (β= 0.66, Wald= 2.85, p= 0.004).

3.2 N-back Load Task

Spatial Monitoring: accuracy. We first assessed whether accuracy in the spatial monitoring task was modulated by the Load condition (i.e., Zero-, One-, and Two-back Task), and whether it was different across target Types (Left, Right, Bilateral, Catch). Accuracy was therefore entered as dependent variable in the mixed model analysis.

Both the fixed main effects (Load: χ^2= 19.62, p< 0.001; Target type: χ^2= 9.17, p= 0.01) yielded significant improvement of the model fit. We then assessed the two-way interaction (against a model containing both main effects) and found a further improvement in model fit (χ^2= 19.04, p< 0.001). Detection accuracy under load for bilateral trials dropped from 94.97% in the One-back condition to 92.93% for Zero- and 87.89% for Two-back; for Right targets dropped from 97.32% in the Zero-back condition to 93.76% for One- and 87.93% for Two-back; performance for Left targets dropped from 98.65% in the Zero-back condition to 96.76% for One- and 92.28% for Two-back. Results are depicted in Fig. 4. The interaction is therefore due to the paradoxical effect found in Bilateral trials, in which the One-back condition led to an improved (although not significant: β= 0.19, Wald= 0.7, p= 0.48) detection performance, whereas for Left (β= 1.1, Wald= 2.64, p= 0.008) and Right trials (β= 1.02, Wald= 3.23, p= 0.001) performance decreased.

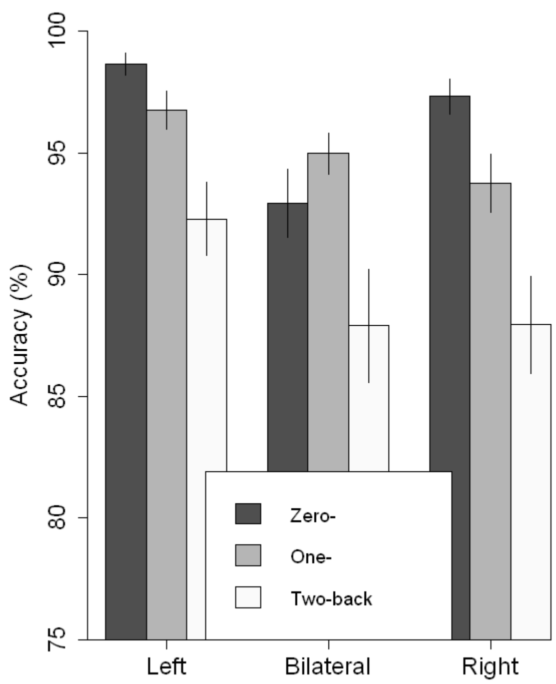

Fig. 4. Accuracy to the primary monitoring task is depicted as a function of target Type (x-axis) and attentional Load. We found evidence for both main effects: performance was worse in bilateral as opposed to unilateral trials, and gradually decreased with increasing working memory Load. However, an interaction was found: accuracy for bilateral trials is not different across Zero- and One-back conditions, whereas the latter worsened participants' performance for Left and Right targets. Error bars depict SEM.

Spatial Monitoring: asymmetry indices. We then analyzed, within Bilateral and Unilateral trials, the proportion of right vs. left responses occurring in each Load condition through AIs. Note that all BFs reported in this section are base 1 BFs, and support the strength of evidence in favor of the null hypothesis (no difference between AIs).

Bilateral targets. AIs, across Load conditions, were not different from 0 (that is, they were not spatially lateralized; BF_{01}= 4.54). There was no different prevalence of right vs. left sided extinction within the Zero- (BF_{01}= 5.57), One- (BF_{01}= 5.78) or Two-back (BF_{01}= 2.7) tasks.

Unilateral targets. Similarly to AIs for Bilateral trials, responses to Unilateral trials were not spatially lateralized (BF_{01}= 3.94, across Load conditions). There was no asymmetry in right vs. left sided omissions within the Zero- (BF_{01}= 3.68), One- (BF_{01}= 5.78) or Two-back (BF_{01}= 3.06) tasks.

Altogether, similarly to the Crossmodal task, results bring evidence in favor of the lack of lateralized asymmetries in healthy subjects tested with our paradigm, also when concurrent task demands were very challenging.

Spatial Monitoring: reaction times. We then assessed whether reaction times (RTs) in the spatial monitoring task were modulated by Load condition, and whether it was different across target Types.

RTs differed across Load conditions ($F_{(2,78)}$= 45.16, p< 0.001, η_p^2= 0.537), participants being faster in detection at baseline (One-back task: M= 489.97 ms, SD= 130.63) and slower with One-back (M= 554.66 ms, SD= 155.54) and Two-back (M= 659.55 ms, SD= 182.49) working memory Load. All Bonferroni corrected post-hoc t-tests reached significance ($t_{(39)} \geq$ 5.54, p<0.001). In addition, RTs differed across Target Type ($F_{(2,78)}$= 5.51, p= 0.006, η_p^2= 0.124). Participants were slower in Bilateral trials (M= 593.55 ms, SD= 147.6) and faster in Left (M= 557.91 ms, SD= 152.48) and Right trials (M= 552.73 ms, SD= 153.98). Post-hoc comparisons showed a significant difference only across Bilateral and unilateral trials ($t_{(39)} \geq 2.7$, $p \leq 0.003$, Bonferroni corrected), but not across Left vs. Right ($t_{(39)} = 0.4$, $p=1$).

Finally, the Load by Type interaction was not significant ($F_{(4,156)} = 1.97$, $p = 0.135$) showing that RTs for different target Types were not modulated by attentional Load in either modality. A Bayesian analysis yielded, coherently, a BF= $8e^{23}$ in favor of the model containing the two main effects (and the random effect of Subject); it was by far the most informative model (6.63 times more likely than the model including only the main effect of Load). The Bayes Factor for the model including the interaction only was equal to 0.038, indicating that the absence of such effect is supported by our data by a factor of 26.29 (BF_{01}). Results are depicted in Fig. 5.

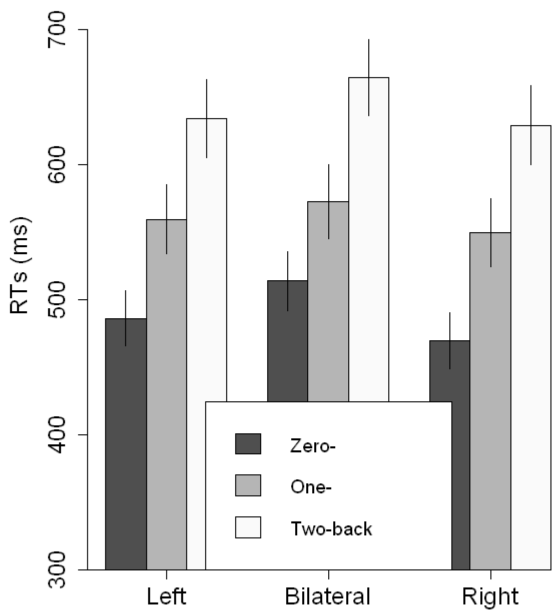

Fig. 5. Reaction times to the primary monitoring task are depicted as a function of target Type (x-axis) and attentional Load. Participants were faster in absence of concurrent task demands (Single task) and slower in dual task conditions (especially the Visual one). They were also faster in responding to unilateral as opposed to Bilateral trials. However, no interaction was observed. Error bars depict SEM.

Concurrent Task: accuracy. We then assessed whether accuracy in the secondary task was modulated by the Load condition (i.e., Zero-, One-, or Two-back tasks), and whether it was different across target Types (Left, Right, Bilateral). Accuracy was entered as dependent variable in the mixed model analysis.

The only significant fixed effect, not surprisingly, was the main effect of Load (χ^2= 85.1, p< 0.001), whereas neither target Type nor the Load by Type interaction reached significance (χ^2≤ 1.97, p≥ 0.74). Performance in the Zero-back task (93.52 %) was better than One-back (84.79 %; β= 1.27, Wald= 5.83, p< 0.001) and Two-back tasks (56.02 %; β= 2.93, Wald= 13.57, p< 0.001) tasks. One- and Two-back tasks also differed (β= 1.65, Wald= 12.87, p< 0.001).

4.0 DISCUSSION

We sought to assess whether very challenging concurrent task demands might hamper spatial monitoring (detection) and, once exceeding a critical threshold, cause lateralized biases to emerge in a healthy population. Beside a primary, speeded, monitoring task, we administered a series of concurrent secondary tasks introducing attentional load in the visual or auditory modalities (Crossmodal Task) or WM load by means of a very challenging n-back feature in the visual domain (N-back Task).

Results clearly show that attentional load do hamper spatial monitoring in terms of both detection accuracy and response times, but without inducing lateralized biases. This is demonstrated by the lack of a two-way Type by Load interaction in both paradigms and by a fine-grained analysis of asymmetry indices. We only observed main effects of Load (performance was slower and less accurate with increasing task demands) and target Type (bilateral trials were slower and less accurate than unilateral ones). Although this latter effect could be at least partly due to response modality (bi- rather than uni-manual), we also consistently found a difference between left- and right-sided targets, performance to the former being more accurate. This is in line with a (subtle) advantage, in healthy persons, for the left side of space; critically, we observed neither a rightward shift of this tendency with increasing attentional load (Pérez et al., 2009), nor its exacerbation (Bonato et al., 2010). It is worth stressing, however, that our load manipulation might not be the most suited for this purpose. Indeed we succeeded in creating an extremely demanding task (with accuracy to secondary tasks dropping from more than 90% to 56%) with parametric manipulation of WM load, but it remains controversial whether we used a real visual WM memory load. Indeed, TPJ deactivation (Anticevic et al., 2010) and more evident behavioural effects (Emrich et al., 2011; Todd et al., 2005) are seen under visual WM load, requiring the encoding, maintenance, retrieval, and manipulation (Baddeley, 1992) of visually presented stimuli that are difficult to name (Phillips, 1974). Given that our visual stimuli were simple shapes, we cannot rule out the possibility that verbal/rehearsal, rather than visual, strategies might have been employed by participants. If this is the case, however, it appears clear that this kind of memory load does not result in a shift in the distribution of spatial attention either. Another possibility, finally, is that spatial tasks requiring discrimination/recognition of stimuli might be more prone to highlight even subtle unbalances that would be missed with simpler detection tasks (Emrich et al., 2011). We will tangentially test this hypothesis in Chapter 3, in the context of a study exploring attentional asymmetries along the sagittal plane.

What reported in this chapter is dissimilar, yet akin, to the classically described PRP effect (Pashler, 1994). First, speed was stressed, when instructing participants, only for the primary/monitoring task, but not for concurrent tasks. Results, however, point to a modulation of reaction times also for the first stimulus, whereas a more common result only concerns the second one. Indeed, both stimuli were simultaneously, instead of serially, presented in our paradigm, leading to the second major difference with PRP paradigms. As a consequence, we cannot provide hints about the time course of this effect, given that SOA was not manipulated (and eventually fixed to 0). It is worth stressing, however, that we always choose to postpone response request to the concurrent task after response to the monitoring one was provided; furthermore, we choose to include a dummy "secondary task" in the baseline (single) condition for the Crossmodal paradigm, in which no information had to be stored in memory but a (perceptual) response selection was also required after response to the monitoring task. These crucial points allow to exclude the possibility that dual-task interference rose at this late, response-selection, stage, but points instead to a critical role of encoding and consolidation of stimuli in memory, that are known to strongly drive dual-task slowing phenomena (Jolicœur & Dell'Acqua, 1998, 1999).

To summarize, results clearly indicate that spatial monitoring could be seriously hampered by concurrent task demands, in both visual and auditory modalities, and by working memory load. Practical consequences might extend to ecological settings in which a primary spatial task is particularly delicate, and outcomes of a less effective spatial monitoring potentially dangerous (e.g., driving). Clinical implications are also neat. It is now acknowledged that attentional load might represent a precious tool to unveil spatial asymmetries either subtle or hidden by compensation processes (Bonato, 2015). However, it is not clear whether multitasking exacerbates core directional biases (Bonato et al., 2010), or rather induces a general rightward shift of attention (Bellgrove et al., 2004; Peers et al., 2006; Pérez et al., 2009). This confound is legitimate because the vast majority of studies focused on patients with USN following right-hemisphere damage (leading to a rightward shift of spatial attention), and the two different accounts cannot be easily disentangled because lead to identical predictions. The critical test would therefore be the study of patients with left-hemisphere lesion: unveiling a leftward attentional bias in this population would support the former hypothesis (as in a single case study reported in Bonato et al., 2010), whereas a rightward one would point to an aspecific, right-oriented, shift (as in Peers et al., 2006). We will test this hyphothesis in the following chapter (Chapter 2).

5.0 ACKNOWLEDGMENTS

I'm grateful to Maria Grazia Di Bono, Chiara Spironelli, and Marco Zorzi for their contribution to experimental design.

CHAPTER II

Multitasking in Clinical Practice: Proof of Concept in Patients with Left Brain Lesion and no Evidence of Lateralized Attentional Disorders

ABSTRACT

Unilateral Spatial Neglect (USN), the most dramatic manifestation of contralesional space unawareness, is a highly heterogeneous syndrome. Beside a number of well-known clinical double dissociations resulting from core spatially lateralized deficits, the severity of USN highly depends on several domain-general factors (such as alertness or sustained attention) and task demands. Here we show that a clinical tool exploiting both lateralized and non-lateralized (i.e., attentional load) factors better capture this complex scenario, being extremely sensitive to spatial disorders and yet conserving specificity properties for lateralized deficits. We asked a group of 10 patients with acquired left hemispheric damage (LHD) to complete a computerized detection test with and without concurring secondary tasks. Despite the lack of clinical signs of right-sided neglect in a comprehensive neuropsychological battery, we found evidence of contralesional space unawareness in a relevant subgroup of patients, which was magnified by concurrent attentional load in both the visual and auditory modalities. No evidence of lateralized biases was found for a control group composed by 8 patients having diagnosis of Mild Cognitive Impairment (MC), showing that a global shrinkage of cognitive resources *per se* is not sufficient to reveal lateralized biases. Clinical implications – especially concerning the management of patients with LHD, for whom attentional disorders are too often under looked – are discussed.

1.0 INTRODUCTION

Unilateral Spatial Neglect (USN) is by far the main reference for the study of spatial-attentional mechanisms under a neuropsychological framework (Halligan, Fink, Marshall, & Vallar, 2003; Vallar, 1998). USN is a disorder often occurring after a brain damage defined as the failure to report, respond to or orient towards stimuli in contralesional space, when this failure cannot be attributed to motor or sensory deficits (Driver & Vuilleumier, 2001; Heilman, Watson, & Valenstein, 1985). The typical form of USN (in the chronic stage of the disease) affects the left side of space, that remains unexplored, and it occurs after a right hemispheric lesion involving one or more different areas within a wide cortical network subserving spatial cognition and attention (Corbetta & Shulman, 2011; Molenberghs, Sale, & Mattingley, 2012). Critical areas include, but are not limited to, the inferior parietal lobe and the temporo-parietal junction (Chechlacz et al., 2013; Karnath, Himmelbach, & Küker, 2003; Mort et al., 2003; Umarova et al., 2011; Vallar & Perani, 1986), insula and superior temporal lobe (Karnath, Berger, Küker, & Rorden, 2004; Karnath, Ferber, & Himmelbach, 2001), the hippocampus and the parahippocampal formation (Mort et al., 2003), basal ganglia (Karnath et al., 2004; Karnath, Himmelbach, & Rorden, 2002), or white matter pathways connecting parietal and frontal areas (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008), and so on, with reports that may seem contradictory but eventually arise from different clinical characteristics of the patients involved (Halligan et al., 2003). For example, a different aetiology (i.e., stroke affecting the middle rather than the posterior cerebral artery, Chechlacz, Terry, et al., 2013), a different duration of the disease (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Karnath, Rennig, Johannsen, & Rorden, 2011), or different clinical deficits and manifestations of USN (e.g., ego-centred vs. object-centred, personal vs. extra-personal, that are known to often occur in isolation and in a doubly-dissociated fashion, Chechlacz, Rotshtein, & Humphreys, 2012; Committeri et al., 2007) may be linked to different lesional correlates. Within this complex issue, a special place is held by the debate around hemispherical asymmetries in the origin of USN, with right-sided lesions that are believed to lead more often to attentional disorders for the left side of space (Beis et al., 2004; Stone, Halligan, & Greenwood, 1993; Weintraub & Mesulam, 1987) especially in the subacute phase (Stone et al., 1991). Historically, epidemiological studies in this regard have been heavily flawed by several confounds, the main one being the need to exclude from the samples patients with severe linguistic disorders (who could not effectively comply with task instructions), thereby describing only a small subgroup of patients presenting a relatively favourable outcome after brain damage (De Renzi, 1982). Hemispherical asymmetries seem to hold, however, also when nonverbal tasks are used and linguistic factors are controlled for (Beis et al., 2004), whereas it is somehow less clear whether the same inbalance is true with respect to symptoms severity (Stone et al., 1991; Suchan, Rorden, & Karnath, 2012). Despite this asymmetry, some degree of attentional inbalance might be unveiled in a substantial proportion of patients with left brain damage when a comprehensive screening battery is administered, hence suggesting that this feature should be well accounted for in the individualized rehabilitational planning (Beis et al., 2004).

USN is, therefore, an highly heterogeneous syndrome, and its behavioural manifestations may encompass a rather wide spectrum (Azouvi et al., 2002; Halligan et al., 2003). In addition to this “core” spatially lateralized feature, several other factors are known to strongly modulate the degree of observed spatial deficits (Bonato, 2012; Husain & Rorden, 2003): alertness (Robertson, Mattingley, Rorden, & Driver, 1998; Thimm, Fink, Küst, Karbe, & Sturm, 2006), sustained attention (Robertson et al., 1997; Robertson, Tegnér, Tham, Lo, & Nimmo-smith, 2008), the presence of increased perceptual demands (Aglioti, Smania, Barbieri, & Corbetta, 1997; Kaplan et al., 1991; Rapcsak, Verfaellie, Fleet, & Heilman, 1989), and, more relevant for our purposes, the presence of increased top-down demands, also when physical properties of the stimuli are kept constant (Bonato, Priftis, Umiltà, & Zorzi, 2013; Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010, 2012; Sarri, Greenwood, Kalra, & Driver, 2009). It is therefore not surprising that several available diagnostic tests for USN have markedly different psychometric properties, such as sensitivity and specificity to USN (Azouvi et al., 2002; Ferber & Karnath, 2001). One common approach, part of the objective neurological examination (Bisiach, Cappa & Vallar, 1983), consists in the detection or confrontation of visually presented stimuli (“detection test”, Bonato, Priftis, Umiltà, & Zorzi, 2013; Bonato & Deouell, 2013; Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010; Làdavas, 1990). Here, one or two lateralized stimuli (e.g., a rapid flick of the index finger for manual examinations, or a flashing dot for computer-based tests) are presented while central fixation (e.g., the nose of the experimenter, or the center of the screen) is maintained, the task being the verbal report of the presence (and detection) of the stimuli; highly suggestive of USN, once visual defects are excluded, is the observed asymmetry between right- and left-sided detection reports, given that patients with USN tend to respond mainly to targets appearing in the ipsilesional side of space. A selective impairment in the detection of bilateral stimuli, the contralesional one being “extinguished”, is also suggestive of a lateralized attentional disorder (i.e., extinction), either conceptualized as an independent disorder or as a milder form of USN (Driver & Vuilleumier, 2001). Bonato and colleagues (2010) recently proposed a modified version of the detection test, where patients are asked to perform the task with and without a concurrent secondary task (attentional load in either the visual or auditory modality). Their multitasking condition proved to be extremely sensitive to subtle lateralized disorders in chronic patients whose spontaneous recovery, or deployment of compensative strategies, is hiding a genuine attentional imbalance (Bonato et al., 2013). For example, several patients showed a flawless performance in detecting stimuli at baseline, in the unimodal condition, whereas additional demands (mimicking an ecological situation in which we are asked to process different sources of information at the same time) could unveil clear biases. When the same paradigm is applied to healthy controls or young volunteers, in contrast, no lateralized deficit is seen (see Chapter 1) despite neural correlates point to both a modulation of early perceptual ERP components (P1) – in the direction of a deactivation of the primary visual areas regardless of the sensory modality relevant for the secondary task (i.e., visual or auditory) – and, for the visual load condition only, a subsequent modulation of the later N2 component seen in the right hemisphere (Bonato, Spironelli, Lisi, Priftis, & Zorzi, 2015). This is coherent with the vast neuroimaging literature pointing to the existence of early, sensory bottlenecks in information processing – mainly related to short-term memory limits within each modality (Linden, 2007; Marois & Ivanoff, 2005) – and a more general, amodal fronto-parietal network acting as a central information relay and sensibly limiting our efficiency in multitasking (Dux, Ivanoff, Asplund, & Marois, 2006; Spence, 2008; Tombu et al., 2011). Within this latter system, a special role in a number of cognitive functions overall shaping the subjective amount of cognitive resources or reserve (Stern, 2002) has been assigned to the right hemisphere (Corbetta & Shulman, 2011; Robertson, 2014). One possibility is that LHD patients, in light of the spared right-lateralized mechanisms, might be able to adequately compensate core spatial deficits, that would therefore be hardly detectable. This could eventually account for the very different prevalence of USN in left- vs right-hemisphere damage, which would be surprising once acknowledged that neural substrates of visuo-spatial attentional mechanism are mostly symmetrical (Corbetta & Shulman, 2011).

It is currently unknown whether LHD patients would show sensitivity to attentional load, thereby mirroring findings on RHD patients, or whether the sparing of right-lateralized attentional mechanisms allows LHD patients to fully compensate for any spatial deficit. In the former case, it is not clear whether multitasking exacerbates core directional biases (Bonato et al., 2010), or rather induces a general rightward shift of attention (Peers et al., 2006; Pérez et al., 2009). The present study aims to clarify this issue, possibly confirming that a clinical tool exploiting both lateralized and non-lateralized (i.e., attentional load) factors, together with their interaction, might be more informative in a clinical setting. A group of 10 consecutive, unselected, inpatients with acquired left hemisphere damage (LHD) will therefore be asked to complete a computerized detection task with and without concurring secondary task. We expect to confirm the higher sensitivity of a dual task setting with respect to the single task condition, also following a single-case report in Bonato et al. (2010) with a similar paradigm, in a clinical group (LHD) in which attentional disorders are believed to be less frequent (Beis et al., 2004; Stone et al., 1993), especially in the subacute phase.

USN has been clearly identified as a reliable predictor of poor functional recovery and rehabilitational outcome (Jehkonen et al., 2000; Katz, Hartman-Maeir, Ring, & Soroker, 1999), hence the early identification of lateralized disorders might lead to an improved rehabilitational plan and assistance (Beis et al., 2004). By means of a control group composed by 8 outpatients diagnosed as having Mild Cognitive Impairment (MCI) – namely a syndrome yielding a global cognitive decline greater than expected given an individual age and education (although with minor negative effects on daily life activities; Gauthier et al., 2006) – we aim at proving that such a task has high sensitivity and it is suitable for highlighting core lateralized disorders rather than global impairments.

2.0 METHODS

2.1 Participants

Ten consecutive stroke patients with LHD took part in the study. They were all admitted to the San Camillo Neurorehabilitation Hospital (Venice-Lido, Italy) to undergo motor rehabilitation for right hemiplegia/hemiparesis and/or language therapy for aphasia. Accordingly, all patients were in the subacute to chronic stage (minimum time from onset: 52 days, see Tab. 1). Eight outpatients having diagnosis of MCI and attending cognitive stimulation protocols were recruited as a control group. All patients gave written informed consent to participate in the study, in accordance to the principles of the Declaration of Helsinki. Common exclusion criteria were the inability to understand task instructions, a history of other neurologic diseases or of substance abuse. All participants were right-handed according to a standard questionnaire (Oldfield, 1971), and presented normal or corrected-to-normal vision. Detailed information is provided in Tab. 1 for personal data and in Tab. 2 for neuropsychological assessment. Mean age was 53.2 years (SD= 11.7) for LHD and 69 years (SD= 11.61) for MCI (LHD were therefore younger than MCI, $t_{(15.2)}$= 2.85, p= 0.012). No differences were found with respect to number of years of education (LHD: M= 12.4 years, SD= 2.99; MCI: M= 9.75 years, SD= 4.02; $t_{(12.62)}$= 1.55, p= 0.145; all t-test are Welch's tests optimized for samples with unequal variances and size).

Brain lesions for all LHD patients were manually reconstructed using MRIcron (Rorden & Brett, 2000). Individual scans (MRI or CT) were reoriented using SPM (Friston, Ashburner, Kiebel, Nichols & Penny, 2007) and then normalized to an age-appropriate template brain by means of the SPM Clinical Toolbox (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) using enantiomorphic normalization (Nachev, Coulthard, Jäger, Kennard, & Husain, 2008). Lesion overlays are depicted in Fig. 1. The maximal overlap occurred in the white matter between the lateral ventricle and the superior end of the insula (MNI X = -30, Y -21 to -7, Z = 20).

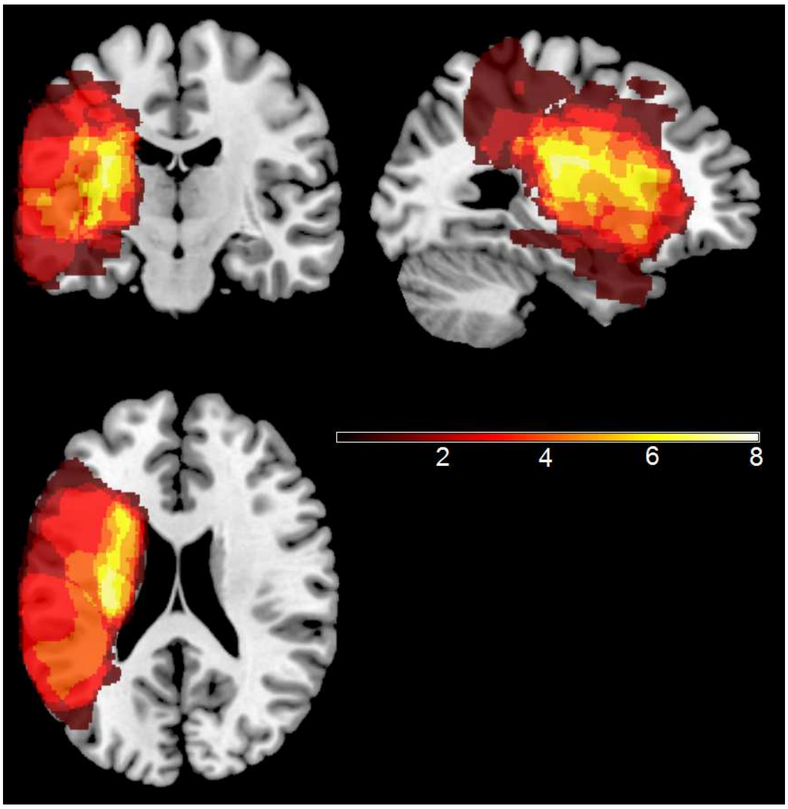

Fig. 1. Lesion overlays. The lesion mapping for LHD, normalized to a template of aged healthy individuals according to the procedure described in Rorden et al. (2012), is shown as an overlay on a standard template using MRIcron (Rorden & Brett, 2000). The different colors code for the number of overlapping lesions from dark red (minimal/no overlap) to white (maximal overlap).

2.2 Neuropsychological Assessment

All patients underwent an in-depth neuropsychological evaluation (Tab. 2). In the LHD group, the conventional part of the Behavioural Inattention Test (BIT, Wilson, Cockburn, & Halligan, 1987) was administered in order to assess visuo-spatial functions. The BIT includes six subtests (lines, letters, and star cancellation, line bisection, figure copy and spontaneous drawing). Each subtest was scored separately, and a global index was obtained. None of the patients in the LHD group showed a lateralized attentional bias, according to the BIT overall cut-off. Furthermore, no patient was below the cut-off in any of the subtests. In Tab. 2 scores are reported separately for right- and left-sided targets. No patient showed any hint of lateralized omissions across any subtest. The average performance in the cancellation tasks is shown in Fig. 2.

The Aachener Aphasie Test (AAT, Luzzatti, Willmes & De Bleser, 1996) was administered to quantify presence and degree of language deficits. The results of the comprehension subtest are reported in Tab. 2. All patients were able to comply with task instructions, and provided either a verbal response or pointed towards cardboards depicting all possible answers (see Methods section).

Subject/Group	**Sex/Age/Education (ys)**	**Etiology**	**Handedness**	**Detection test**	**Lesional Volume (cc)**	**Time from stroke (days)**
1/LHD	M/46/11	H	R	-	27	115
2/LHD	F/49/13	H	R	-	15	318
3/LHD	M/60/13	H	R	-	5	2632
4/LHD	F/53/13	H	R	-	79	299
5/LHD	F/52/13	I	R	-	246	145
6/LHD	M/47/13	H	R	-	79	52
7/LHD	M/64/17	I	R	-	165	370
8/LHD	M/41/13	I	R	-	46	313
9/LHD	F/41/13	H	R	+ (Contralesional omissions)	136	260
10/LHD	M/79/5	H	R	-	1	57
1/MCI	M/56/17		R			
2/MCI	M/49/11		R			
3/MCI	M/84/8		R			
4/MCI	F/73/9		R			
5/MCI	M/72/10		R			
6/MCI	F/73/5		R			
7/MCI	F/79/5		R			
8/MCI	M/66/13		R			

Tab. 1 Demographical and neurological data. LHD and MCI groups: M/F: male, female; R/L: Right-handed, Left-handed. LHD: I/H: ischemic, hemorrhagic; +/-: presence, absence of contralesional omissions.

The presence of contralesional omissions/extinction was assessed through detection test. The examiner sat in front of the patient, at a distance of about one meter, positioning his hands at the patient's visual periphery. For each trial the experimenter moved either his right or left index finger only, or both fingers simultaneously. The participant had to say or point at the side where a movement was perceived. Sixty trials were performed (30 in the upper and 30 in the lower quadrant, and 20 on the right, left, or both sides).

The Rey-Osterrieth complex figure test (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2014) was administered to broadly evaluate a range of visuo-spatial abilities such as planning, organizational, and strategic abilities together with visuo-perceptual and visuoconstructional functions. The Mini Mental State Examination (MMSE; Magni, Binetti, Bianchetti, Rozzini, & Trabucchi, 1996) and Raven's progressive matrices (Carlesimo, Caltagirone & Gainotti, 1996) were also administered to investigate overall cognitive functioning. These last three tests were also part of the neuropsychological assessment of the control group of MCI patients. The diagnosis of MCI was made accordingly to Petersen (2004) criteria. All patients complained about cognitive deficits in everyday life, and at least one relative supported this complaint. Global cognitive functioning, as assessed through MMSE and Raven's matrices (therefore including orientation in space/time and abstract reasoning), was spared (see Tab. 2), whereas they showed a deficitary performance in at least one task within a standardized screening battery assessing a broad range of cognitive functions.

Subject/ Group	**MMSE (Cut-off: 24)**	**RAVEN (Cut-off: 18.96)**	**Rey-Osterrieth complex figure- Copy/Recall (Cut-off: 28.87/9.46)**	**BIT (Cut-off: <130)**	**BIT-Barrage-L/R Targets cancelled (max 18/18)**	**BIT-Star Cancellation Task- L/R Targets cancelled (max 27/27)**	**BIT-Letters Cancellation Task- L/R Targets cancelled (max 20/20)**	**AAT - Comprehension**
1/LHD	30	30.8	34.75/16	142	18/18	27/27	20/18	9
2/LHD	27.9	31.8	35.25/19.75	146	18/18	27/27	20/20	9
3/LHD	27.5	29.8	27.25*/13.75	138	18/18	25/26	20/20	8
4/LHD	n.a.	25.3	26.75*/12.75	144	18/18	27/27	20/20	6
5/LHD	n.a.	32.8	35.25/14.75	140	18/16	27/27	19/18	4
6/LHD	24.9	26.3	33/6.5*	136	18/18	26/27	16/16	2*
7/LHD	n.a.	22.6	32/22.75	145	18/18	27/27	20/20	7
8/LHD	25.9	31.8	32.5/24	145	18/18	27/27	20/19	9
9/LHD	n.a.	30.8	31.5/7*	145	18/18	27/27	20/20	4
10/LHD	20.7*	19	7.75*/8.75*	132	17/18	27/27	16/18	-
1/MCI	27	31.6	36/2.75*					
2/MCI	27	33.1	38.75/14.75					
3/MCI	26.7	29.1	26.75*/8.75*					
4/MCI	25.4	27.3	26.25*/15.25					
5/MCI	25.4	34.6	38/18.75					
6/MCI	25.3	27.2	28.75*/15.75					
7/MCI	21.7*	33	28.75*/13.25					
8/MCI	26.2	33.4	34.75/11					

Tab. 2. Neuropsychological assessment. MMSE (Mini Mental State Examination, Magni et al., 1996), Raven's progressive matrices (Carlesimo et al., 1996), and Rey-Osterrieth complex figure (Copy and Recall, Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2014): scores corrected for age and education are reported. *: performance below cut-off. BIT (Behavioural Inattention Test, Wilson, Cockburn, & Halligan, 1987): global scores and raw scores at cancellation subtests are reported. AAT (Aachener Aphasie Test, Luzzatti, Willmes & De Bleser, 1996): results from the comprehension subtest are reported, classified according to a standard nine points scale (lower values index a more severe deficit). -: data not available. n.a.: unable to assess.

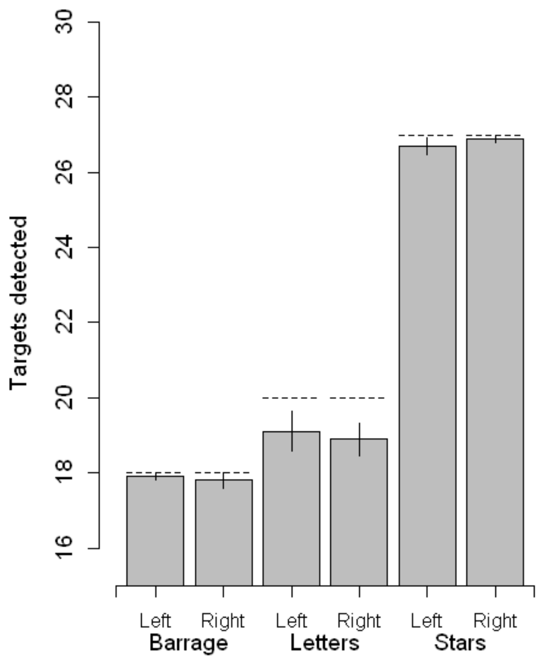

Fig. 2. Cancellation tasks. The mean number of items correctly detected is shown for each BIT cancellation subtest as a function of their side on the testing sheet. Dashed lines represent the maximum number of targets for the specific subtest. Error bars represent SEM.

2.3 Apparatus, stimuli, and procedures

Patients were individually tested in a quiet room, sitting comfortably at a distance of about 60cm from a 19-inch computer monitor. There were three experimental conditions: the single-task condition and two dual-task conditions (visual vs. auditory). Each trial started with a black screen (1000 ms), followed by a white fixation cross (about 1cm wide) that was presented in the center of the screen for 800 ms. The fixation cross flickered for 200 ms before target presentation as a warning signal and to redirect overt attention to the screen center. The lateralized visuospatial target was a white disk (diameter: 8mm) presented against the black background for a duration of 100ms. The target could appear unilaterally, on the left or the right side of the display (lateral distance from fixation: 170mm), or bilaterally (both on the left- and on the right side). “Catch” trials, in which no target was actually displayed on the screen, were also included to assess a potential spatial bias in responses. The three target locations (left, right, bilateral) and the catch trials were equiprobable (i.e., 25% of each type) and presented in random order. Simultaneously with the lateralized target(s) and for the same duration (100 ms), a visual shape (a line drawing chosen randomly among triangle, square and circle) was shown at fixation and a sound (an environmental sound chosen randomly among train whistle, doorbell, and hammer) was presented through binaural earphones. Once the 100ms time window elapsed, a noisy screenshot was presented until the beginning of the following trial, as to minimize retinal after-image.

Patients always had to report the position of the target(s) (i.e., “no target”, “right”, “left”, or “both” sides) as first response. This was the only request for the single task condition, whereas in the dual-visual or dual-auditory conditions they also had to report the central shape or the presented sound, respectively. It is worth to emphasize that the sensory stimulation was therefore identical across the three conditions. In other words, the manipulation was purely top-down, based on the presence/absence of concurrent task demands. In order to facilitate patients with difficulties in naming, responses were provided either verbally and/or by pointing to an ad-hoc cardboard depicting all possible answers. Patients’ responses were then coded by the experimenter using a computer keyboard.

Participants were allowed to rest after each trial, if necessary. The experimenter monitored eye movements and started each trial only when fixation was maintained. Trials affected by eye movements were marked and discarded offline in the data analyses. The experiment was divided in 6 blocks, each condition (single, auditory, or visual) being repeated twice (i.e., two blocks per condition). The single task condition was administered in the first and in the last block in order to assess the potential effects of fatigue or sustained attention problems. Accordingly, the dual task conditions were performed in blocks 2 to 5 – with a fixed alternating order (i.e., visual-auditory-visual-auditory). A practice phase, consisting of 21 trials, was carried out before starting the experiment to allow patients familiarizing with the primary task. During this phase the experimenter repeatedly ensured that the patient fully understood task requirements. Each session comprised 36 trials (9 trials for each type of lateral target). The occurrence of the different shapes or sounds (3 x 3) was balanced within each block. Overall, the experiment consisted of 216 trials (3 load conditions x 4 types of target x 18 trials per cell).

3.0 RESULTS

Results were analyzed with the open-source software R (R Core Team, 2015). Data obtained from the practice phase were dismissed. Trials invalidated by eye movements (<0.1%) were discarded as well. Data were analyzed through *mixed-effects multiple regression models* (Baayen et al., 2008) using the lme4 package for R (Bates, Maechler, Bolker, & Walker, 2014). A great advantage of mixed models is that they are based on single trial data (rather than on averaged data), they do not assume independence amongst observations, and the model fitting procedure takes into account the covariance structure of the data, including random effects (i.e., individual variability). This approach is particularly interesting for the analysis of patients' data, which are typically more noisy than the data of healthy participants (see Zorzi et al., 2012, for a previous application of mixed models to neglect patients' data; also see Goedert, Boston, & Barrett, 2013). All models had a logistic link-function, which is appropriate for a dependent variable with binary distribution (i.e., accuracy).

As a first step we defined a model containing the random effects. Linear mixed models generalize best by including the maximum random structure that does not prevent model convergence (Bates, Kliegl, Vasishth, & Baayen, 2015). Random intercepts and random slopes were introduced sequentially and their effect on model fit was assessed using a log-likelihood test (that is, we compared the residuals of each model and choose the one with significantly lower deviance as assessed by a chi squared test). The model with the final random effects structure was then used to introduce the fixed effects. We used a stepwise approach, adding main effects before interactions, and used the same log-likelihood tests to assess whether the improvements in the model fit were statistically significant.

3.1 Effects of Attentional load on spatial monitoring

We first assessed whether performance in the spatial monitoring task was modulated by the Load condition (i.e., Single Task, Visual Dual Task, Auditory Dual Task), and whether it was different across Target type (Left, Right, Bilateral, Catch) and across Groups (LHD, MCI). Accuracy was entered as dependent variable in the mixed model analysis. The random structure included Participant as random intercept and the random slopes for Load and Target type. In other words, individual variability was accounted for both in terms of overall accuracy (intercept) and across the different experimental conditions (random slopes). None of the fixed main effects of Target type and Group yielded significant improvement of the model fit ($\chi^2 \leq 5.18$, $p \geq 0.085$), whereas the main effect of Task did ($\chi^2 = 7.3$, $p = 0.026$). We then assessed two-way interactions (against a model containing only the relative main effects): the Load by Target type ($\chi^2 = 20.2$, $p = 0.002$) and Group by Target type ($\chi^2 = 8.01$, $p = 0.046$) interactions improved model fit, whereas Group by Load ($\chi^2 = 4.91$, $p = 0.085$) did not. The three-way interaction Group by Load by Target type, finally, did not improved model fit ($\chi^2 = 10.63$, $p = 0.1$) with respect to the model containing all main effects and two-way interactions.

The three-way interaction (Group by Load by Target type) is depicted in Figure 3. Despite it failed to reach significance, visual inspection of the graphs suggests that the multitasking conditions affected performance for bilateral and right-sided targets, but only for LHD patients. We therefore fitted separate mixed models for MCI and LHD patients. The random structure remained identical in all models.

LHD Group. Neither of the fixed main effects was found to significantly improve the model fit (Load: $\chi^2 = 2.27$, $p = 0.32$; Target type: $\chi^2 = 3.35$, $p = 0.34$). However, the Load by Target type interaction improved model fit ($\chi^2 = 26.38$, $p < 0.001$). Notably, detection accuracy under load dropped for bilateral trials from 80.4% to 65% for auditory (z= -2.67, $p = 0.007$) and to 58.9% for visual load (z= -4, $p < 0.001$), with a difference also between visual and auditory (z= -2.16, $p = 0.03$).

For contralesional (i.e., right) targets accuracy dropped from 92.2% to 69.1% for auditory (z= -3.3, *p*< 0.001) and to 62% for visual load (z= -4.6, *p*< 0.001), the two dual task conditions also differing (z= -2.24, *p*= 0.025). All contrasts report the Wald z value and relative, uncorrected, p value. Performance for ipsilesional targets (see Tab. 3) and catch trials remained high (> 96.1%) and it was not modulated by load condition. The parameters of the random and fixed effects of the final model are reported in Tab. 3.

MCI Group. Neither of the fixed main effects improved the model fit (Load: χ^2= 2.39, *p*= 0.3; Target type: χ^2= 2.65, *p*= 0.45). Moreover, the fit did not improve when adding the two-way interaction (χ^2= 4.04, *p*= 0.67). Indeed, accuracy remained high across conditions.

To summarize, we found that multitasking induced a selective impairment in detecting bilateral and contralesional targets in LHD, whereas the performance of MCI patients was unaffected. We therefore proceeded to investigate how errors were spatially distributed across conditions.

Random effects:								
Groups	**Name**	**Variance**	**SD.**	**Corr.**				
Subject	**(Intercept)**	2.46	1.57					
	Side - Bilateral	7.15	2.6	0.01				
	Side - Catch	0.25	0.5	0.22	-0.3			
	Side - Right	2.6	1.6	-0.33	0.72	-0.82		
	Load - Auditory	0.76	0.88	0.16	0.25	-0.92	0.66	
	Load - Visual	1	1	-0.33	0.33	-0.99	0.86	0.86
Fixed effects:		**Estimate**	**Estimate**	**SE**	**z value**	**p**		
	(intercept)	5.52	1	5.36	<0.001***			
	Single -Bilateral	-2.38	1.3	-1.83	0.07			
	Single - catch	-1.55	1	-1.53	0.12			
	Single - Right	-1.8	1.1	-1.64	0.1			
	Auditory - Bilateral	-4.3	1.4	-3.13	<0.01**			
	Auditory - Catch	-1.14	1.1	-1	0.31			
	Auditory - Right	-3.92	1.2	-3.3	<0.001***			
	Auditory - Left	013	1.1	0.12	0.9			
	Visual - Bilateral	-5.23	1.4	-3.78	<0.001***			
	Visual - Catch	-0.86	1.2	-0.73	0.46			
	Visual - Right	-4.81	1.2	-3.9	<0.001***			
	Visual - Left	-1.29	1	-1.33	0.18			

Tab. 3. Details of the final model for LHD patients. Factors were dummy coded with left targets in the single task as reference level. Parameters of the random effects are reported in the top panel. SD = standard deviation, SE = standard error. Parameters of the fixed effects are reported in the bottom panel. Note that the β coefficient (Estimate) represents the adjustment with respect to the reference level.

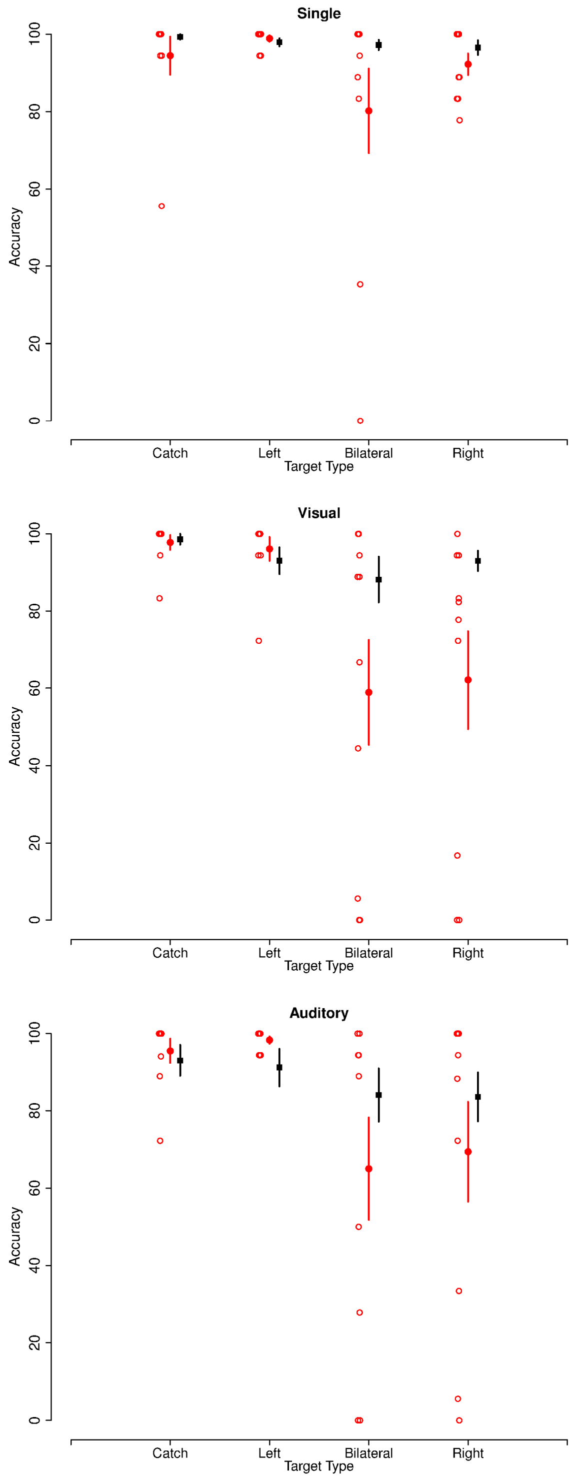

Fig. 3. Accuracy in the spatial monitoring task is depicted for each Load condition (single task, visual dual task, auditory dual task) as a function of Target type (left, right, bilateral, catch) and Group (LHD: red circles;

MCI: black squares). Error bars represent SEM. Individual performance of LHD patients is shown using red empty circles.

3.2 Asymmetry Indices

We computed Asymmetry Indices (AI) for unilateral, bilateral and catch trials to investigate how errors were spatially lateralized. The AIs for bilateral and catch trials were (separately) computed by subtracting the individual proportion of “left” responses from the proportion of “right” responses. A negative AI indexes that “left” responses prevailed among errors while positive AI reveals prevalence of “right” responses. For unilateral trials AIs were obtained by subtracting the proportion of omissions for right-sided targets from the proportion of omissions for left sided targets. The resulting index is similar to the previous one, with negative values representing a leftward bias and positive values representing a rightward bias. Note that all AI values express the asymmetry in terms of proportion of errors. That is, a value of -1 indicates that all of the right targets but none of the left targets were missed, whereas a value of 0 indicates that an equal number of left and right targets were missed (or that no targets were missed). For each AI, we first assessed whether it significantly differed from 0 (thereby indexing spatial bias) by means of a one-sample t-test (across all Load conditions). If that was the case, we proceeded with assessing the modulatory effect of attentional Load. Comparisons between groups were not performed due to violation of normality, different sample size, and different variances of AI.

Unilateral targets. AI were not significantly different from 0 in the MCI group ($t(7)= -0.84$, $p= 0.43$), whereas they were overall negative in LHD ($t(9)= -2.65$, $p= 0.026$). One-way repeated measures ANOVA showed an effect of Load ($F(2,18)= 5.06$, $p= 0.018$, $\eta_p^2= 0.359$), with AI decreasing from -0.06 in the single task to -0.29 in the auditory and -0.3 in the visual task ($t(9)>2.43$, $p< 0.037$), but with no differences between the two dual tasks ($t(9)= 0.24$, $p= 0.82$).

Bilateral targets. AI were positive but not significantly different from 0 in the MCI group ($t(7)= 1.5$, $p= 0.178$), whereas they were overall negative in LHD ($t(9)= -2.6$, $p= 0.029$). One-way repeated measures ANOVA showed an effect of Load ($F(2,18)= 5.46$, $p= 0.033$, Greenhouse-Geisser corrected, $\eta_p^2= 0.378$), with AI decreasing from -0.2 in the single task to -0.34 in the auditory ($t(9)$= 2, p= 0.071) and -0.41 in the visual task ($t(9)$= 2.56, p= 0.03). Auditory and Visual tasks did not differed ($t(9)$= 2.05, p= 0.07).

Catch trials. AI were not different from 0 both in LHD ($t(9)$= -0.8, p= 0.47) and MCI ($t(7)$= 1.87, p= 0.1) patients. This suggests that the asymmetry of responses in LHD patients in unilateral and bilateral trials cannot be attributed to a response bias (i.e., an overall tendency to respond “left”).

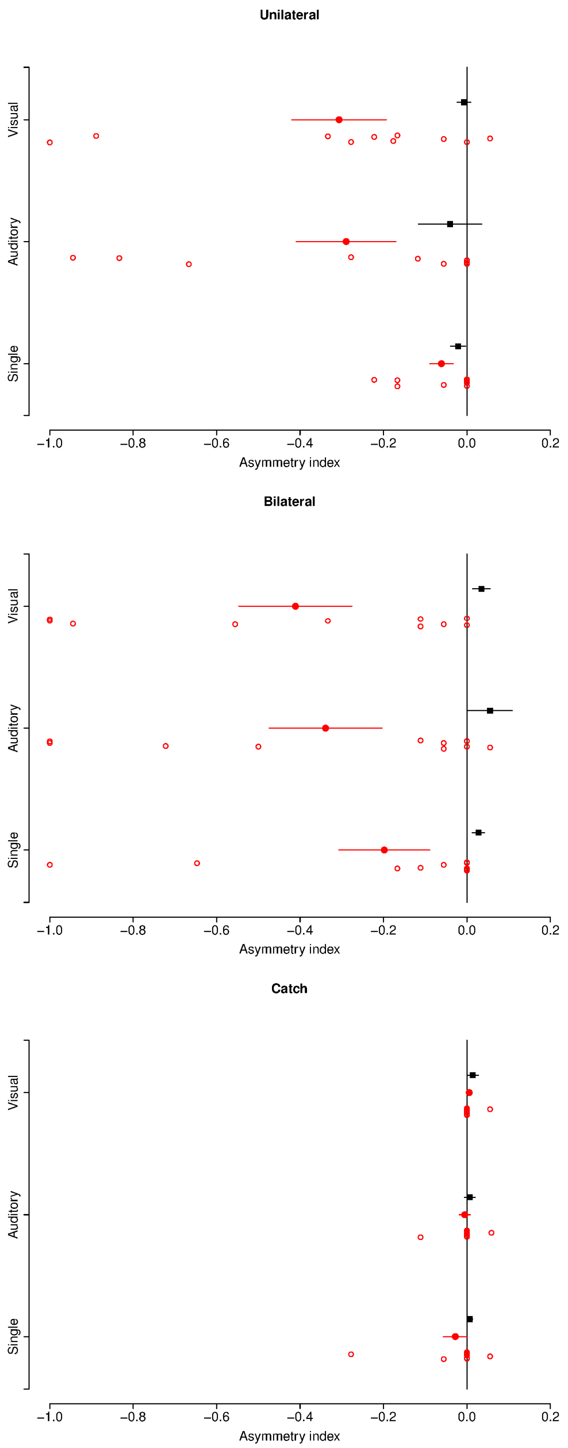

Fig. 4. The Asymmetry Index is depicted for each type of target (unilateral, bilateral, catch) as a function of Load condition (single task, visual dual task, auditory dual task) and Group (LHD: red circles; MCI: black squares). Values express the asymmetry as the proportion of errors and the sign its direction, with negative values indexing a leftward bias (e.g., a value of -1 means that all and only right targets are neglected). Individual values for LHD patients are shown as red empty circles. Error bars represent SEM.

Individual analysis. To determine how many LHD patients presented with a pattern of right neglect in the unilateral trials or extinction in the bilateral trials, we assessed the individual AI against the MCI group used as the control sample (Crawford & Howell, 1998). Note that this method is robust even in the face of severe violations of normality (Crawford et al, 2006).

Unilateral trials. Patients 4, 7 and 9 showed significant asymmetry in the single task ($t(7) \leq -2.7$, $p \leq 0.03$), which persisted in the auditory dual task ($t(7) \leq -2.75$, $p \leq 0.029$) and in the visual dual task ($t(7) \leq -6.62$, $p < 0.001$). Strikingly, the visual dual task induced a spatial bias in patients 2, 5, 6, and 8 ($t(7) \leq -3.25$, $p \leq 0.014$). In summary, while only three patients over ten presented contralesional omissions at baseline, multi-tasking revealed contralesional deficits in additional four cases in the visual load condition.

Bilateral targets. Patients 4, 5, 7 and 9 showed a significant asymmetry in the single task ($t(7) \leq -3.12$, $p \leq 0.017$). The same patients consistently showed a spatial bias in both the visual ($t(7) \leq -9.44$, $p(s) < 0.001$) and the auditory ($t(7) \leq -3.45$, $p(s) \leq 0.01$) dual tasks. Finally, patient 2 presented a severe extinction pattern in the visual dual task only ($t(7) = -5.89$, $p < 0.001$).

3.3 Fatigue and sustained attention

We asked whether fatigue, or deficit in sustained attention, could partially account for the impaired spatial monitoring performance of LHD patients. Note that the single task was performed both at the beginning (i.e., first block of trials) and at the end (i.e., last block of trials) of the experiment. Therefore, a significant drop in performance between the first and last block would suggest that the effect of multitasking is somewhat confounded with fatigue. A mixed-effects model was fitted to the accuracy data from the single task trials. The random effects matrix included random slopes for Block (first or last) and Target type, in addition to the random intercept for

Participant. Notably, Block did not improve model fit when it was entered as fixed main effect (χ^2= 2.82, p= 0.09) or in the two-way interaction with Group (χ^2= 1.52, p= 0.22). This shows that fatigue (or, conversely, learning) had no effect (see Fig. 5 for a graphical representation). Note that accuracy (collapsed across Target type) slightly dropped in MCI patients (from 99.3% to 96.2%), but it slightly improved (89.6% to 93.3%) in LHD patients.

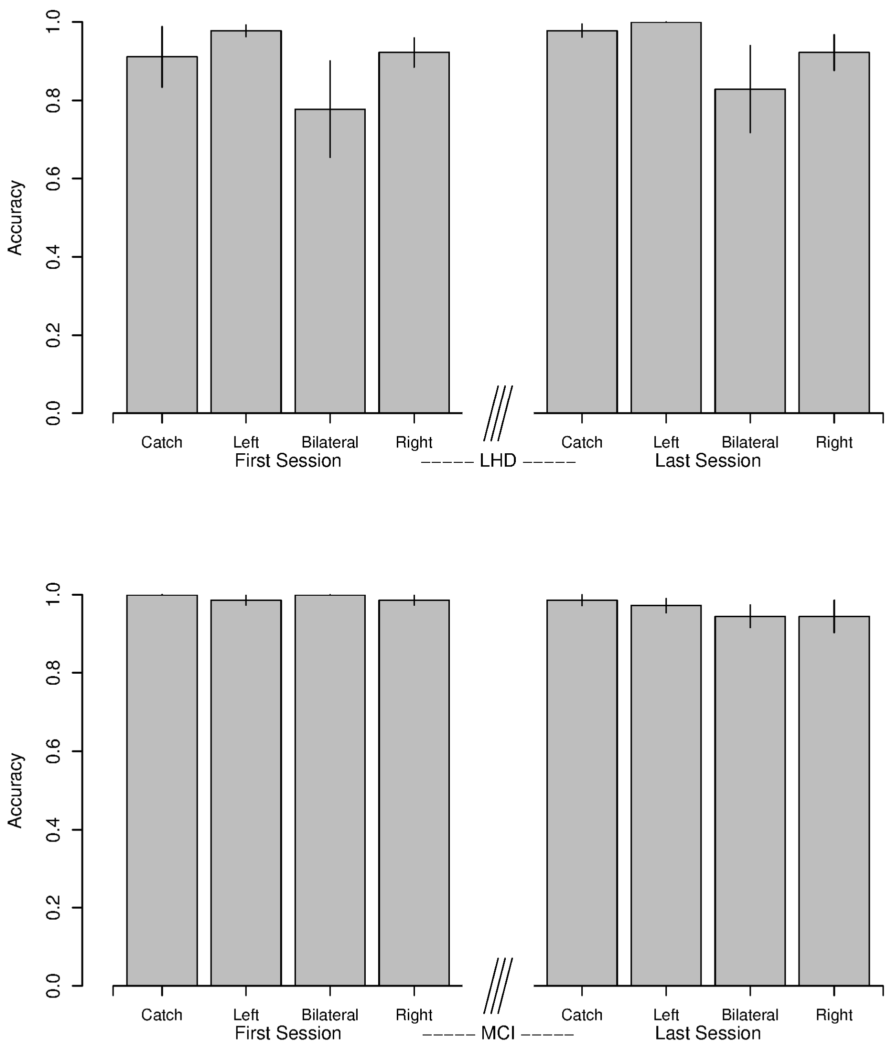

Fig. 5. Performance of LHD (top panel) and MCI (bottom panel) patients in the first block and in the last (i.e., sixth) block of the spatial monitoring task. In both blocks patients only had to report target side. Error bars represent SEM.

3.4 Secondary task

As a final analysis we assessed whether accuracy in the secondary task differed as a function of Type of load (visual vs. auditory) or Group (LHD vs. MCI). A mixed-effects model was fitted to the accuracy data. The random effects structure included random intercept and slope for Type of load, in addition to a random intercept for Participant. When the main effects of Type of load and Group were entered as fixed effects, only the former significantly improved model fit (χ^2= 4.18, p=0.04 vs. χ^2= 0.52, p= 0.47). The Group by Type of load interaction did not improve the fit (χ^2= 0.83, p= 0.36). The visual (secondary) task was overall more difficult (β= -1.12, OR= 0.325, z= -2.7, p= 0.007), resulting in about 76.12% of correct responses against 88.35% of correct responses for the auditory task, but the two groups of patients did not show reliable differences.

4.0 DISCUSSION

We investigated the effects of attentional load (i.e., multitasking) on a spatial monitoring task in a group of stroke patients with chronic lesion involving the left hemisphere. We found that concurrent task demands, regardless of the sensory modality of attentional load (visual or auditory), reveal a pattern of contralesional targets omission (right neglect and/or right extinction). In contrast, no lateralized deficits was found in the control group of patients with Mild Cognitive Impairment.

Several changes to the original paradigm of Bonato et al. (2010) have been introduced in the present study to further improve its design and to make it more suitable for testing LHD patients, which are often characterized by linguistic deficits. First, all alphanumerical stimuli were removed. Bonato and colleagues presented a letter at fixation (to be reported in the visual dual task) and an auditory number (for the auditory dual task). Moreover, in the previous version of the auditory task the request of counting forward, twice and by steps of two, was made, whereas in the current one this kind of working memory load was removed. Second, the spatial monitoring task was prioritized over the concurrent task by asking patients to always report the lateralized target first (unlike in Bonato et al., 2010). This allows to exclude that spatial omissions were caused by the delayed response or by interference from the concurrent task. Third, catch trials were introduced to exclude the presence of any response bias. Fourth, the single task was re-administered in the last block of the experiment, thereby allowing to exclude that lateralized deficits in spatial monitoring emerge as a result of fatigue or drop in sustained attention.

Although all LHD patients showed normal performance in a classic paper-and-pencil assessment battery for neglect, few of them (4 patients out of 10) showed extinction at baseline ("left" responses to bilateral targets in the single task), thereby revealing the high sensitivity of a test employing brief target duration (Bonato & Deouell, 2013). When a secondary visual task was introduced, one more patients (hence 5/10) showed extinction. As expected, the dual-task paradigm revealed that extinction was not present in some LHD patients. This might index the genuine absence of core lateralized disorders; alternatively, it might suggest that non-spatial attentional resources are sufficient for an optimal compensation of spatial deficits (Bonato, 2015).

While the finding of an extinction pattern seems consistent with the hypothesis of between-hemifield competition in conditions of double simultaneous stimulation (Driver & Vuilleumier, 2001; Kinsbourne, 1987; Miller, Gochin, & Gross, 1993), the emergence of a pattern of right neglect under multitasking is particularly striking because unilateral right targets, as opposed to bilateral targets, are not subject to bottom-up competition. A significant asymmetry in the detection of unilateral targets in the single task was found only in three patients, whereas under visual load it was present in seven patients out of 10. These results clearly show that subtracting non-spatial attentional resources to perform a concurrent task hinders visuospatial processing and reveals attentional imbalances caused by the unilateral brain damage.

We propose that the effect of multitasking is best understood as an interaction between spatial and non-spatial components of attention. More specifically, concurrent task demands recruit non-spatial, supramodal, attentional resources which are otherwise recruited to perform spatial monitoring. In the ERP study on healthy participants by Bonato et al. (2015), the same load manipulation employed in the present study modulated the amplitude of the first positive component (P1) and shifted its neural generators, suppressing the signal in the early visual areas during both visual and auditory dual tasks. Moreover, later N2 contralateral components were particularly influenced by the concurrent visual task and were related to increased activation of the right supramarginal gyrus, suggesting a high sensitivity of the right hemisphere to load manipulations. Lisi, Bonato, & Zorzi, (2015) showed that the top-down allocation of supramodal attentional resources in a similar multitasking paradigm modulates pupil dilation. Cognitively-related pupil dilation has been linked to a neurotransmitter system, the locus coeruleus–noradrenergic neuromodulatory system (Aston-Jones & Cohen, 2005), which is thought to have a central role in the functional integration of the attentional networks (Corbetta, Patel, & Shulman, 2008).

The much higher prevalence of spatial neglect after right hemisphere compared to left hemisphere lesions has been classically attributed to brain asymmetries in spatial processing (Kenneth M. Heilman & Van Den Abell, 1979) or in interhemispheric inhibition (i.e., stronger inhibition by the right hemisphere; Kinsbourne, 1987). The latter model seems to better explain the pathological leftward bias observed in LHD patients under multitasking. That is, increasing attentional load might boost the imbalance in interhemispheric inhibition, thereby causing stronger suppression of left hemisphere activity. It is worth noticing, however, that the pathological leftward bias described here is unlikely to reflect an exacerbation of the subtle leftward bias described in healthy participants (i.e., pseudoneglect; Jewell & McCourt, 2000), as detailed in Chapter 1. Thus, one viable explanation of the present results is that neural activity in the bilateral dorsal frontoparietal network, which is symmetrical in the healthy brain (Corbetta & Shulman, 2011), becomes strongly asymmetrical under the joint influence of left hemisphere damage and increased left hemisphere inhibition induced by attentional load.

A related, yet alternative, perspective to interpret the present findings can be found by referring to structural limits in the human brain – such as those hampering peripheral perception in healthy subjects under visual load (Lavie, 2005) – or amodal networks acting as central information bottlenecks (Dux et al., 2006; Tombu et al., 2011). These aspects are major determinants in several cognitive processes, including perception and spatial awareness, but typically their contribution in healthy participants is mostly detectable in terms of modulation of response times (but see Chapter 1, for discussion, and Emrich, Burianová, & Ferber, 2011). The presence of neurological deficits can emphasize these structural limits, perhaps by affecting visual working memory capacity (Danckert & Ferber, 2006; Husain et al., 2001; Malhotra et al., 2005; Pisella, Berberovic, & Mattingley, 2004), and produce more striking behavioral effects, such as the inability to perceive a lateralized target. This is often the case in patients with USN, where the co-occurrence of core lateralized deficits and of non-spatial impairments (Husain & Rorden, 2003) determine the complex clinical manifestations of USN. This fits nicely, finally, with the experimental induction of “transient visual neglect” in healthy participants under heavy visual working memory load (Emrich et al., 2011),

Attentional disorders in patients with LHD are often considered uncommon, particularly in the subacute stage (Ringman et al., 2004). One might object that this difference is a consequence of excluding from the samples patients with severe linguistic disorders (who may fail to comply with task instructions), thereby describing only selected and overall less impaired patients (De Renzi, 1982; Bonato, Sella, Berteletti & Umiltà, 2012). In a study on 80 unselected LHD patients, Beis and colleagues (2004) observed neglect in less than 15% of cases when considering either cancellation or drawing tasks alone. However, when the presence of neglect signs in any test was taken as diagnostic criterion, the percentage of patients presenting some degree of neglect increased to 40% (Beis et al., 2004). This indicates that lateralized attentional disorders might be revealed in a substantial proportion of LHD patients using a comprehensive screening battery and a more lenient diagnostic criterion. Here we showed that multitasking reveals marked lateralized spatial deficits in a substantial proportion of patients, and that in the same subgroup the clinical gold standard for diagnosis, namely paper-and-pencil testing, did not show any sign of deficit.

This approach will be a useful tool for clinicians willing to assess thoroughly visuo-spatial functions, especially those who often notice a mismatch between standard paper and pencil neuropsychological assessment and behavioural observation showing that, in everyday life, difficulties due to lateralized defects might be present in face of a near-ceiling performance in classic diagnostic tests. As we discussed, this common situation might be due to a more or less preserved neural network subserving aspecific cognitive functions, that would be efficient enough to compensate for lateralized biases in simple tasks (i.e., cancellation tasks) but not for more complex ones. Paper and pencil tasks are convenient tools but lack some ecological validity allowing a straightforward generalization to life activities (e.g., walking in a crowded street, driving, cooking) in which, beside a primary monitoring duty, one is also engaged in concurrent processing of multiple sources of information. For this reason, a task being able to assess both spatial and non-spatial attentional functions, together with their interaction, is in principle more suited to provide ecological outcome indications. However, to confirm this crucial point, a large correlational study is needed to test whether asymmetry indices drawn from this paradigm (and the difference across load conditions) are better predictors of functional independence measures assessed through standardized scales. Without this compelling evidence and normative data obtained from elderly healthy persons, the test described here would remain, from a clinical point of view, just another diagnostic test for which the threshold is set particularly high.

5.0 ACKNOWLEDGMENTS

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CHAPTER III

Spatial Attention in Depth: Asymmetries in the Sagittal Plane

ABSTRACT

The literature on spatial-attentional asymmetries is vast and heterogeneous. Attentional resources do not appear to be equally distributed along the three main axes stemming from the body, nevertheless much less research has been devoted to the study of the sagittal (close to far) one. Here we report a series of experiments aimed at assessing whether performance in a fine-grained perceptual task (i.e., shape discrimination) differs for stimuli presented in the close or far space with respect to the observer (or at different perceived depths following a visual illusion, i.e. Ponzo's illusion). Results point to a distance effect in shape discrimination, with stimuli presented in the near space being classified faster than more distant ones despite equal retinal size (and the farther shape appearing illusorily bigger). This effect was found to arise from body- rather than hand-centred reference frames and was abolished when stimuli were not presented in a canonical and ecologically more frequent fashion (i.e., with closer shapes presented in the lower visual field and distant shapes presented in the upper one). Results are discussed in terms of an attentional account claiming that comparatively more attentional resources are allocated in close proximity of the body.

1.0 INTRODUCTION

Spatial and hemispheric asymmetries hold a special place within the literature on human visual and attentional system(s). Although general consensus has been reached about the notion that attention is not uniformly distributed along the three orthogonal axes (Gawryszewski, Riggio, Rizzolatti, & Umiltá, 1987; Shelton, Bowers, & Heilman, 1990), the majority of experiments has been carried exploiting two dimensional screens, thereby neglecting the sagittal (near-to-far) plane (Couyoumdjian, Nocera, & Ferlazzo, 2003; Losier & Klein, 2004).

The horizontal, left-to-right, axis is by far the most extensively studied. A subtle advantage for processing the left side of visual space has been clearly established in a variety of different tasks and paradigms (Jewell & McCourt, 2000; Nicholls & Roberts, 2002). One of the reasons for why the horizontal dimension is over-represented might be attributed to the crucial contribution of neuropsychological studies exploring the so-called Unilateral Spatial Neglect (USN) syndrome. USN is a disorder often occurring after a brain damage defined as the failure to report, respond to or orient towards stimuli in space (Driver & Vuilleumier, 2001; Jacobs, Brozzoli, & Farnè, 2012). The typical and most common form of USN affects the left side of space, that remains unexplored, and occur after a right hemispheric lesion involving one or more different areas within a wide cortical network subserving spatial cognition and attention (Corbetta & Shulman, 2011; Molenberghs et al., 2012). The study of horizontal USN thereby provided several hints concerning left-to-right asymmetries, but despite a vertical form of spatial neglect has been described (Làdavas, Carletti, & Gori, 1994; Pitzalis, Spinelli, & Zoccolotti, 1997; Shelton et al., 1990) much less attention was devoted to asymmetries between the upper and lower visual field. Overall, such studies provided mixed results, either highlighting subtle upward (Drago, Foster, Webster, Crucian, & Heilman, 2009; Jeerakathil & Kirk, 1994; Nicholls, Mattingley, Berberovic, Smith, & Bradshaw, 2004) or downward (Danckert & Goodale, 2001; He, Cavanagh, & Intriligator, 1996; Levine & McAnany, 2005) biases or advantages, likely due to the different tasks at play. The same is true for the third, sagittal, axis, with double dissociations found in USN patients – i.e., patients showing a more severe deficit for near than for far space (Halligan & Marshall, 1991) or vice versa (Cowey, Small, & Ellis, 1994) – suggesting that different and at least partly segregated neural systems might subserve visual processing at different depths (Bjoertomt, Cowey, & Walsh, 2002).

A common distinction is typically made between the space within arm reach (peripersonal) and the space beyond it (extrapersonal). When healthy persons are engaged in simple detection of visual stimuli, they are faster in responding to stimuli appearing closer to their body (Downing and Pinker, 1985; Gawryszewski et al., 1987), suggesting that more attentional resources are allocated there. A more specific (or perhaps partly different) manifestation of this phenomenon has been described for the space surrounding the hands. Visual stimuli are detected faster when appearing closer to the perceived position of one's own hand (that is, also when visual input is lacking, e.g. when the hand is occluded, the proprioceptive one appears sufficient for this effect to emerge; Reed, Grubb, & Steele, 2006, but see Di Pellegrino & Frassinetti, 2000). One possibility is that enhanced attentional processing might be functional to a more reactive behaviour and defensive response towards potentially harming or noxious stimuli (Graziano & Cooke, 2006; Makin, Holmes, Brozzoli, Rossetti, & Farnè, 2009). For example, looming objects are known to strongly capture human visuospatial attention (Franconeri & Simons, 2003; Lin, Murray, & Boynton, 2009) perhaps in light of the activity of multisensory brain areas such as the ventral Intraparietal area (vIP) and the precentral gyrus (Graziano & Cooke, 2006). Multimodal – visual, tactile and, to a lesser extent, auditory – neurons in these areas show a greater response to stimuli near to or approaching the body, their putative function being the coding and maintaining of a safety burden around the self, and possibly coordinating defensive behaviour whenever necessary (Graziano & Cooke, 2006). Another, at first glance complementary, account claims that objects lying in the near proximity of the hands and body might more often be ideal candidates for manipulation, and the enhanced and flexible attentional processing for near space might thereby reflect an attempt to maximize manipulation efficiency (Abrams, Davoli, Du, Knapp III, & Paull, 2008; Farnè & Làdavas, 2000). Several authors argued that the functional linkage of peripersonal space and actions or affordances could eventually explain why processing of the near space more heavily relies on a dorsal visual stream optimized for action, whereas far space processing mostly depends on a ventral stream mainly devoted to perception (Goodale & Milner, 1992; Milner & Goodale, 2008; Previc, 1990; Weiss et al., 2000).

Both these accounts seem to implicate that the rapid detection, as opposed to detailed identification, of targets would be more efficient for stimuli appearing closer to the body, in both cases in light of the more extensive exploiting of parietal networks (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000) or multisensory areas (Graziano & Cooke, 2006) mainly relying on magnocellular processing (Milner & Goodale, 2008; Previc, 1990). This has been generally confirmed through a variety of different paradigms (Franconeri & Simons, 2003; Gawryszewski et al., 1987; Reed et al., 2006). The latter account, however, predicts a possible advantage for far space in more complex tasks such as target identification or discrimination. If processing of far space mainly depends on a ventral pathway heavily relying on parvocellular processing, indeed, one could expect an improved performance in fine-grained perceptual tasks (e.g., stimulus discrimination). However, to the best of our knowledge, no study specifically addressed this issue.

In a series of experiments we sought to assess: 1) whether discrimination of visually-presented stimuli differs according to perceived depth (i.e., whether classification of geometrical shapes improves for stimuli perceived to be farther away despite equal retinal size); 2) whether this effect is modulated by the proprioceptive information of one’s own hand in the close proximity of one of the to-be-identified shapes; 3) whether a visual illusion (i.e., Ponzo’s illusion) inducing depth cues on a 2-dimensional screen is sufficient for this effect to arise; 4) whether confounds related to lower/upper visual field (i.e., near objects are, in everyday life, more often perceived in the lower visual field) have a role in driving this effect.

The first two aims were accomplished by asking healthy participants to discriminate the geometrical shape of stimuli visually presented in a virtual environment, either close (i.e., 50 cm) or distant (i.e., 300 cm) but with identical retinal size. Concurrently, the position of the non-dominant hand was manipulated, allowing us to test whether proprioceptive feedback of having the hand placed very close to the position of appearance of near stimuli (i.e., 50 cm) could boost their classification speed in light of an enhanced attentional processing.

We foretell that we eventually found the very opposite effect, that is: we observed faster reaction times in discriminating stimuli appearing near the self, as opposed to stimuli appearing farther away; we found no evidence for a sensible role of (proprioceptive) hand position in modulating this effect. This result was further confirmed in a subsequent experiment depicting the same environment in a 2-dimensional, non-immersive fashion (i.e., on a standard computer screen). In both these scenarios stimuli appearing illusorily closer to participants were also presented in the lower visual field, in an ecologic fashion and in order to exploit perspective cues (our choice of having the same retinal size for close and far targets would have resulted otherwise in the lack of a depth percept in the context of a Ponzo illusion). In the third experiment we therefore coped with this possible confound by using mirror images created by flipping original, 2-dimensional stimuli along the horizontal axis; in other words, we created a scenario where near shapes were presented in the upper visual field, whereas far shapes were presented in the lower one. The distance effect described in the first two experiments was abolished, suggesting that the lower visual field is not driving the effect (otherwise we would have observed the opposite pattern) but also that a more canonical perceptual scenario is necessary for this effect to emerge.

2.0 EXPERIMENT 1

2.1 METHODS

2.1.1 PARTICIPANTS

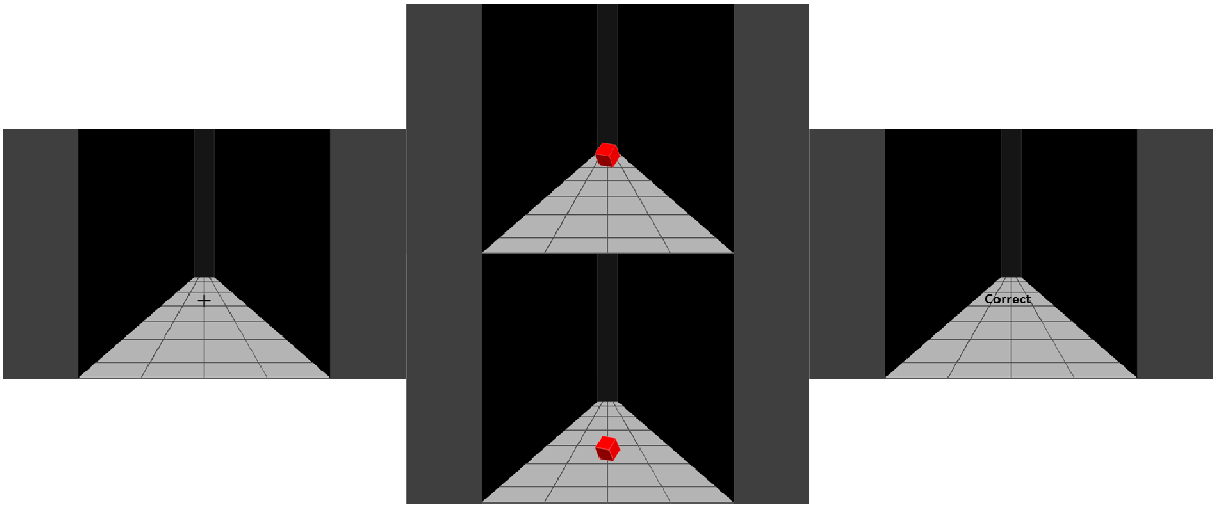
Twenty undergraduate volunteers, half males and half females, joined the experiment after giving informed written consent. They were all students of scientific subjects at the University Claude Bernard of Lyon, recruited through web advertising and compensated with 15 euros for their participation. They were all native French speakers with no history of neurological or psychiatric disorders and normal or corrected-to-normal vision. The mean age of the sample was 23.4 years (SD= 3.13); two individuals reported to be left-handed.

The study followed the Declaration of Helsinki standards and was approved by the referring Ethical Committee.

2.1.2 APPARATUS AND STIMULI

Participants set in a dark, quiet room, their head restrained by a chinrest, wearing a virtual reality headset (Oculus Rift™). The experiment was implemented with Unity 5.1.2 and the Oculus runtime 0.6, used to create the virtual environment, timely display experimental stimuli on the screen, and record responses data. It ran on a computer with an Intel Core I7 and a AMD FirePro M6000, on windows 7. The experiment logic was design using finite state machine with fixed timer based transition, and response time was measured using the System.Diagnostics.Stopwatch C# class. The scene was rendered in an Oculus Rift DK2, with a resolution of 960x1080 per eye, a frequency of 75Hz, a field of view equal to 106°.

The virtual environment consisted of an empty room (see Fig. 1, for a 2d exemplificative rendering). Different conditions were obtained by presenting shapes (cube, sphere, with similar retinal size) of different colors (red, green, and blue) and at different positions (close, 50 cm, or far, 300 cm, from the observer) in the environment. Note, hence, that “close” shapes where designed to be reachable whereas distant ones were not. The retinal size of the shapes, furthermore, was kept constant across distances (resulting, in light of the perspective, in the more distant shape appearing illusorily larger). A further rendering included a cross on the front ground, that was used as a fixation point across all trials. The position of the cross was adjusted as to be perceived midway between close and distant shapes. Participants provided responses by means of keyboard presses (N and M keys on a standard QWERTY keyboard) using the index and middle fingers of their dominant hand.



Fixation	Stimulus	Feedback
500 ms	750 ms (or until response)	1000 ms

Fig. 1 Experimental design. After a 500 ms fixation phase, either a cube or a sphere was presented on the screen, in the context of an empty room and at different distances. Participants had to respond to the shape in a fast and accurate fashion. A 1000 ms long feedback text was then displayed as a function of their response.

2.1.3 PROCEDURE

Each trial was composed by a first fixation phase (500 ms), followed by the presentation of a stimulus randomly chosen among the combination of shape (cube or sphere), color (red, green, blue), and distance (close or far). Stimuli were presented up to a maximum of 750 ms, and were replaced by a feedback text (lasting 1000 ms) as soon as a response was provided (Fig. 1). Participants were told that responses slower than 500 ms and faster than 100 ms would have been discarded, as to discourage extremely fast or slow responses; they were consequently asked to respond in a fast and accurate fashion as a function of the presented shape (index finger for cube, middle finger for sphere if responding with their right-dominant hand, the opposite for left-handers). In our design the distance of the shapes was therefore irrelevant to the task at play, and orthogonal to response.

All participants underwent a brief (24 trials) practice phase before starting the experiment, which comprised other four blocks of 60 trials each for the first part. The whole procedure was repeated twice, with a subtle but critical manipulation defining the two sessions: we asked participants to place their non-dominant hand in two different positions, namely close to the chin-rest (about 10 cm from their body) or farther apart (roughly 50cm from the self and therefore almost touching the virtual shape if this was presented in the near peripersonal space). The order for Hand Position was counterbalanced across subjects.

2.1.4 ANALYSIS

Data obtained from the practice phase were dismissed. The proportion of correct responses for each distance was first obtained, together with the proportion of valid responses (that is, responses that were both accurate and given within the 100-500 ms time window). Mean reaction times (RTs) were then obtained from valid trials only.

Results were analyzed with the open-source software R (R Core Team, 2015). Accuracy and validity indices were analyzed through logistic regression analysis using the lme4 package for R (Bates, Maechler, Bolker, & Walker, 2014); analysis were performed over single trial data (i.e., not collapsed across conditions) to better account for individual variability (Subject was therefore introduced as random effect).

The effect of Distance (Close, Far) and Hand Position (Close, Far) on RTs, instead, was assessed by means of ANOVA; a Bayesian ANOVA and t-tests (Rouder et al., 2009) were also performed through the BayesFactor package for R (Morey & Rouder, 2015) to further complement analysis and obtain a straightforward index (i.e., Bayes Factor) to quantify the strength of evidence for each model and combination of factors. Besides, a Bayesian perspective allows to quantify the strength of evidence for a null hypothesis, whereas a frequentist one is unable to do so (that is, lack of evidence is not evidence for a null effect, Kass & Raftery, 1995).

2.2 RESULTS

Distance did not affect the odds to produce an accurate response ($\beta = -0.08$, $z = -0.85$, $p = 0.396$); Hand Position as main effect or in interaction with Distance had no significant role as well ($|z| \leq 1$, $p \geq 0.315$).

However, when assessing the proportion of valid trials (that is, the proportion of correct responses given within the time-limits) a main effect of Distance was found (β = -0.15, z= -2.04, p= 0.042), suggesting that performance in identifying more distant shapes in a precise and rapid manner is overall worse (78.8% far vs. 81.3% close). Hand Position had no impact on this index, neither alone (β = -0.07, z= 0.88, p= 0.38) nor in interaction with Distance (β = -0.021, z= -0.2, p= 0.84).

RTs, finally, markedly differed across viewing Distances (Fig. 2), participants being faster in categorization when shapes appeared close (M= 382.8 ms, SD= 15.45) rather than far (M= 391.3 ms, SD= 16.7; $F_{(1,19)}$= 19.3, p< 0.001, η_p^2= 0.5). Hand Position was not found to modulate participants' performance neither alone ($F_{(1,19)}$= 0.51, p= 0.48) nor in interaction with Distance ($F_{(1,19)}$= 0.025, p= 0.87). A Bayesian analysis yielded a BF= 74.8 in favour of the model containing only the main effect of Distance, that was therefore by far the most informative model (i.e., 2.87 times more informative than the model also containing the main effect of Hand Position, BF= 25.9). The Distance by Hand Position interaction was not supported by data as well: when the full model (BF= 8.04) was compared against the model including the two main effects (BF= 25.9) we found it to be 3.3 times worse, meaning that our data actually support the lack of interactive effect (Position of the hands does not interact with Distance, and specifically does not result in faster RTs when the hand is kept near the shape appearing closer to the participant).

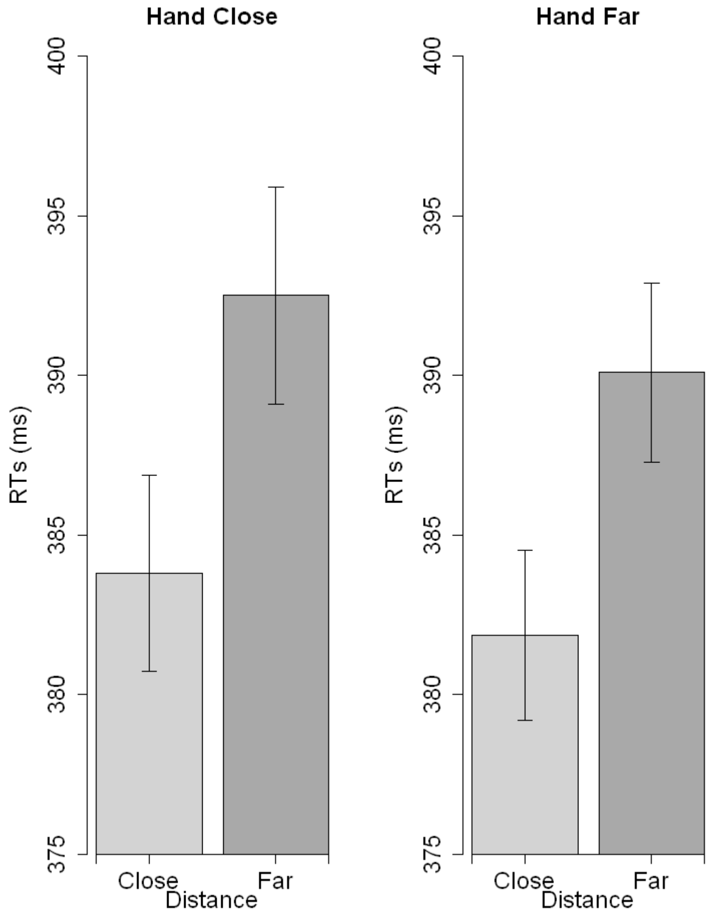


Fig. 2 Mean reaction times (ms) as a function of Hand Position and Distance to which shapes were presented. Error bars depict SEM. Speed of shape discrimination was faster when targets appeared in the peripersonal as opposed to extrapersonal space, and was unaffected by proprioceptive information about hand position. .

To summarize: we observed faster RTs when participants discriminated shapes appearing closer to them. The lack of a similar finding over accuracy suggests the absence of speed-accuracy trade-offs. This advantage for near shapes was not modulated by the proprioceptive information indicating that the hand could be more or less closer to the area of space where the nearest shape was actually presented, despite we hypothesized a possible further advantage in the case of spatial proximity.

Results are counterintuitive for at least two reasons: first, we were expecting an advantage for far in light of the putative increased relevance of the parvocellular pathway for this portion of space; second, more distant shapes appear illusorily bigger, hence in principle perceptual processing could be easier. In the next experiment we sought to test whether this effect is confirmed and also emerges following visual illusions of depth (i.e., Ponzo illusion) in a 2-dimensional plane, and therefore excluding the potential role of accommodation or convergence movements of the eyes.

3.0 EXPERIMENT 2

3.1 METHODS

3.1.1 PARTICIPANTS

Thirty-two undergraduate volunteers, half males and half females, took part in the experiment after giving informed written consent. They were all students of scientific subjects at the University Claude Bernard of Lyon, recruited through web advertising and compensated with 15 euros for their participation as in experiment 1. They were all native French speakers with no history of neurological or psychiatric disorders and normal or corrected-to-normal vision. The mean age of the sample was 21.8 years (SD= 2.52); two individuals reported to be left-handed.

The study followed the Declaration of Helsinki standards and was approved by the referring Ethical Committee.

3.1.2 APPARATUS AND STIMULI

Participants set in a dark, quiet room, their head restrained by a chinrest, facing a 15 inches large screen at a distance of approximately 57 cm. The open-source software OpenSesame (Mathôt, Schreij, & Theeuwes, 2011) was used to timely display experimental stimuli on the screen and record responses data. Stimuli were obtained by using professional designing software (SolidWorks, © 2002-2015 Dassault Systèmes, Waltham, MA, U.S.A.). The rendering of an empty room (see Fig. 1, for an example of the stimuli employed) was designed as to maximize depth cues by exploiting a Ponzo-like illusion. Different stimuli were obtained by adding shapes (cube, sphere) of different colours (red, green, and blue) and at different positions (close or far with respect to the putative observer) to the front ground of the scene. The retinal size of the shapes, approximately

2.2°, was kept constant across distances (resulting, in light of the Ponzo-like illusion, in the more distant shape appearing larger). A further rendering included a cross on the front ground, and was used as a fixation point across all trials. The position of the cross was adjusted as to be perceived midway between close and distant shapes in the final, two dimensional stimuli. Participants provided responses by means of keyboard presses (N and M keys on a standard QWERTY keyboard) using the index and middle fingers of their dominant hand.

3.1.3 PROCEDURE AND ANALYSIS

Procedure and statistical analysis were identical to experiment 1 (Fig. 1 and paragraph 2.1.3), with the exception that we dropped the Hand Position factor. Participants were asked to keep their non-dominant hand in a comfortable position either on their thigh or in close proximity of the chinrest.

3.2 RESULTS

Distance did not affect the odds to produce accurate or valid responses ($p=0.21$ and $p=0.56$, respectively).

RTs, however, markedly differed across viewing Distances, participants being faster when shapes appeared close (M= 391.1 ms, SD= 16.9) rather than far (M= 396.3 ms, SD= 17.6; $t_{(31)}= 3.86$, $p<0.001$, paired, two-tailed, Cohen's d= 0.3). A Bayesian t-test yielded a BF= 56.4, suggesting that our data strongly support the alternative hypothesis (Fig. 3).

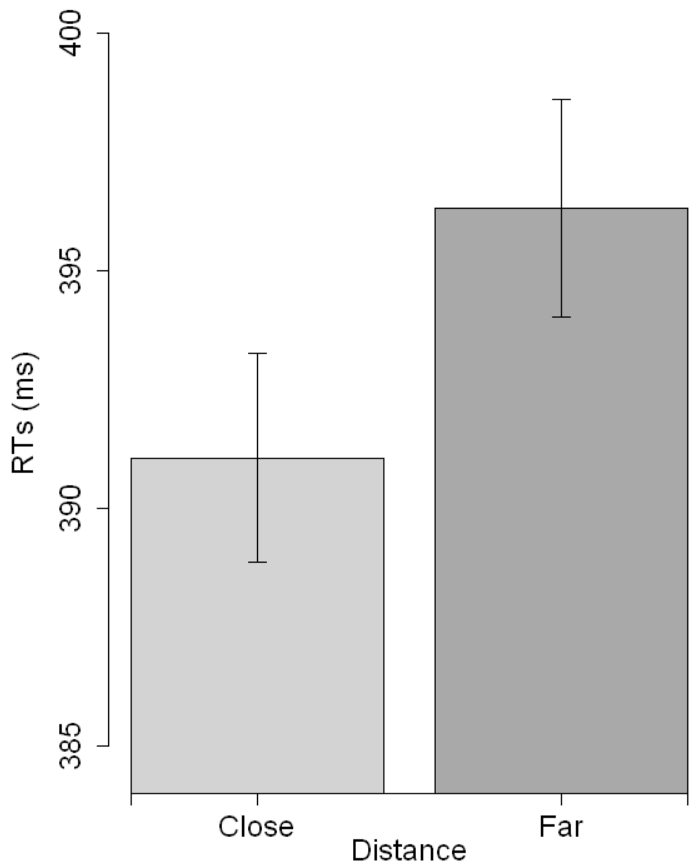


Fig. 3 Mean reaction times (ms) as a function of the Distance to which shapes were presented. Error bars depict SEM. Speed of shape discrimination was faster when targets appeared illusorily closer.

To summarise: we replicated the effect found in exp. 1 – close objects being discriminated faster than more distant ones – and found that a visual illusion (i.e., Ponzo) was sufficient for this effect to emerge.

In both the first and second experiments close shapes were also presented in the lower visual field, whereas distant ones were presented above fixation. To assess whether this confound could drive the effect – that is, perceptual processing might overall improve for stimuli appearing in the lower visual field, regardless of perceived distance – we ran a third experiment, identical to the second with the exception that stimuli were mirror-reversed along the horizontal axis (that is, shapes appearing close were presented in the upper visual field).

To define an appropriate sample size we ran a statistical power analysis: when using the effect size obtained in exp. 2 (Cohen's d= 0.3) a power of 80% (i.e., a probability of at least 80% of yielding a significant effect in a sample given the presence of a true effect in the population) was found to be reached starting from a sample size bigger than N= 19.

4.0 EXPERIMENT 3

4.1 METHODS

4.1.1 PARTICIPANTS

Twenty undergraduate volunteers, eleven females (55%), joined the experiment. They were all recruited from the Department of Psychology of the University of Padua, Italy. They were all native Italian speakers with no history of neurological or psychiatric disorders and normal or corrected-to-normal vision. The mean age of the sample was 22.75 years (SD= 3.67); three individuals reported to be left-handed.

The study followed the Declaration of Helsinki standards and was approved by the referring Ethical Committee.

4.1.2 APPARATUS AND STIMULI

The experimental setting closely mirrored that of experiment 2. The only difference was that the same images used for exp. 2 (Fig. 1) were mirror-reversed along the horizontal axis. By means of this approach we were able to present close shapes in the upper side of space and far shapes in the bottom one, but without introducing other potentially different low-level features.

4.1.3 PROCEDURE AND ANALYSIS

Procedure and statistical analysis were identical to experiment 2 (Fig. 1 and paragraph 3.1.3).

4.2 RESULTS

Distance did not affect the odds to produce accurate or valid responses (p=0.48 and p=0.18, respectively).

RTs, similarly, did not differed across viewing Distances, close (M= 411.8 ms, SD= 12.25) and far (M= 410.5 ms, SD= 10.83) stimuli being equally fast ($t_{(19)}$= 1, p= 0.33, paired, two-tailed). A Bayesian t-test yielded a BF= 0.36 (BF_{01}= 2.75), suggesting that data were 2.75 more likely to occur within the null hypothesis (Fig. 4).

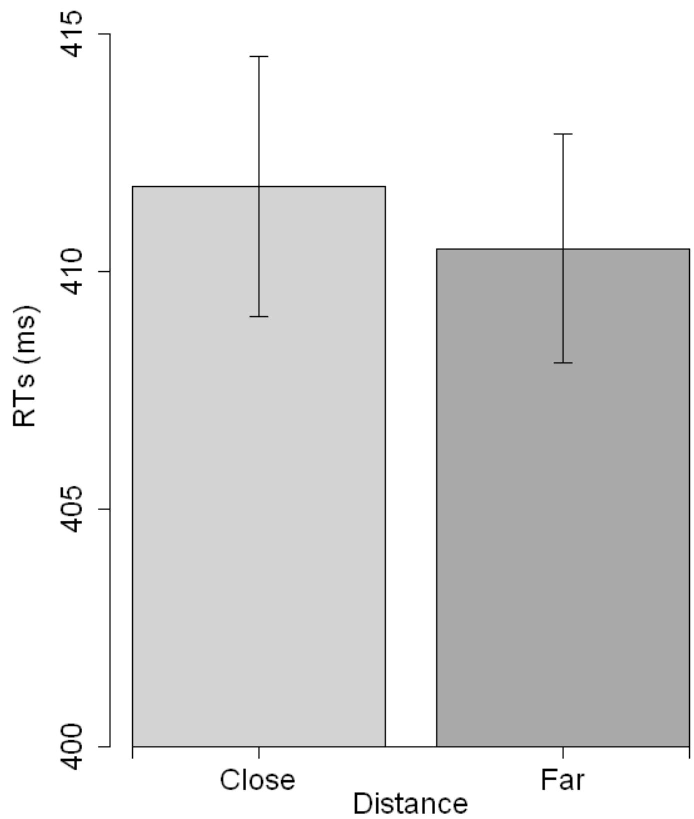


Fig. 4 Mean reaction times (ms) as a function of the Distance to which shapes were presented. Error bars depict SEM. In this experiment shapes appearing illusorily closer to participants appeared in the upper visual field, whereas shapes appearing farther away were presented in the lower space. With such arrangement no differences in discrimination speed were found.

5.0 DISCUSSION

We presented a series of experiments aimed at assessing whether performance in a perceptual task (i.e., shape discrimination) is modulated by the perceived distance at which targets are presented. Different shapes, with the same retinal size, appeared either close or far from participants, in a virtual environment (exp. 1) or in the context of a visual illusion introducing depth cues (i.e., Ponzo illusion, exp. 2). We found that participants were faster when targets were presented in the peripersonal as opposed to extrapersonal space.

This finding points against the notion of an upper visual field mainly specialized in fine-grained perceptual tasks as opposed to a lower visual field mainly devoted to tasks requiring high temporal and spatial resolution (e.g., detection; Previc, 1990). However, the mere upper/lower visual field distinction does not appear to explain, alone, the distance effect we described. When we reversed the contingency between near and far shapes (that is, when near shapes were presented in the upper visual field, exp. 3) we observed that the advantage in processing closer stimuli was abolished, but the pattern was not reversed. This suggests that the hemispace of stimuli presentation alone was not the principal driver of this effect (otherwise we would have obtained an advantage for targets appearing in the lower visual field, namely perceived to be more distant), but that an interaction with perceived depth was also at play. One possibility is that when stimuli are presented in a canonical and statistically over-learned (close/lower – far/upper) configuration the effects of a visual illusion are stronger and more clear (anecdotally speaking, participants indeed reported a worse depth illusion in exp. 3). However, this interpretation remains speculative at present.

Results drawn from the first two experiments might suggest, instead, that an increased amount of attentional resources is generally deployed in the space surrounding the body (Gawryszewski et al., 1987), perhaps leading to enhanced processing of stimuli regardless of the task at play. Potentially noxious, harming or to-be-manipulated objects are more relevant when appearing within personal space; our results are therefore not in contradiction with accounts claiming that ecological functions (e.g., defensive behaviours, affordances or actions) drove specific neural areas to be specialized in processing objects lying in peripersonal space. However, the range of tasks that could benefit for this attentional boost appears to be wider than simple detection, also extending to more perceptually demanding tasks (i.e., discrimination).

In exp. 1, finally, we failed to modulate the distance effect by manipulating the position of participants' hand. If the spatial frame of reference mainly responsible for this behavioural effect were hand-centred we should have observed faster reaction times for stimuli displayed close to the participants' hands. Assuming that proprioceptive information could be enough to highlight behavioural advantages (Reed et al., 2006), this was not the case, pointing to a more general body-centred spatial reference.

6.0 ACKNOWLEDGMENTS

This chapter reports preliminary results of a series of experiments carried out in Lyon (France) during my stay at the INSERM laboratories, hosted by the ImpAct team. I'm grateful to Alessandro Farné and Fadila Hadj-Bouziane for their constant and kind support in every experimental phase. I would like to thank Alexandre Kabil, Clément Desoche, and Anael Belle for their help with the virtual reality experiment.

SECTION 2

Shifting Visuo-Spatial Attention to Probe its Role in Cognitive Functions

CHAPTER IV

Visual Optokinetic Stimulation: Evidence for a Bidirectional Link between Mental Arithmetic and Spatial Attention

ABSTRACT

Growing evidence suggests that spatial attention is involved in mental arithmetic. For example, over-estimation for addition and under-estimation for subtraction of non-symbolic numbers, a pattern known as Operational Momentum (OM), is thought to reflect shifts of spatial attention on the mental number line during mental calculation. In the present study we investigated whether optokinetic stimulation (OKS), inducing an oculomotor reflex that causes overt shifts of spatial attention, may affect mental arithmetic. Participants performed additions or subtractions of symbolic numbers during horizontal (experiment 1, N=24) or vertical OKS (experiment 2, N=24); gaze position was recorded with an eye-tracker. We observed that downward OKS was able to modulate the proportion of positive decade errors (occurring more often during subtractions with respect to additions) by restraining this kind of procedural mistake. Moreover, we found that eye movements were strongly affected by the type of operation, with subtraction leading to a leftward and downward shift of gaze position and addition leading to a rightward and upward shift. In conclusion, our results support the hypothesis of a bidirectional link between spatial attention and mental arithmetic, the vertical dimension being more prone to highlight behavioural effects perhaps because more deeply grounded in our experience with addition and subtraction of quantities.

1.0 INTRODUCTION

The SNARC effect (Spatial Numerical Association of Response Codes, Dehaene, Bossini, & Giraux, 1993) is one of the most robust findings in experimental psychology. When participants are asked to classify one number as smaller or larger than a reference (e.g., the number “4” with respect to number “5”), or when they are asked to classify one number as odd or even, they are typically faster and more accurate when responding to small numbers in the left side of space, and to large numbers in the right side; conversely, more errors and slower reaction times are seen for “incongruent” trials, namely when the response must be given to the left for large numbers or to the right for small numbers (also see Wood, Willmes, Nuerk, & Fischer, 2008). This congruency effect refers to the idea of a left-to-right oriented Mental Number Line (Dehaene, 1992; Restle, 1970), that, at least in western countries and left-to-right reading systems (Dehaene et al., 1993; Göbel, Shaki, & Fischer, 2011; Shaki, Fischer, & Petrusic, 2009), would arrange numerosities in a spatially ordered fashion, from the smallest to the largest. Hence, advantages would be seen when responses to a number are given in a portion of space that is congruent with its position on the MNL, like advantages occur when responding to a physical stimulus appearing on the same side of the response key (i.e., the Simon effect, Simon & Wolf, 1963; Simon, 1969), although this analogy is debated (Gevers, Caessens, & Fias, 2005; Mapelli, Rusconi, & Umiltà, 2003; Rusconi, Turatto, & Umiltà, 2007). Indeed, an alternative account of the SNARC effect (Fias, van Dijck, & Gevers, 2011; Proctor & Cho, 2006), maintains that verbal, rather than visuospatial interactions, have to be considered the source of the spatial-numerical association. This account is supported by behavioural (Gevers et al., 2010; Keus & Schwarz, 2005), computational (Gevers, Verguts, Reynvoet, Caessens, & Fias, 2006), and electrophysiological (Gevers, Ratinckx, De Baene, & Fias, 2006; Keus, Jenks, & Schwarz, 2005) evidence, suggesting that the SNARC may arise in a response-related stage, and its origin would be conceptual rather than spatial. However, many other findings support the idea of a spatially characterized MNL, including neuropsychological (Zorzi et al., 2012; Zorzi, Priftis, & Umiltà, 2002; for a review, see Umiltà, Priftis, & Zorzi, 2009) and neuroimaging (Cutini, Scarpa, Scatturin, Dell’Acqua, & Zorzi, 2012; Dehaene, Piazza, Pinel, & Cohen, 2003; Hubbard, Piazza, Pinel, & Dehaene, 2005; Knops, Thirion, Hubbard, Michel, &

Dehaene, 2009) studies. At the origins of this arrangement, according to recent frameworks (Fischer, 2012; Myachykov, Scheepers, Fischer, & Kessler, 2014), may reside “situated” aspects of cognition, reflecting flexible representations rapidly changing as a function of task demands or available resources (e.g., Vuilleumier, Ortigue, & Brugger, 2004). An example of more deeply rooted aspect of numerical cognition, reflecting “grounded” aspects and hence physical invariants of the surrounding environment (Fischer, 2012; sometimes referred to "tropisms", Myachykov et al., 2014) is the universal tendency to associate small magnitudes with lower space and large magnitudes with upper space (Ito & Hatta, 2004; Shaki & Fischer, 2012). It follows the prediction that vertical spatial-numerical associations should be more robust than horizontal ones (Fischer & Brugger, 2011; e.g., Wiemers, Bekkering, & Lindemann, 2014).

A further line of research corroborating the spatial characteristics of numbers explores the so called attentional-SNARC effect, which may be considered as a particular form of attentional momentum (Hubbard, 2014). Besides the spatial effects found in numerical tasks, indeed, the processing of numbers (and magnitudes) has been found to re-allocate attentional resources in space. This can be seen, for example, in simple detection tasks, when participants are faster when responding to stimuli appearing in the left side of space after the presentation of a small number or for stimuli on the right side after the presentation of a large number (Fischer, Castel, Dodd, & Pratt, 2003; Galfano, Rusconi, & Umiltà, 2006; Ristic, Wright, & Kingstone, 2006). This may be explained in terms of a different allocation of attentional resources in space after the elaboration of magnitudes. Indeed, Casarotti, Michielin, Zorzi, & Umiltà (2007) found that numbers may affect a Temporal Order Judgment task, where volunteers are asked to report which one of two visually presented stimuli occur first: left-sided stimuli were perceived to occur before right-sided stimuli if a small number was presented as a cue, while an advantage for right-sided stimuli was evident after the presentation of large numbers. Besides, the presence of visually (Bonato, Priftis, Marenzi, & Zorzi, 2008; Di Luca, Pesenti, Vallar, & Girelli, 2013; Fischer, 2001) or auditorily presented (Blini, Cattaneo, & Vallar, 2013; Cattaneo, Fantino, Mancini, Mattioli, & Vallar, 2012; Cattaneo, Fantino, Tinti, Silvanto, & Vecchi, 2010) numerical information might modulate the performance of healthy persons and patients in visuospatial tasks like line bisection (Cattaneo et al., 2012, 2010; Fischer, 2001), cancellation (Di Luca et al., 2013) or visual straight ahead (Blini et al., 2013) tasks, thus establishing a further link between numbers and space or spatial attention (but see Galfano et al., 2006, van Dijck, Abrahamse, Acar, Ketels, & Fias, 2014, and Zanolie & Pecher, 2014, for contrasting results or evidence that this effect is very small).

Critically, the SNARC effect seems to extend to many other physical dimensions, like time (Vallesi, Binns, & Shallice, 2008), pitch (Rusconi, Kwan, Giordano, Umiltà, & Butterworth, 2006), or brightness (Kadosh, Kadosh, & Henik, 2008), leading some authors to suggest that all these variables may have a common origin and share a common metric system (Bueti & Walsh, 2009; Walsh, 2003). A recent extension of the SNARC effect was made by Pinhas, Shaki, & Fischer (2014), where spatial associations were found for operation signs (namely, the plus sign was associated to faster right-sided responses while the converse was found for the minus sign). The research was motivated by the growing number of results showing that mental arithmetic also shows spatial biases (Fischer & Shaki, 2014) akin to those found for single digits. For example, the so-called Operational Momentum effect (OM) was first documented by McCrink et al. (2007) and reflects the tendency found in healthy subjects of overestimating the results of additions and underestimating the results of subtractions. Although different, non-spatial, accounts hold for the OM (Fischer & Shaki, 2014) the authors suggested that the observed OM might be ascribed to a movement along an internal numerical continuum. The Operational Momentum has now been described with a variety of tasks, differing for the numerical notation (i.e., non-symbolic: Knops, Dehaene, Berteletti, & Zorzi, 2014; Knops, Viarouge, & Dehaene, 2009; McCrink et al., 2007; McCrink & Wynn, 2009; symbolic: Inglis, Gilmore, & Attridge, 2009; Longo & Lourenco, 2007; Pinhas & Fischer, 2008; Zorzi et al., 2002), the response modality (e.g., multiple choice: Knops et al., 2014; McCrink et al., 2007; pointing to a location along a visual segment: Klein, Huber, Nuerk, & Moeller, 2014; Pinhas & Fischer, 2008; verbal response: Dormal, Schuller, Nihoul, Pesenti, & Andres, 2014; Longo & Lourenco, 2007; Zorzi et al., 2002; dot production: Lindemann & Tira, 2011), and other potentially relevant variables (for a review, see Hubbard, 2014) sometimes leading to a peculiar modulation of the OM itself.

Another potential confound of the results is the overall tendency of healthy subjects to mislocate the center of visual lines (Jewell & McCourt, 2000) as well as numerical mental lines (Cattaneo, Fantino, Silvanto, Tinti, & Vecchi, 2011; Cattaneo et al., 2010; Longo & Lourenco, 2007) towards the left (i.e., “pseudoneglect”, see Jewell & McCourt, 2000). These results were obtained after the first neuropsychological studies of patients with Unilateral Spatial Neglect (USN) provided useful insights for the debate, given that the main difficulty of these patients is essentially visuo-spatial. USN, in fact, is a disorder consisting in the failure to report, respond to or orient towards stimuli in the contralesional side of space (Heilman, Watson, & Valenstein, 1985; Vallar, 1998), that remains unexplored. Given that USN occurs more often after a right brain damage – especially, but not only, affecting the inferior parietal lobe (Corbetta & Shulman, 2011; Molenberghs, Sale, & Mattingley, 2012; Mort et al., 2003; Vallar & Perani, 1986) – the unexplored part of space is usually the left (left-USN). Clinically, USN may be highlighted with several different tests. One common clinic tool for the diagnosis of USN – although its sensitiveness and specificity is debated (Ferber & Karnath, 2001, also see Chapter 5) – is the line bisection test (E Bisiach, Bulgarelli, Sterzi, & Vallar, 1983; Schenkenberg, Bradford, & Ajax, 1980), where patients are simply asked to bisect a visually presented physical line; in this case a clear bisection bias towards the affected (right) hemisphere is often observed, whereas healthy or brain-damaged persons without USN are usually fairly accurate despite subtle leftward bisections (Jewell & McCourt, 2000).

Crucially, USN may extend, in some cases, to the mental representation of images, if spatially characterized, in example the mental representation of a familiar environment (i.e., a famous or familiar square, Bisiach & Luzzatti, 1978) or a geographical map (i.e., the map of France, Rode, Perenin, & Boisson, 1995). Zorzi, Priftis, & Umiltà (2002), therefore, asked to four USN patients to mentally bisect number intervals, reasoning that a spatial MNL would be disrupted by USN. Indeed, the four patients showed, compared to controls, a rightward bisection error, resembling the characteristic bias observed with physical lines. Notably, the rightward shift was linearly related to the interval length and shorter lines are linked to a leftward error, a phenomenon also common in USN and known as “crossover effect” (Marshall & Halligan, 1989). On the other hand, the same task administered to healthy persons is linked with a subtle leftward error similar to pseudoneglect (Cattaneo et al., 2011; Loftus, Nicholls, Mattingley, Chapman, & Bradshaw, 2009; Longo & Lourenco, 2007), highlighting a striking similarity of number and line bisection tasks, despite double dissociations may occur (Doricchi, Guariglia, Gasparini, & Tomaiuolo, 2005; also see Aiello et al., 2012, for a contrasting view).

More recently, these observations were extended to mental arithmetic and, specifically, to the Operational Momentum, by the finding that USN patients present an increased error rate when performing subtractions with respect to additions (Benavides-Varela et al., 2014; Dormal et al., 2014); these results were interpreted as due to a defective ability to shift attention towards the left side of the mental number line (Dormal et al., 2014), hence suggesting a causal role of spatial attention in mental arithmetic. Specifically, Dormal et al. (2014) asked 14 patients with USN to compute both additions and subtractions, and found that, while mental addition was overall roughly spared, the performance in subtractions was relatively worse in patients, especially when the second operand was large (and a borrowing operation was always involved). This is in line with several neuropsychological studies that – starting with the seminal study by Hécaen, Angelergues, & Houillier (1961), that first introduced the term "spatial acalculia" – describe several calculation deficits that are secondary to visuo-spatial ones (Ardila & Rosselli, 1994; Boller & Grafman, 1983, and de Hevia, Vallar, & Girelli, 2008, for review).

The role of spatial attention in numerical cognition, however, is still debated. Studies showing that magnitudes (Cattaneo et al., 2012; Fischer et al., 2003; Ishihara, Jacquin-Courtois, Rode, Farnè, & Rossetti, 2013) or operations (Klein et al., 2014; Masson & Pesenti, 2014; Pinhas & Fischer, 2008) may induce shifts of spatial attention typically do not clarify whether the observed shift is functional to the mental processing of numbers or computations or rather is a mere side-effect of this processing itself, and different non-spatial accounts have been proposed as alternative explanations for different behavioural effects (e.g., the SNARC effect: Fias et al., 2011; Proctor & Cho, 2006; the observed bias in the bisection of a numeric interval: Aiello et al., 2012; Doricchi et al., 2005). However, a growing number of studies is starting to manipulate spatial attention in order to explore potential causal effects in the numerical domain, thereby providing new evidence in this direction, consistently with the observation that domain-spacific (numerical) abilities and representations alone does not fully explain the observed OM bias (Knops et al., 2014). This is best seen when USN patients are administered with techniques that have been devised for rehabilitational purposes, hence tapping on visuospatial attributes (e.g. prismatic adaptation: Fortis, Ronchi, Calzolari, Gallucci, & Vallar, 2013; Rossetti et al., 1998; optokinetic stimulation, OKS: Kerkhoff, Keller, Ritter, & Marquardt, 2006; Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990; Pizzamiglio et al., 2004) and improvements are also observed in the numerical domain. The rightward shift in number bisection, in particular, appears to be modulated by both prismatic adaptation (Rossetti et al., 2004) and optokinetic stimulation (Priftis, Pitteri, Meneghello, Umiltà, & Zorzi, 2012) in neglect patients, in a way that is similar to what happens for physical line bisection (Pizzamiglio et al., 1990; Rossetti et al., 1998), although in an extremely variable and dissociable fashion (Pitteri, Kerkhoff, Keller, Meneghello, & Priftis, 2014). Salillas, Granà, Juncadella, Rico, & Semenza (2009), moreover, also found that leftward coherent motion on the screen background (a procedure that is similar to optokinetic stimulation, Mattingley, Bradshaw, & Bradshaw, 1994) may abolish what has been found to be a peculiar marker of USN patients when assessed with the classical SNARC effect for magnitude judgments, namely the selective impairment (i.e., slower reaction times and higher error rate) for the number immediately preceding the reference (e.g., number “4” when the reference is number “5”), regardless of its absolute value (Vuilleumier, Ortigue, & Brugger, 2004b) or the employed notation (e.g., symbolic or non-symbolic, Masson, Pesenti, & Dormal, 2013).

Less attention has been devoted to the study of visuospatial and attentional manipulations in the healthy brain while engaged in numerical tasks. Only recently an emerging research field devoted to explore the role of embodiment over cognition approached the numerical domain, that indeed seems an ideal topic to test embodied concepts (Fischer, 2012). Hartmann, Grabherr, & Mast (2012, experiment 2) found that a vestibular stimulation (*via* whole body motion) critically interacts with numerical categorization as assessed by a SNARC effect for magnitude comparisons in a way that is coherent with a left-to-right arrangement of numbers along a mental number line, namely with leftward motion leading a facilitation for small numbers and rightward motion leading to an advantage for large numbers (also see Loetscher, Schwarz, Schubiger, & Brugger, 2008). A similar result was recently obtained when optokinetic nystagmus was induced in young healthy participants engaged in an auditory SNARC paradigm (Ranzini et al., 2014), where rightward optokinetic stimulation was found to abolish the advantage in reaction times that is usually seen for small numbers in these tasks, possibly because of a logarithmic compression of numbers in the mind (Dehaene, 2003; Longo & Lourenco, 2007). The linkage between these different manipulations, we believe, is likely to be the shifts in spatial attention that have been independently associated with all these techniques (e.g., Figliozzi, Guariglia, Silvetti, Siegler, & Doricchi, 2005). Indeed, Stoianov, Kramer, Umiltà, & Zorzi (2008) found that a visuospatial cue appearing in different portions of space could facilitate the processing of a number if congruent with its position along the mental number line. Unfortunately, much less attention has been devoted to the study of more complex numerical tasks, such like mental arithmetic, and only a few studies tried to understand whether the Operational Momentum is also modulated by visuospatial techniques.

The aim of the present study was to test whether OKS may affect the performance in mental arithmetic. Investigating the effect of OKS on mental calculation is particularly interesting for several different reasons. First, OKS represents a strong explicit manipulation of spatial attention, due to the well-established link between eye movements and spatial attention (Casarotti, Lisi, Umiltà, & Zorzi, 2012; Moore, Armstrong, & Fallah, 2003). Second, eye-movements have been linked to other aspects of numerical cognition in previous studies (e.g., Loetscher, Bockisch, Nicholls, & Brugger, 2010; Schwarz & Keus, 2004). Third, neural overlap between coding of eye movements and arithmetic operations has been observed in the functional neuroimaging study of Knops et al. (2009), in which decoding of saccade direction from an eye-movement area in the posterior parietal cortex was predictive of type of operation (addition vs. subtraction) during mental calculation. Nevertheless, the available evidence regarding the link between eye movements / attention and mental arithmetic remains mainly correlational. Thus, a study explicitly manipulating eye movements should add valuable insights into this issue. In addition to investigating the effect of OKS on calculation, we also investigated the opposite direction of the link between eye movements and arithmetic. That is, we asked whether eye movements, recorded during the task by means of an eye-tracker, would be spatially biased as a function of the type of operation (addition vs. subtraction, Hartmann, Mast, & Fischer, 2015; Klein et al., 2014; Pinhas & Fischer, 2008). Finally, OKS is a flexible tool, and allows testing for spatial numerical associations along both the horizontal and vertical dimensions, the latter appearing highly relevant in the numerical domain (Fischer & Brugger, 2011; Loetscher et al., 2010; Schwarz & Keus, 2004, experiment 2; Wiemers, Bekkering, & Lindemann, 2014).

We therefore ran two experiments administering horizontal (experiment 1) or vertical (experiment 2) OKS. In brief, we were especially interested in the distribution of responses following a manipulation of spatial attention through OKS, expecting to selectively exacerbate underestimations following leftward or downward OKS and overestimations following rightward or upward OKS. We wondered, specifically, whether the pattern of procedural errors (e.g., decade errors), known to be particularly affected by spatial deficits, could be modulated as well in the same direction. Finally, we expected to confirm the opposite effect, namely an effect of calculations on eye movements, with subtractions leading to leftward/downward and additions to rightward/upward shift of gaze position (Hartmann, Mast, & Fischer, 2015).

2.0 EXPERIMENT 1

In the first experiment we assessed whether horizontal optokinetic stimulation has a role in mental calculation.

2.1 Participants

Twenty-four participants were enrolled in this study. They were all students recruited at the University of Padua, naïve to the purposes of the experiment, right-handers, native Italian speakers, with no history of neurological disorders, and normal or corrected to normal vision. They all joined voluntarily and gave written informed consent prior to participate in the present study. The study followed the Declaration of Helsinki standards and was approved by the Ethical Committee of the University of Padua. The sample was composed of 10 males (41%), mean age was 21.71 years (range=20-27, SD=1.57), mean years of formal education were 13.64 (range=13-16, SD=1.25).

2.2 Apparatus and stimuli

Eye movements were monitored online and recorded at 60hz with a Tobii T120 screen-based eyetracker (Tobii Technology, Sweden), which was also used to present OKS (moving bars) through its embedded 17-inch TFT monitor. E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) was used to run the arithmetic tasks; OKS was implemented on a different PC but presented on the eye-tracker's screen.

Each participant performed 60 operations for each of the three OKS conditions (plus 6 practice items taken from a different set of stimuli at the beginning, 6 + 60 + 60 +60 = 186 items overall). Within each block, participants performed 30 additions and 30 subtractions (see stimuli in Appendix 1); all problems' results were large (>20), as to facilitate estimations. Additions had a mean correct result of 83.5, while subtractions' result was lower (mean: 39.9). Participants performed the same operations, with the same numbers, in each OKS condition, in order to allow the comparison of the performance between items with identical difficulty.

2.3 Procedure

The experiment was carried out in a quiet and dimly lit room. The participant was sit in front of the screen at a distance of approximately 40cm. At the beginning of each OKS moving block, the experimenter firstly presented the moving bars and ensured that the participant's OKN was triggered before the beginning of the task. The task consisted in performing arithmetical operations (additions and subtractions) while OKS was visually presented. Stimuli were all presented acoustically via stereo headphones, in the following order: 1) an alert sound ("beep"), preceding the three elements of the operation; 2) a first numerical operand; 3) an operator ("plus" or "minus"); 4) a second numerical operand. Stimuli were obtained from a vocal synthesizer to be as clear as possible. Responses were given vocally, and latencies were collected via a microphone that triggered a voice-key. Participants were asked to be as accurate as possible, but also fast; they were strongly encouraged to provide an estimate if one operation took too long, and, in any case, to provide a response before proceeding with the next trial. All the elements were presented to the participants while observing OKS in three conditions: static, leftward, and rightward. The static

OKS control condition was always performed as first or last (counterbalanced across participants); the order of moving OKS conditions (left- or right-ward) was also counterbalanced across participants and baseline position. Within each block, stimuli were randomly presented to the participants, and three breaks (one every 20 items) were provided as to allow the participant to rest the eyes. The whole experiment lasted from 50 to 60 minutes.

The alert sound lasted less than 1 second, as the two operators; numbers lasted from about 1 second to about 1.5 seconds, depending on the length of the number word (note, however, that even if within the same block different numbers require different presentation times we are comparing the same stimuli across each OKS condition). Starting from the presentation of the second number, participants had 6 seconds to provide an answer: after this time limit, gaze tracking was stopped and the experimenter urged them to provide an estimated response. The reason of this short time-limit was threefold: 1) promoting estimation as opposed to complex arithmetic procedures; 2) promoting errors as opposed to correct answers, as to better analyze their distribution; 3) the need to collect a quantity of eye-tracker data that is sufficient for a posteriori analysis but not too demanding for the eye-tracker itself. The Tobii T120 eye-tracking system, in fact, was enabled to collect data at every step of the procedure (namely during the alert, the first number, the operator, the second number, and the response intervals).

2.4 Behavioural data

Two main dependent variables were computed on participants' responses. One was the mean Shift from the correct result, obtained by subtracting the correct response from the participants' response (excluding decade errors); this provides an index reflecting under- or over-estimation of the results due to pure estimation errors (units). The second was the proportion of decade errors (both positive and negative) within each Type and OKS condition, which provides an index of error in the use of calculation procedures thought to be more tied to spatial processes. A separate analysis of estimation vs. procedural errors is also suggested following visual inspection of the distribution of responses (depicted in Fig. 1); responses, indeed, were found not to be homogeneously and normally distributed, with multiple relative peaks in correspondence of decade errors, confirming that they rely on partly different mechanisms.

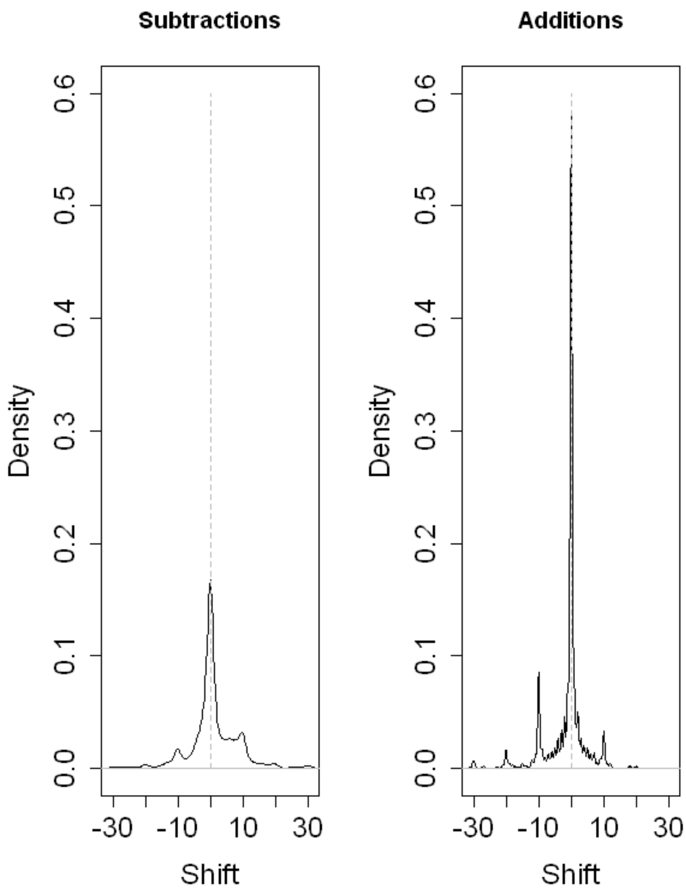


Fig. 1: The distribution of responses is depicted as a function of Operation Type, collapsed across OKS conditions and subjects. A value of 0 for Shift corresponds to a correct response, whereas negative and positive values reflect under- or over-estimation of the correct result, respectively. Additions (rightmost panel) were more accurate than subtractions (leftmost), but in both cases the distribution does not follow a Gaussian curve, mainly because of decade errors. Negative decade errors occurred more often in additions, whereas in subtractions participants committed more frequently positive decade errors. We therefore proceed in analyzing separately estimation and procedural errors.

2.4.1 Description of indices and analysis

Shift. The mean shift from the correct result reported by participants was used to assess the presence of OM. We excluded from analysis deviant eye movements (that may perhaps indicate difficulties in maintaining the nystagmus or some lapse of attention, respectively). Trials with deviant eye movements (3.16%) were automatically identified by the eye-tracker and later discarded during off-line analysis. Horizontal eye-wandering was tolerated along the full length of the screen, while vertical eye-wandering had to be limited to an area covering 2/3 of the vertical screen, and centered in the middle of the vertical axis. More than two samples in a row outside this confidence area resulted in the eye-tracker reporting eye movements as deviant, possibly indicating difficulties in maintaining the OKN. Few trials where participants refused to respond (e.g., because they failed to store one number in memory) were also discarded (0.18%). Finally, trials where decade errors were made (10.95%, see below) were discarded as well, in order to operationally isolate estimation errors from procedural ones. The mean values of Shift for each OKS (left, right, static) x Type (addition, subtraction) conditions were then submitted to a 3 x 2 repeated measures ANOVA.

Decade Errors. Trials with deviant eye movements were discarded. The proportion of procedural errors (namely, where the observed Shift value was of 10, 20 or 30, either positive or negative) was then computed with respect to the overall remaining number of trials. The mean values for each OKS x Type conditions were then arcsine transformed and submitted to a 3 x 2 repeated measures ANOVA. Post-hoc analysis were carried by using both Bonferroni corrected t-tests and Bayesian t-tests (Rouder, Speckman, Sun, Morey, & Iverson, 2009) through the BayesFactor package for R (Morey & Rouder, 2015), as to further complement analysis and obtain a straightforward index (i.e., Bayes Factor, BF) to quantify the strength of evidence for each contrast (Kass & Raftery, 1995). Note that this approach exploit objective (default) priors (Rouder, Morey, Speckman, & Province, 2012), proposed as to decrease researchers' degrees of freedom, given that BFs partly depend on priors choice. Besides, a Bayesian perspective allows to quantify the strength of evidence for a null hypothesis (evidence for absence of an effect), whereas a frequentist one is unable to do so (that is, lack of evidence is not evidence for a null effect, Kass & Raftery, 1995).

2.4.2 Results

Shift. The main effect of Type of Operation was the only significant effect ($F(1,23)=9.03$, $p=0.006$, $\eta_p^2=0.282$); additions were overall linked to under-estimation, while subtractions were more likely to induce over-estimations, which is a pattern with the opposite direction with respect to the classic OM. Neither the main effect of OKS ($F(2,46)=0.57$, $p=0.57$, $\eta_p^2=0.024$) nor the Type by OKS interaction ($F(2,46)=0.89$, $p=0.42$, $\eta_p^2=0.037$) were significant (Fig. 2).

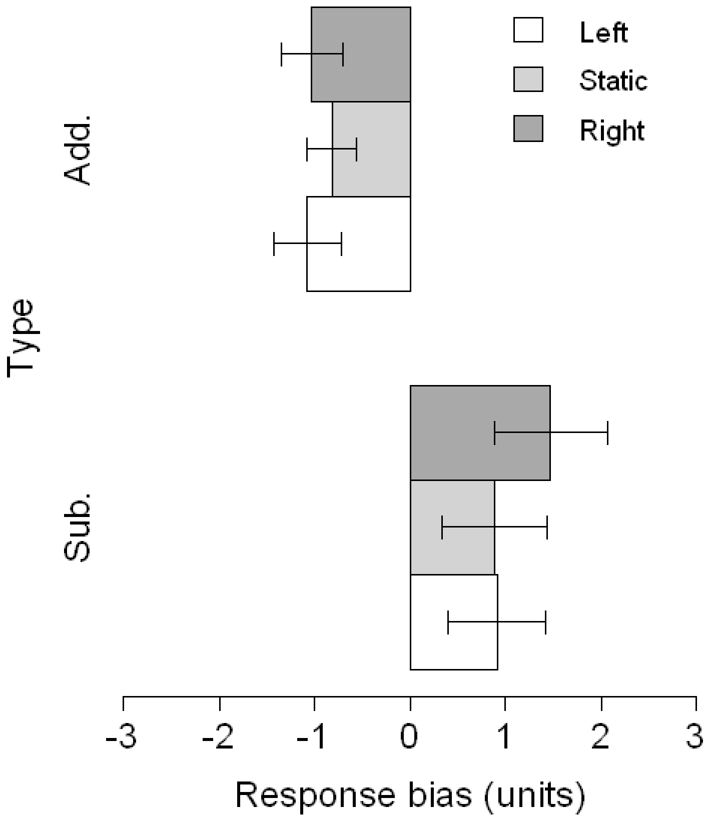


Fig. 2: The mean estimation error is depicted as a function of Operation Type and OKS. Note that the OM effect was reversed, with under-estimation for additions and over-estimation for subtractions. No effects of horizontal OKS were found. Error bars represent SEM.

Decade Errors. The main effect of Type ($F(1,23)=11.96$, $p=0.002$, $\eta_p^2=0.342$) yielded significance when analyzing negative decade errors, with no main effect of OKS ($F(2,46)=1.93$, $p=0.16$, $\eta_p^2=0.08$) or interactions ($F(2,46)=0.14$, $p=0.87$, $\eta_p^2=0.006$). Specifically, negative decade errors were more frequent (8.8%) during addition than subtraction (4%). A similar pattern was obtained for positive decade errors, where Type was found to be significant (F(1,23)=8.56, p=0.008, η_p^2=0.271) and an effect of OKS was not highlighted neither alone (F(2,46)=1.42, p=0.25, η_p^2=0.058) nor in interaction (F(2,46)=0.04, p=0.97, η_p^2=0.002) with Type. Subtractions were in this case more likely to induce positive decade errors (6.2%) than additions (2.8%, see Fig. 3).

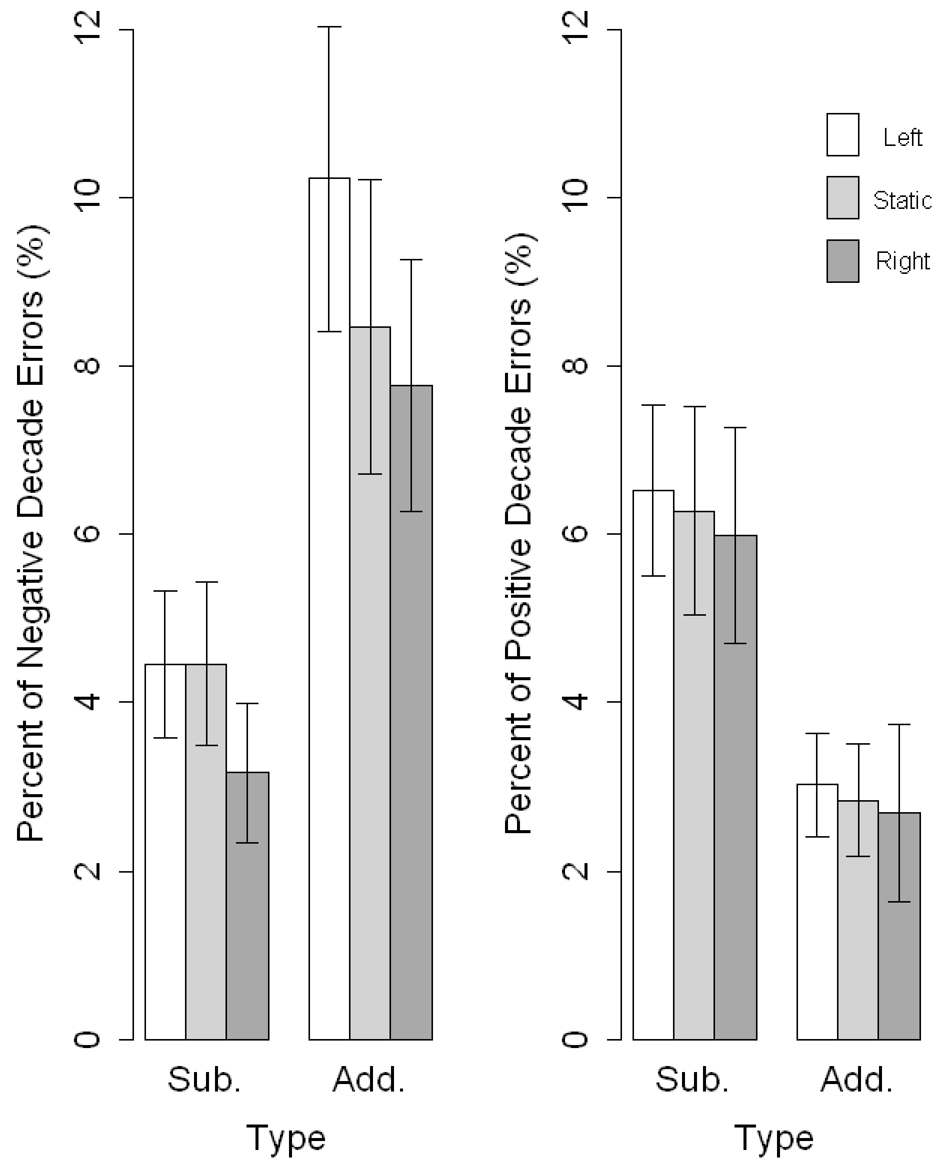


Fig. 3: The percentage of decade errors (i.e., responses deviating from the correct result by a multiple of 10 units) is depicted as a function of operation Type and OKS; the left panel reports negative decade errors, whereas the right panel reports positive decade errors. Negative decade errors were more frequent in

additions, positive in subtractions, but no modulatory effect of horizontal OKS was found. Error bars represent SEM.

2.5 Eye-tracking data

When considering eye-tracking data, we adopted as dependent variables both the mean position of the eyes along the horizontal or vertical axis of the screen and the shift in eye position occurring between different phases of the trial.

2.5.1 Description of indices and analysis

The Tobii eye-tracker was enabled to collect gaze data during all the trials, allowing to record the position of the eyes on the horizontal and vertical axis. Deviant eye movements were first excluded from analysis (3.16%). The following dependent variables were computed: i) the mean position of the eyes (both on the horizontal and vertical axis) during the response phase (MeanR); the mean shift of the eyes occurred from the second number phase to the response phase (ShiftSNR), obtained by subtracting the mean eye position during the presentation of the second number from MeanR. Note that the contrast of interest here is not within the different OKS directions, but rather within the different Operation Types. If arithmetical operations are performed along a mental number line, with subtractions linked with a leftward/downward movement and additions with a rightward/upward movement, then, within each OKS condition, the two operations might influence oculomotor control as revealed by gaze position. Therefore, the smallest MeanR and ShiftSNR values are expected for subtractions, indicating a leftward bias, while additions should be linked with higher values, indicating a rightward bias (downward or upward, respectively, when considering the vertical axis).

As a control analysis we also considered gaze indices for a phase of the trial where no effect of Type of operation is expected. In particular, we computed the mean position of the eyes during the presentation of the first number (MeanFN) and the mean shift observed from the alert sound to the first number presentation phase (ShiftAFN).

Other data exclusions depended on eye-tracker failures in recording a sufficient number of gaze samples at each phase of the trial (namely: alert, first number, operator, second number and response phase). 3.22% of trials where no gaze data were collected during the response phase were discarded. From the remaining data, further exclusions were made stepwise when analyzing ShiftSNR (1.94%), MeanFN (1.13%) or ShiftFNA (2.68%), depending on the remaining available gaze data within each trial phase.

All eye-movement indices were submitted to a 3 x 2 ANOVA (OKS x Type).

2.5.2 Results

X axis. When submitting MeanR and MeanFN to ANOVA only the main effect of OKS, not surprisingly, was present (for MeanR: $F(2,46)=7.69$, $p=0.001$, $\eta_p^2=0.25$; for MeanFN: $F(2,46)=24.45$, $p<0.001$, $\eta_p^2=0.515$). The effect of Type missed significance for both MeanR ($F(1,23)=3.66$, $p=0.068$, $\eta_p^2=0.137$) and MeanFN ($F(1,23)=1.93$, $p=0.178$, $\eta_p^2=0.077$); no interactions were found (all $ps>0.1$). The same analysis on the displacement indices yielded a similar pattern, with the difference that Type, when considering ShiftSNR, was found to have a significant effect ($F(1,23)=9.37$, $p=0.006$, $\eta_p^2= 0.29$), suggesting a leftward displacement of the eye position during subtractions and a rightward displacement during additions in the response phase only (see Fig. 4). This effect was not present during the corresponding control (i.e., non-calculation) phase (ShiftAFN: $F(1,23)=0.43$, $p=0.52$, $\eta_p^2=0.018$). The main effect of OKS was also present during the response phase only (ShiftSNR: $F(2,46)=7.21$, $p=0.005$ – Greenhouse-Geisser corrected, $\eta_p^2=0.24$; ShiftAFN: $F(2,46)=0.79$, $p=0.45$, $\eta_p^2=0.033$), but with no interactions with Type (all $ps>0.6$).

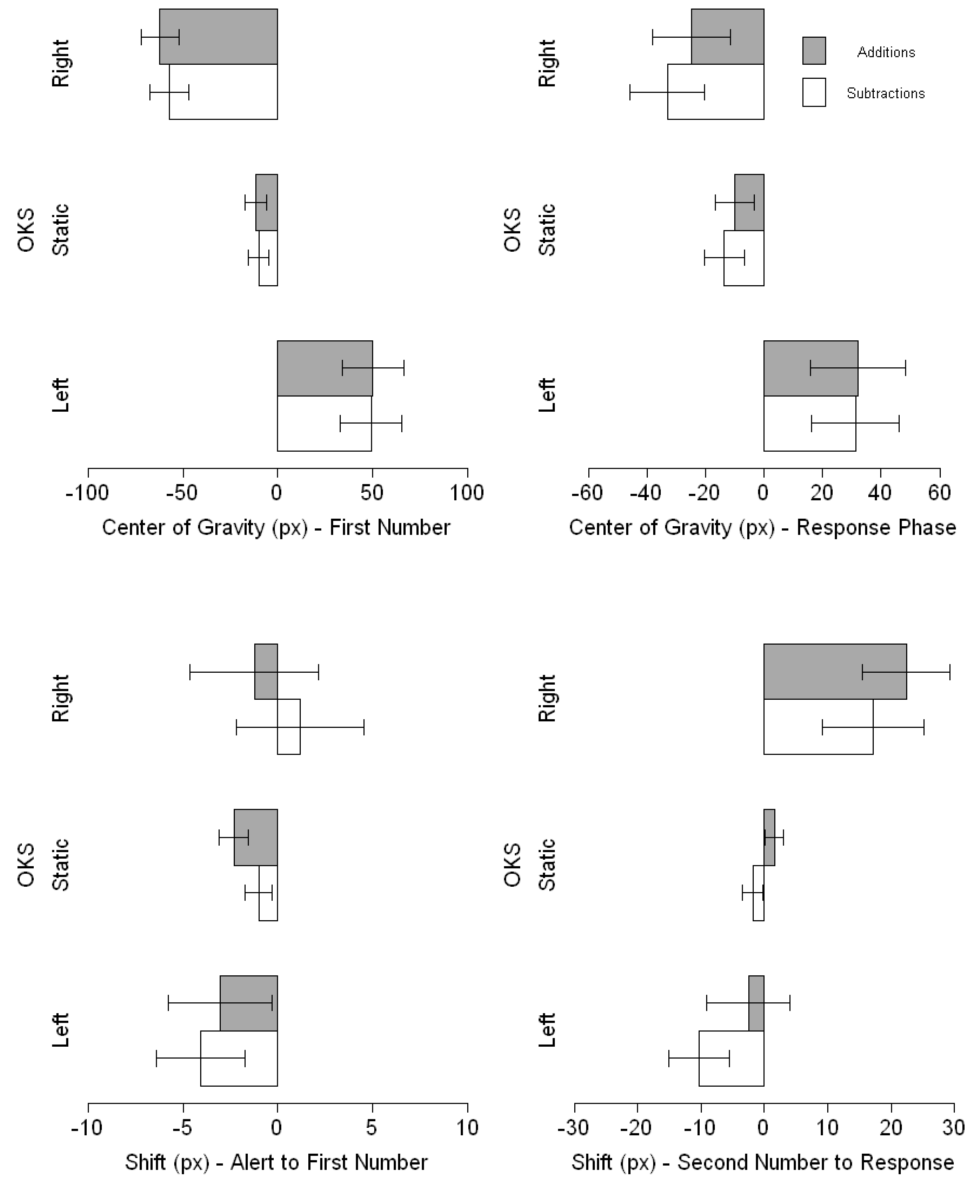


Fig. 4: Pattern of eye movements along the horizontal axis. Top panels: mean position of the eyes (in pixels with respect to the center) during the presentation of the first operand and during the response phase. Bottom panels: mean shift of gaze position in the same phases with respect to the preceding ones. The reference for the first operand phase was the presentation of the alert tone, whereas for the response phase the reference was the presentation of second operand. Negative values indicate leftward displacement and positive values a rightward one. Note that gaze position shifts during the response phase only, with a leftward shift of the eyes during subtraction and a rightward shift during addition regardless of OKS. Error bars represent SEM.

Y axis. Analysis of MeanFN and MeanR showed no effect of OKS (p=0.58 and p=0.395, respectively). Nevertheless, the effect of Type was significant for MeanR (F(1,23)=16.5, p<0.001, η_p^2= 0.42), suggesting an overall downward displacement of the eye position during subtractions and a (comparatively) upward displacement during additions (see Fig. 5). Results were corroborated by the analysis of the displacement indices. ShiftAFN showed a significant effect of OKS, F(2,46)=3.8, p=0.03, η_p^2= 0.141, but no effect of Type, F(1,23)=0.29, p=0.59 and η_p^2= 0.013. Conversely, ShiftSNR showed a significant effect of Type, F(1,23)=12.51, p=0.002 and η_p^2= 0.352, but no effect of OKS, F(2,46)=0.25, p=0.78, η_p^2=0.01). No interaction was found to be significant (all ps>0.2).

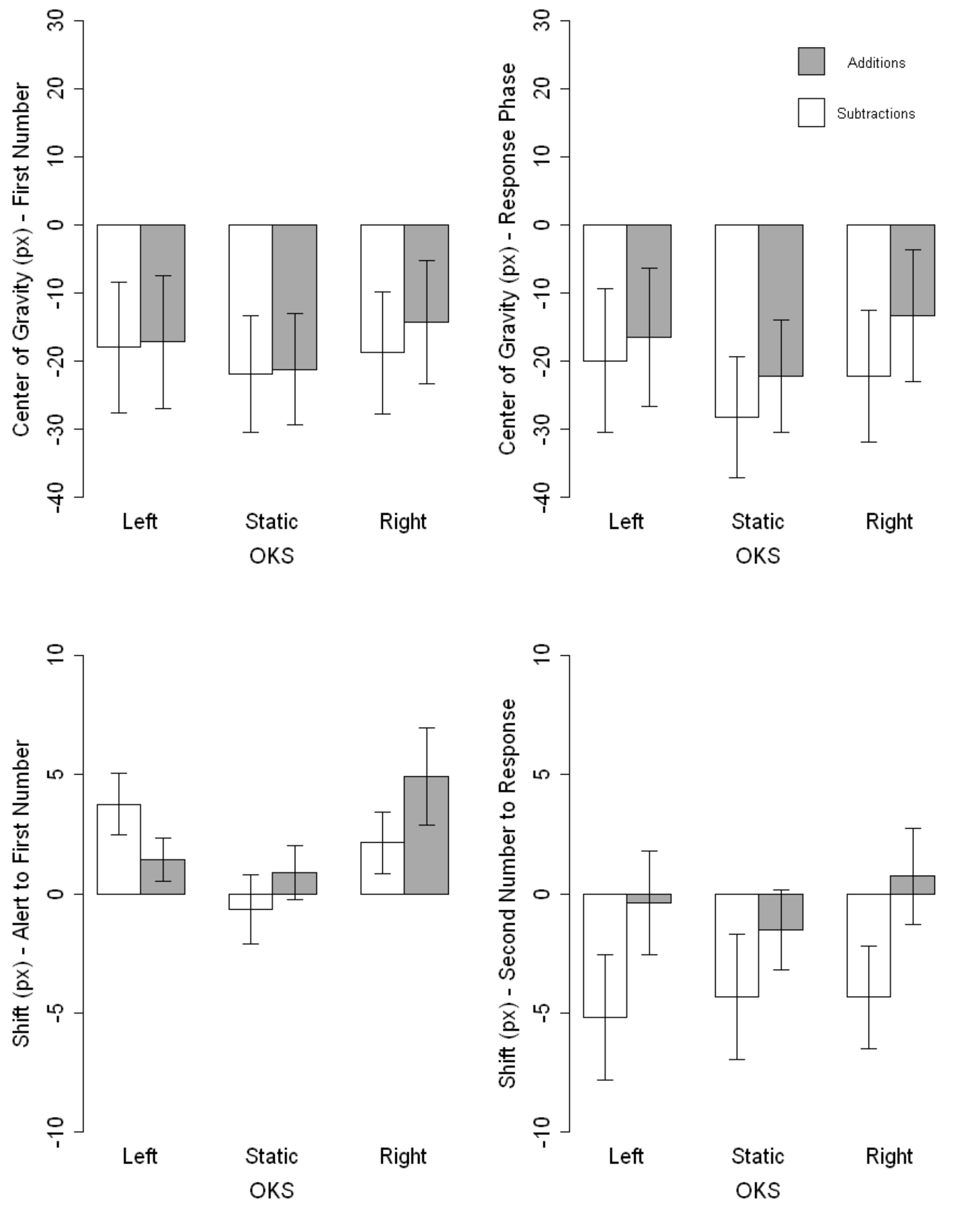


Fig. 5: Pattern of eye movements along the vertical axis. Top panels: mean position of the eyes (in pixels with respect to the center) during the presentation of the first operand and during the response phase. Bottom panels: mean shift of gaze position in the same phases with respect to the preceding ones. The reference for the first operand phase was the presentation of the alert tone, whereas for the response phase the reference was the presentation of the second operand. Negative values indicate downward displacement and positive values a (comparatively) upward one. Note that gaze position shifts during the response phase only, with a downward shift of the eyes during subtraction and an upward shift during addition. Error bars represent SEM.

3.0 EXPERIMENT 2

In the second part we administered vertical OKS to explore whether shifts of spatial attention occurring along the vertical plane are more suitable to modulate error distribution. Indeed, in the previous experiment we showed that operation Type affects oculomotor behaviour also in the vertical dimension, additions leading to upward movements of the eyes with respect to subtractions.

3.1 Participants

Participants of experiment 2 were enrolled with the same modalities of experiment 1. The sample was composed of twenty-four participants (as for exp. 1), 7 males (29%), mean age was 24.62 years (range=20-32, SD=3.11), mean years of formal education were 14.45 (range=13-18, SD=1.66).

3.2 Apparatus, stimuli, and procedure

Setting, stimuli, and procedures were identical to exp. 1, the main difference being the directions of OKS stimulation: we used, beside a static/baseline condition, downward and upward OKS stimulations. Counterbalancing remained the same as well.

3.3 Behavioural data

3.3.1 Description of indices and analysis

The mean shift from the correct result was obtained. We excluded deviant eye movements (9.23%); differently from experiment 1, participants were free to wander along the vertical axis but confined to the 2/3 of the horizontal axis length. Trials where participants refused to respond were also discarded (0.07%). Finally, trials where decade errors were made were also discarded (9.7%), in order to operationally isolate estimate errors from procedural ones.

3.3.2 Results

Shift. The main effect of Type of Operation was confirmed to be significant ($F(1,23)=8.04$, $p=0.009$, $\eta_p^2=0.259$), additions bringing about a more pronounced under-estimation of results with respect to subtractions. Neither the main effect of OKS ($F(2,46)=0.85$, $p=0.43$, $\eta_p^2=0.035$) nor the Type by OKS interaction ($F(2,46)=1.62$, $p=0.2$, $\eta_p^2=0.066$) were significant (Fig. 6).

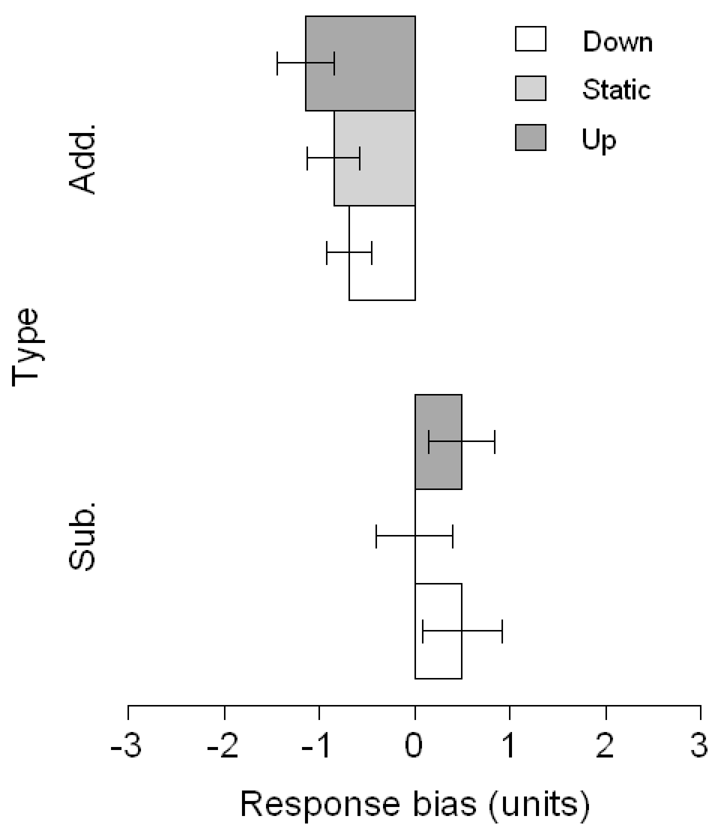


Fig. 6: The mean estimation error is depicted as a function of Operation Type and OKS. Note that the OM effect was reversed like in experiment 1, with under-estimation for additions and over-estimation for subtractions. No effects of vertical OKS were found, neither alone nor in isolation. Error bars represent SEM.

Decade Errors. The main effect of Type ($F(1,23)=0.99$, $p=0.33$, $\eta_p^2=0.04$) was not significant when analyzing negative decade errors. There were no main effect of OKS ($F(2,46)=0.45$, $p=0.63$, $\eta_p^2=0.02$) nor the interaction ($F(2,46)=1.65$, $p=0.2$, $\eta_p^2=0.07$). For positive decade errors, instead, the main effect of Type ($F(1,23)=13.62$, $p=0.001$, $\eta_p^2=0.372$) yielded significance, with no main effect of OKS ($F(2,46)=0.75$, $p=0.48$, $\eta_p^2=0.03$) but an OKS by Type interaction ($F(2,46)=6.3$, $p=0.004$, $\eta_p^2=0.215$); follow-up t-test comparisons (Bonferroni corrected) showed that the effect of Type (with subtractions yielding an overall increased rate of positive decade errors) is abolished with concurrent downward OKS ($t(23)=0.159$, $p=1$, BF=0.2) whereas it is robust in the static condition ($t(23)=2.99$, $p=0.022$, BF=6.94) and magnified in upward OKS ($t(23)=3.86$, $p=0.002$, BF=42.64) condition. In other words, during downward OKS our data support the lack of Type effect as more likely by a factor of 4.6 (1/0.22), whereas at baseline (static OKS) evidence is roughly 7 times more strong in favor of its existence; much more evidence for this effect is found for upward OKS (6.15 times stronger to that at baseline).

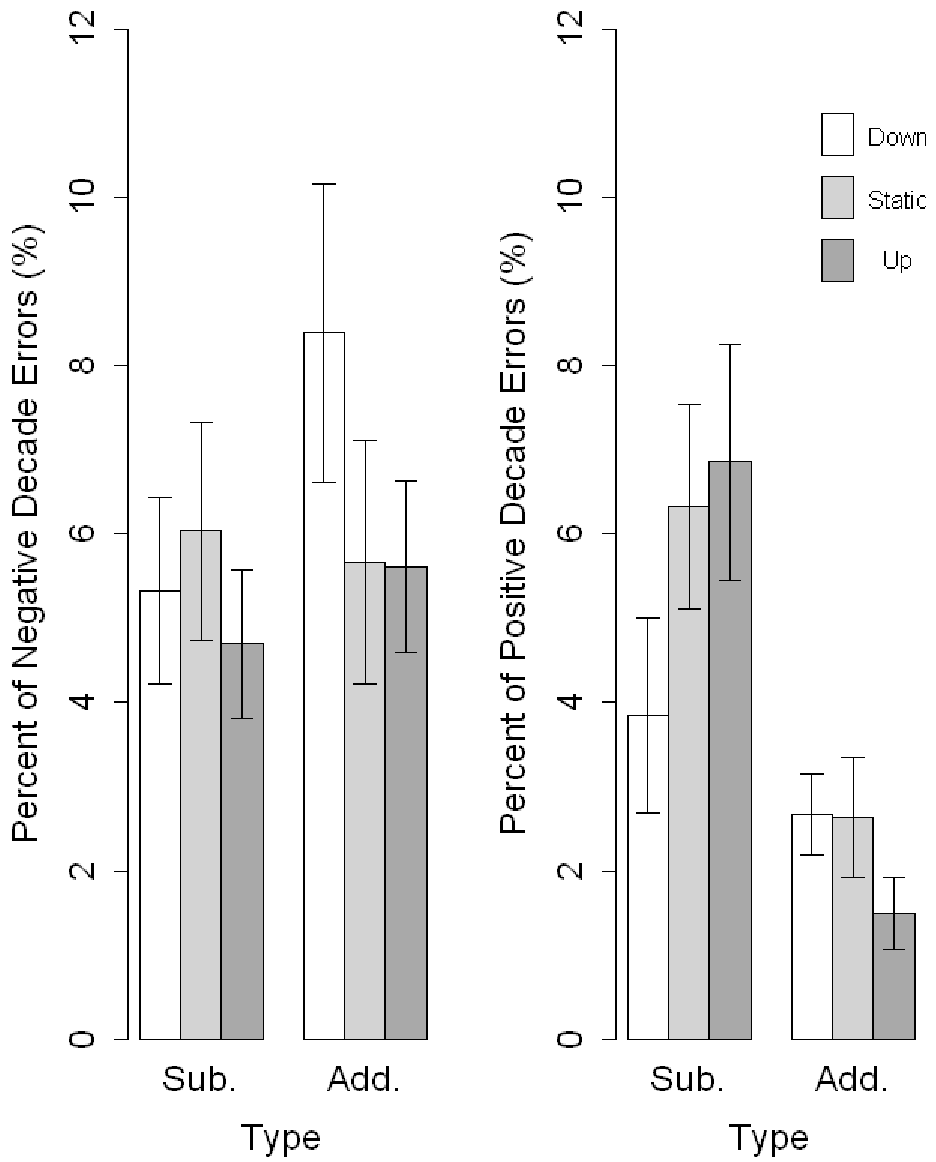


Fig. 7: The percentage of decade errors (i.e., responses deviating from the correct result by a multiple of 10 units) is depicted as a function of operation Type and OKS; the left panel reports negative decade errors, whereas the right panel reports positive decade errors. Positive decade errors were more frequent in subtractions, but they were also modulated by vertical OKS, with downward OKS abolishing this effect and upward one enhancing it. Error bars represent SEM.

3.4 Eye-tracking data

3.4.1 Description of indices and analysis

When considering eye-tracking data, we adopted as dependent variables both the mean position of the eyes along the horizontal or vertical axis of the screen and the shift in eye position occurring between different phases of the trial, as in experiment 1. Deviant eye movements (9.23%), and trials where no gaze data were collected during the response phase (0.26%) were discarded. Further exclusions were made stepwise when analyzing ShiftSNR (0.48%), MeanFN (0.6%) or ShiftFNA (2.24%).

3.4.2 Results

X axis. When MeanR, MeanFN, and ShiftAFN were submitted to ANOVA no effect was found to be significant. The analysis on ShiftSNR (bottom-right in Fig. 7) yielded a significant main effect of OKS ($F(2,46)=6.27$, $p=0.004$, $\eta_p^2=0.21$): both moving OKS conditions, with respect to the static one, are associated to a rightward shift of the eyes during the final stage of the calculation only. The effect of Type was not significant ($F(1,23)=1.23$, $p=0.28$, $\eta_p^2=0.05$) and opposite in direction with respect to the horizontal group.

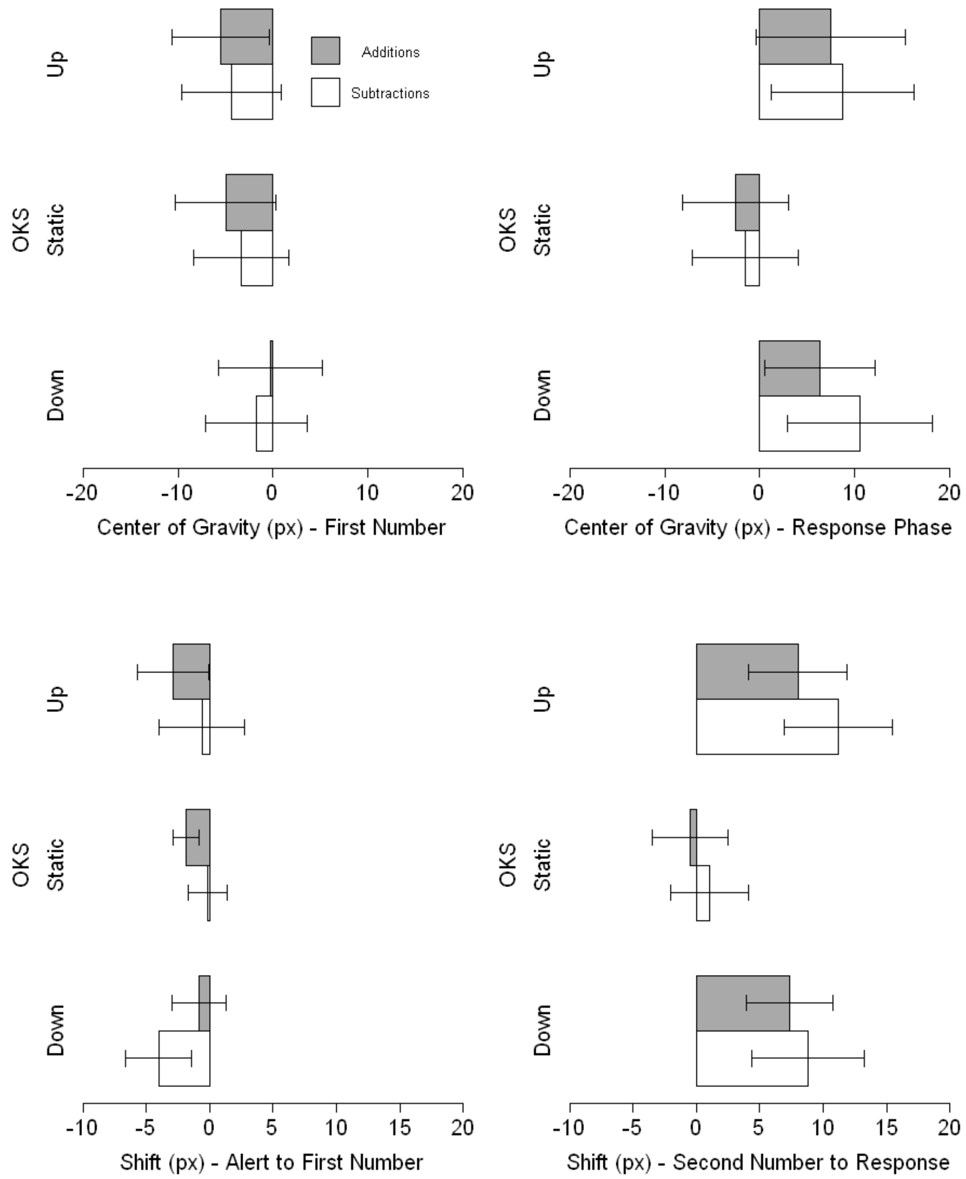


Fig. 8: Pattern of eye movements along the horizontal axis. Top panels: mean position of the eyes (in pixels with respect to the center) during the presentation of the first operand and during the response phase. Bottom panels: mean shift of gaze position in the same phases with respect to the preceding ones. We found no effect of operation Type in modulating oculomotor behaviour along the horizontal axis, differently from experiment 1. Error bars represent SEM.

Y axis. When we tested MeanFN and MeanR we found no main effect of OKS and, but only for MeanR, an effect of Type (F(1,23)=6.7, p=0.16, η_p^2=0.226), suggesting an overall downward displacement of the eye position during subtractions and an upward displacement during additions only during a late stage of the trial. Results are corroborated by the analysis of the displacement indices (ShiftAFN Vs ShiftSNR), that are highly coherent in this same direction (main effect of Type: $F(1,23)=0.12$, $p=0.72$, $\eta_p^2=0.005$ Vs $F(1,23)=16.11$, $p=0.001$, $\eta_p^2=0.41$). ShiftSNR also showed a significant OKS main effect ($F(2,46)=1.41$, $p=0.25$, $\eta_p^2=0.057$ Vs $F(2,46)=16.15$, $p<0.001$, $\eta_p^2=0.41$, Greenhouse-Geisser correction applied in the latter case) showing that, during these late stages, central fixation was more difficult to maintain, and gaze was more easily affected and shifted towards the OKS direction. Finally, the interaction OKSxType was only significant when analyzing ShiftSNR ($F(2,46)=4.34$, $p=0.019$, $\eta_p^2=0.159$, Greenhouse-Geisser correction applied); post-hoc (uncorrected) analysis showed that Type effect was only present during upward OKS ($t(23)=1.82$, $p=0.005$, BF=8.25). Type, despite the graphical trend, had no effects during downward OKS ($t(23)=3.07$, $p=0.081$, BF=0.89) or at baseline (static condition, $t(23)=1.13$, $p=0.27$, BF=0.38).

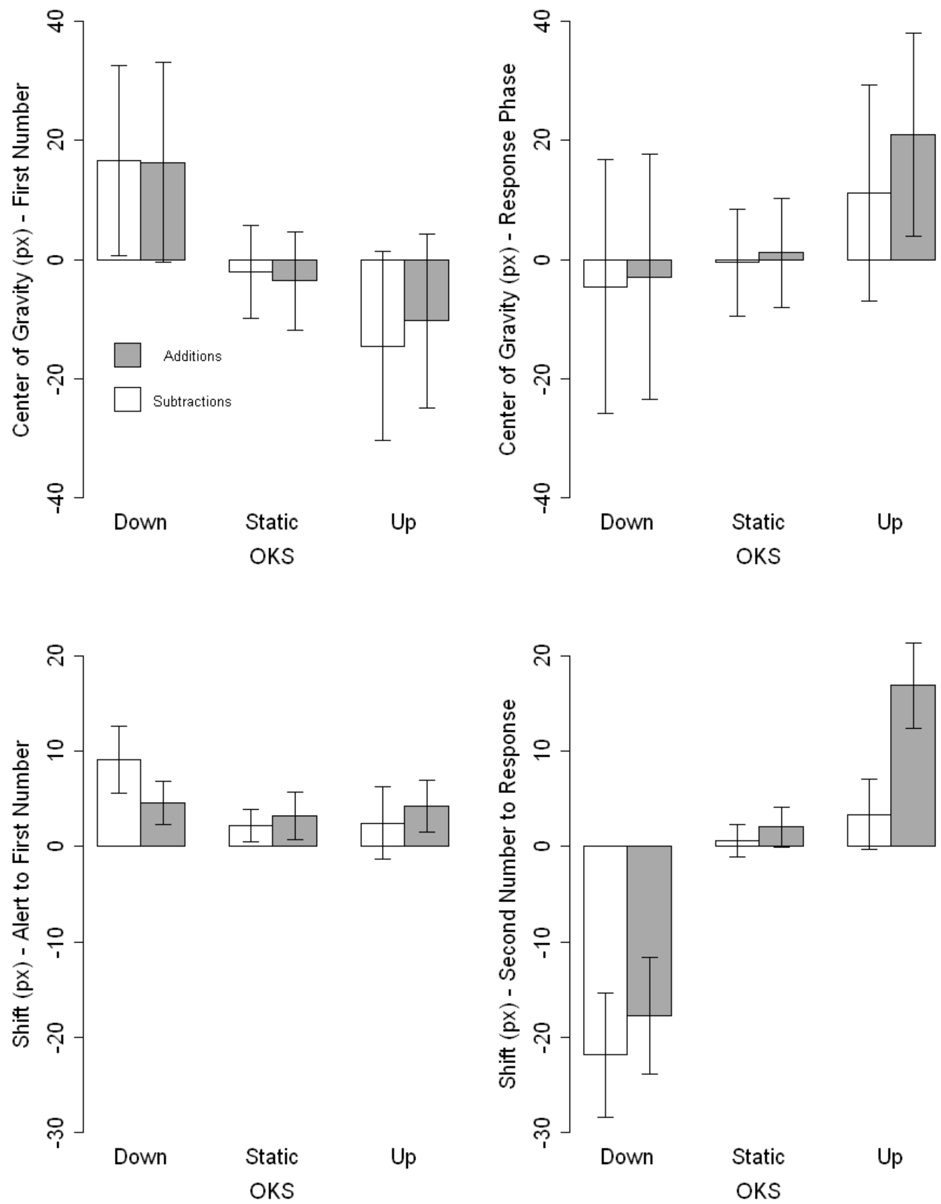


Fig. 9: Pattern of eye movements along the vertical axis. Top panels: mean position of the eyes (in pixels with respect to the center) during the presentation of the first operand and during the response phase. Bottom panels: mean shift of gaze position in the same phases with respect to the preceding ones. Gaze position shifts during the response phase only, with a downward shift of the eyes during subtraction and an upward shift during addition; an interaction with OKS was also found, suggesting that this effect is magnified during upward optokinetic stimulation. Error bars represent SEM.

4.0 DISCUSSION

In the present study we explored the effects of OKS, a technique that induces shifts of spatial attention secondary to a shift in eye movements (OKN), on mental calculation. Our aim was to investigate both the potential modulation of arithmetic performance by OKS (from spatial attention / eye movements to the calculation domain) and the complementary effects of operation type (subtractions vs additions) on eye movements (from the calculation domain to eye movements / spatial attention).

The results of the arithmetic task, in terms of accuracy of response, showed an overall pattern of underestimation for additions and overestimation for subtractions. Note that this pattern is reversed with respect to the classic OM-effect, which consists in overestimation of the result during addition and underestimation during subtraction. This discrepancy can be ascribed to a number of different reasons. The first important difference between our study and many others in literature is the modality of both stimuli presentation and response, which is auditory/verbal rather than visual/motor. Linguistic stimuli are thought to recruit partly different mechanisms and cognitive strategies, perhaps less relying on the analogical features of numbers (Hubbard, 2014); studies employing verbal stimuli often found the "pseudoneglect" phenomenon (Göbel, Calabria, Farnè, & Rossetti, 2006; Loftus et al., 2009; Longo & Lourenco, 2007; Zorzi et al., 2002), namely an overall tendency to underestimate the correct result. However, this could only account for the results we obtained with additions, where a leftward bias (i.e., underestimation) was indeed observed, but not with subtractions, for which we found the opposite trend. We suggest that our procedure fully induced and exploited an analogue representation of numbers, despite the linguistic nature of stimuli and response. Once that this is acknowledged, several insights may be drawn from the vast literature exploring the simple line bisection task. For example, studies exploring the effect of forced scanning direction (left to right vs right to left) in line bisection found that "pseudoneglect" is only found or stronger when the visual line is canonically explored from its leftmost part towards the right, whereas a forced leftward scanning of the segment typically leads to rightward bisection errors or smaller "pseudoneglect" (Brodie & Pettigrew, 1996; Chokron, Bartolomeo, Perenin, Helft, & Imbert, 1998; one of the largest performance modulator according to the meta-analysis by Jewell

& McCourt, 2000). Given that subtractions, differently from additions, could be characterized by a leftward movement along the MNL (an established view further corroborated by our results regarding eye-movements, see below), the observed over-estimation for subtractions may be explained in light of this different "scanning" direction. However, more studies are needed in order to clarify this issue, possibly evaluating the OM across different notations (i.e., symbolic and non-symbolic) and similar response modalities.

Although OKS did not consistently modulate the overall estimation error, we observed a modulation of the probability of procedural errors during mental calculation. The tendency to commit positive decade errors (operationally defined as a response larger than the correct result by a multiple of 10 units) was higher for subtractions with respect to additions, but downward OKS was found to abolish this feature. Results thereby suggest that this kind of procedural errors might rely, to some extent, on spatial processes, in fully agreement with neuropsychological observations (de Hevia et al., 2008), and that they are subserved by different cognitive mechanisms.

The results of our study do not exclude the possibility that manipulations of spatial attention may also influence other aspects of mental calculation. For example, the higher variability of response that is typically associated with approximate calculation (which could be enforced by a much shorter response deadline) might be a prerequisite for observing a reliable spatial bias in terms of mean response. Furthermore, spatial manipulations typically induce subtle effects in healthy participants, while the effect is often dramatic in patients suffering from visuospatial disorders; hence, neuropsychological studies on USN patients may also help in clarifying this issue, given that they show higher variability and uncertainty in response (Bonato et al., 2008), and they are more likely to be affected by techniques like OKS (also see Priftis et al, 2012).

Results drawn from eye movements, on the other hand, are clear-cut, and corroborate recent studies (Hartmann, Mast, & Fischer, 2015). In our study subtractions, with respect to additions, were consistently linked to a leftward displacement of gaze position, rightward for additions. Notably, this displacement was only observed during the response phase and not at other points of the trial, possibly because the MNL was activated only in the actual calculation phase. Moreover, the type of arithmetic operation had also an effect on the vertical dimension, with subtractions linked to an overall downward displacement of the eyes with respect to additions. This latter effect was to be highly reliable, being also identified when OKS was administered in a vertical dimension; a vertical stimulation, in the meantime, was also the only one capable to modulate behavioural performance in terms of occurrence of procedural errors. The effects highlighted on the vertical plane, thus, fit nicely with the idea of stacking and removing items from a pile (Fischer & Brugger, 2011), corroborating the view that, in numerical cognition, the vertical dimension is highly relevant, being grounded because of universal (physical) constraints (Fischer, 2012; Myachykov et al., 2014; Wiemers et al., 2014).

Altogether, results are coherent with the fMRI study of Knops et al. (2009), where saccade-related activity in the posterior parietal cortex was found to be good predictor of the type of mental operation participants were engaged into; the link between eye movements and mental arithmetic is thus further corroborated, and in this chapter we added new evidence in favour of a causal relation.

In summary, we have found a signature of the effect of eye-movements / spatial attention in mental arithmetic (i.e., a modulation of decade errors accordingly to the direction of OKS) and an effect of calculation on eye-movements (as indexed by a shift in gaze position depending on the operation type). Altogether, our results suggest the existence of a bidirectional link between eye-movements and mental arithmetic which we suggest to be mediated by the orienting of spatial attention in mental number space.

5.0 ACKNOWLEDGMENTS

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Appendix 1: Stimuli

Stimulus	First Number	Operator	Second Number	Correct	Stimulus	First Number	Operator	Second Number	Correct
1	88	minus	64	24	**16**	77	minus	34	43
2	82	minus	57	25	**17**	87	minus	44	43
3	92	minus	67	25	**18**	81	minus	37	44
4	94	minus	68	26	**19**	82	minus	38	44
5	55	minus	28	27	**20**	81	minus	35	46
6	61	minus	34	27	**21**	71	minus	24	47
7	62	minus	35	27	**22**	74	minus	27	47
8	93	minus	66	27	**23**	93	minus	46	47
9	82	minus	54	28	**24**	87	minus	36	51
10	88	minus	55	33	**25**	97	minus	44	53
11	97	minus	64	33	**26**	81	minus	27	54
12	62	minus	28	34	**27**	91	minus	37	54
13	83	minus	48	35	**28**	92	minus	35	57
14	84	minus	49	35	**29**	96	minus	34	62
15	81	minus	45	36	**30**	92	minus	29	63

Stimulus	First Number	Operator	Second Number	Correct	Stimulus	First Number	Operator	Second Number	Correct
1	27	plus	29	56	**16**	48	plus	37	85
2	34	plus	27	61	**17**	43	plus	45	88
3	29	plus	33	62	**18**	35	plus	53	88
4	27	plus	36	63	**19**	63	plus	26	89
5	49	plus	23	72	**20**	54	plus	35	89
6	49	plus	26	75	**21**	66	plus	25	91
7	33	plus	45	78	**22**	36	plus	56	92
8	56	plus	25	81	**23**	59	plus	34	93
9	53	plus	28	81	**24**	28	plus	65	93
10	37	plus	44	81	**25**	65	plus	29	94
11	44	plus	38	82	**26**	45	plus	49	94
12	36	plus	46	82	**27**	67	plus	28	95
13	34	plus	48	82	**28**	33	plus	64	97
14	26	plus	56	82	**29**	63	plus	35	98
15	47	plus	37	84	**30**	43	plus	55	98

CHAPTER V

Galvanic Vestibular Stimulation: Testing a Novel Protocol to Induce Spatial Representational Biases

ABSTRACT

A vestibular account for Unilateral Spatial Neglect (USN) has been recently proposed (Karnath & Dieterich, 2006); indeed, patients with USN, vestibular disorders, or even healthy humans receiving vestibular stimulation (either Caloric, CVS, or Galvanic, GVS) show similar behavioural manifestations and neural markers. Above all, both CVS and GVS are well-known and effective rehabilitational techniques, and have been found to alleviate USN symptomatology. GVS, in particular, seems promising because it is potentially able to overcome intrinsic technical limitations of CVS. GVS stimulates the vestibular system through low intensity electric currents applied at the basis of the VIII cranial nerve, but the best parameters for its administration are still subject of ongoing research. We devised a novel protocol exploiting electrical stimulation following a sinusoidal trend, a feature that was meant to cope with habituation phenomena occurring within the vestibular system. This protocol successfully modulated, in 24 healthy participants, the subjective straight ahead and, to a minor extent, visual vertical, that were shifted rightwards and clockwise with Right-anodal configuration, but was ineffective in a line bisection task. Results are discussed in light of the vestibular account for USN; in particular, it is suggested that spatial inattention and a distortion in metric representation of space are independent, doubly-dissociable constructs, so that vestibular disorders or CVS/GVS are more likely to affect the latter (Péruch et al., 2011). Perspectives to test this claim are also discussed.

1.0 INTRODUCTION

Unilateral Spatial Neglect (USN) is a disorder often occurring after a brain damage that consists in the failure to report, respond to or orient towards stimuli in contralesional space (Heilman, Watson, & Valenstein, 1985; Vallar, 1998). The main clinical form of USN affects the left side of space, that remains unexplored, and occur after a right hemispheric lesion involving one or more different areas within a wide cortical network subserving spatial cognition and attention (Corbetta & Shulman, 2011; Molenberghs et al., 2012). Critical areas include, but are not limited to, the inferior parietal lobe and the temporo-parietal junction (Chechlacz et al., 2013; Karnath, Himmelbach, & Küker, 2003; Mort et al., 2003; Umarova et al., 2011; Vallar & Perani, 1986), insula and superior temporal lobe (Hans-Otto Karnath et al., 2004, 2001), the hippocampus and parahippocampal formation (Mort et al., 2003), basal ganglia (Karnath et al., 2004; Karnath, Himmelbach, & Rorden, 2002), or white matter pathways connecting parietal and frontal areas (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008), and so on, with reports that may seem contradictory but eventually arise from different clinical characteristics of patients involved (Halligan et al., 2003). For example, a different aetiology (i.e., infarctions affecting the middle rather than the posterior cerebral artery, Chechlacz, Terry, et al., 2013), a different duration of the disease (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Karnath, Rennig, Johannsen, & Rorden, 2011), or different clinical deficits and manifestations of USN (e.g., ego-centred vs. object-centred, personal vs. extra-personal, that are known to often occur in isolation and in a doubly dissociated fashion, Chechlacz, Rotshtein, & Humphreys, 2012; Committeri et al., 2007) may be linked to different lesional correlates.

Another clinical manifestation of contralesional space un-awareness is the so-called “extinction” phenomenon (Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010; Driver & Vuilleumier, 2001; Làdavas, 1990). While USN patients usually fail to perceive and report stimuli in the contralesional space regardless of the presence of stimuli in the ipsilesional space, patients with extinction present this deficit only when a second stimulus is concurrently presented in the ipsilesional (spared) side of space (that is, when two stimuli are presented, only the ipsilesional one is reported, while the contralesional is “extinguished”); single stimuli presented alone are usually detected flawlessly in either the ipsi- and the contra-lesional side of space. Critical areas for extinction are also debated, but a key role seems to be played by the temporo-parietal junction (TPJ) as highlighted by imaging (Chechlacz, Rotshtein, et al., 2013; Karnath, Himmelbach, & Küker, 2003; Ticini, de Haan, Klose, Nägele, & Karnath, 2009), neuropsychological (Friedrich, Egly, Rafal, & Beck, 1998), and interference (TMS) studies (Chica, Bartolomeo, & Valero-Cabré, 2011; Meister et al., 2006) underline. The role of the intraparietal sulcus (IPS) is less clear, though it may be involved in supporting multi-item competition (de Haan et al., 2012). Chechlacz, Rotshtein, et al. (2013) found, in particular, that the (multisensory) TPJ was a common substrate for both visual and tactile extinction, thus suggesting that this area may play a crucial role in identifying salient events in space in a modality-independent fashion.

A comprehensive review of the neuroanatomical basis of USN and extinction, however, it is beyond the purposes of this chapter. Of particular interest, instead, is the striking similarity and overlap of this network and the so called “Primary Vestibular cortex” (PVc), as pointed out by Karnath & Dieterich (2006), as well as the evidence linking spatial and vestibular disorders. Inputs originating from the vestibular system and the inner ears’ organs seem to be represented, at a cortical level, in a multisensory (and therefore not strictly “primary”) network including the superior temporal cortex (STc), the insula and the TPJ, namely critical areas for USN and extinction, mainly of the non-dominant (right) hemisphere (Karnath & Dieterich, 2006). Those conclusions are drawn from imaging studies (Dieterich & Brandt, 2008, for a review; Lopez, Blanke, & Mast, 2012, and zu Eulenburg, Caspers, Roski, & Eickhoff, 2012, for meta-analysis) of patients with vestibular disorders (Alessandrini et al., 2013; Bense et al., 2013; Bense et al., 2004; zu Eulenburg, Stoeter, & Dieterich, 2010) or healthy persons after peripheral vestibular stimulation, i.e., Caloric Vestibular Stimulation (CVS; Bottini et al., 1994, 2001; Dieterich et al., 2003; Fasold et al., 2002; Suzuki et al., 2001) or Galvanic Vestibular Stimulation (GVS; Eickhoff, Weiss, Amunts, Fink, & Zilles, 2006; Lobel, Kleine, Bihan, Leroy-Willig, & Berthoz, 1998). CVS and GVS are peripheral stimulation techniques that induce an imbalance between the vestibular organs of the inner ears (e.g., cold water irrigation of the left ear cause an inhibition of the left vestibular organs as the ultimate result of the induced termic gradient), producing symptoms similar to those reported by patients with vestibular disorders (Been, Ngo, Miller, & Fitzgerald, 2007; Fitzpatrick & Day, 2004; Lidvall, 1961; Zink, Bucher, Weiss, Brandt, & Dieterich, 1998). These symptoms, in particular, consist in a subjective vertigo sensation, mild nausea, headache and spatial disorientation (Been et al., 2007) on one hand, and nystagmus and a tonic shift of eyes and head along the horizontal axis on the other hand (Karnath & Dieterich, 2006). The activation and deactivation pattern induced by either a vestibular stimulation (e.g., cold water irrigation of one ear) or a vestibular disorder (e.g., vestibular neuritis), indeed, are very similar and consist in an enhanced activation of the multisensory PVc with a concurrent decreased activation of visual and somatosensory areas (Bense et al., 2013; Dieterich & Brandt, 2008; Karnath & Dieterich, 2006), the main difference being that while vestibular stimulation produces a bilateral activation, a vestibular disorder activates the vestibular cortex in a unilateral fashion (i.e., contralaterally to the labyrinthine failure, see Brandt, Dieterich, Strupp, & Glasauer, 2012).

Furthermore, as Karnath & Dieterich (2006) pointed out, patients with vestibular neuritis or healthy persons receiving CVS present behavioural signs akin to those presented by USN patients, in particular an horizontal shift of head and eyes and nystagmus; other authors, therefore, raised the question of whether a peripheral vestibular lesion may cause USN-like symptoms (Brandt et al., 2012; Choi et al., 2013; Chokron, Dupierrix, Tabert, & Bartolomeo, 2007). Indeed, patients with left vestibular loss may present a contra-lateral shift in the perceived body midline (Hamann, Weiss, & Ruile, 2009; Saj et al., 2013) that is similar to the bias occasionally found in USN patients (Karnath, Schenkel, & Fischer, 1991; Richard, Rousseaux, Saj, & Honoré, 2004; Saj, Honoré, Richard, Bernati, & Rousseaux, 2010; Saj et al., 2006; but see Farnè, Ponti, & Làdavas, 1998, and Pizzamiglio, Committeri, Galati, & Patria, 2000, for no evidence of such a bias as a distinctive feature of USN) and healthy persons receiving CVS (Karnath, Sievering, & Fetter, 1994). Similarities between USN patients and healthy subjects after CVS are seen when monitoring the spontaneous exploration behaviour of an empty space in the visual (Karnath, Fetter, & Dichgans, 1996) and tactile modality (Karnath, Himmelbach, & Perenin, 2003). Ventre-Dominey, Nighoghossian, & Denise (2003) found directional anomalies in the Vestibulo-Ocular Reflex (VOR) in brain-damaged patients that were more pronounced when USN was present. Particular biases, moreover, are seen in patients with peripheral vestibular disorders, when exploring the representational space, leading Borel, Lopez, Péruch, & Lacour (2008) to the conclusion that a vestibular loss may affect the internal representation of space and its metric properties (also see Guariglia, Piccardi, Iaria, Nico, & Pizzamiglio, 2005; Péruch, Borel, Magnan, & Lacour, 2005; Péruch et al., 2011). Unilateral spatial neglect, vestibular disorders, and vestibular stimulation techniques appear therefore strictly related.

Indeed, CVS and GVS may be successfully employed as an effective (yet transient, see Kerkhoff & Schenk, 2012) tool for the rehabilitation of USN and related disorders (Kerkhoff & Schenk, 2012; Vallar, Guariglia, & Rusconi, 1997, for a review). Beneficial effects of CVS, in particular, have been widely explored and confirmed (Cappa, Sterzi, Vallar, & Bisiach, 1987; Kerkhoff & Schenk, 2012; Rode & Perenin, 1994; Rubens, 1985; Vallar et al., 1997), and are known to extend also to neglect-related symptoms like anosognosia (Cappa et al., 1987; Rode et al., 1992; Ronchi et al., 2013), somatoparaphrenia (Bisiach, Rusconi, & Vallar, 1991; Rode et al., 1992) or hemianesthesia (Bottini et al., 2005; Vallar, Sterzi, Bottini, Cappa, & Rusconi, 1990). Vallar, Guariglia, & Rusconi (1997) reviewed the literature concerning different peripheral stimulation techniques and argued that effects shall not be attributed to aspecific activating effects over one hemisphere; in particular, CVS is particularly effective for deficits that are spatial in nature and for neural networks mainly belonging to the right hemisphere. For example, while CVS reduced the symptoms of right-USN in one left brain-damaged patient, the same procedure did not affect any manifestation of a dysphasic disorder in the same patient (Vallar, Papagno, Rusconi, & Bisiach, 1995), arguing against an aspecific activation of the contra-lateral hemisphere (although effects may be seen also for non-spatial tasks with a left-hemisphere predominance, e.g. Bächtold et al., 2001). This is consistent with imaging and animal studies that, as mentioned above, circumscribe the PVc, with high convergence, to the Superior Temporal cortex (STc), insula and TPJ, anatomical findings that are closely related to those regarding USN (Karnath & Dieterich, 2006) and extinction. It is worth noting that the stimulation of contralesional limbs (Robertson & North, 1993) is linked to a remission of USN symptoms, an observation that independently led Robertson, Tegnér, Goodrich, & Wilson (1994) to propose a vestibular account of USN.

Nevertheless other peripheral stimulation techniques – for example a proprioceptive neck-vibratory stimulation (Bottini et al., 2001), or a visual optokinetic stimulation (Dieterich, Bucher, Seelos, & Brandt, 1998; Dieterich, Bense, Stephan, Yousry, & Brandt, 2003) – are also known to activate this multisensory network and consequently ameliorate the symptoms of USN (Kerkhoff & Schenk, 2012, and Vallar et al., 1997, for reviews; for neck-vibration: Ceyte, Cian, Nougier, Olivier, & Roux, 2006; Karnath, Christ, & Hartje, 1993; Karnath, 1995; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002; for optokinetic stimulation: Karnath, 1996; Kerkhoff, Keller, Ritter, & Marquardt, 2006; Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990).

Once the strict intertwining between vestibular areas and networks subserving spatial attention is acknowledged, it appears clear that vestibular stimulation techniques might represent a precious and effective tool in both clinical and experimental settings. The aim of the present study was to test the effectiveness of Galvanic Vestibular Stimulation (GVS) in inducing spatial biases in a sample of healthy young individuals. GVS is a peripheral stimulation of the VIII cranial nerve through small intensity currents applied over the mastoid bones, behind the ears. Despite less attention has been devoted to the effects of GVS in clinical practice (as opposed to CVS), several reports confirm that also this kind of stimulation is indeed effective in restoring visuo-spatial deficits of USN (Kerkhoff & Schenk, 2012; Kerkhoff et al., 2011; Rorsman, Magnusson, & Johansson, 1999; Utz, Keller, Kardinal, & Kerkhoff, 2011). It is worth stressing that CVS, though very effective in restoring spatial deficits, was gradually abandoned because benefits were short-lasting (often disappearing after 10-15 minutes from treatment); one possible explanation of this short-living effect is the need of restrain administration to a brief (30-60s) session, in light of technical limitations and, most notably, adverse effects such as nausea or vertigo (although these effects are sensibly reduced in brain damaged patients with respect to healthy persons, Kerkhoff & Schenk, 2012). GVS in this sense appears particularly interesting because more prone to more extended rehabilitation protocols (e.g., one daily session for a 1-2 weeks period), more suitable to prolonged administration (e.g., sessions lasting up to 20-30 minutes), and linked to minor adverse effects (Utz, Korluss, et al., 2011). Although much more research is needed to test its long-term effectiveness, GVS appears therefore a potentially useful and easy-to-use clinical tool. In addition, GVS is part of the non-invasive brain stimulation techniques (NIBS) family: NIBS rose quickly in recent years, proving to be safe and promising tools to modulate cortical activity in a target site (Been et al., 2007), often proving a causal relationship between brain areas and behavioural indices or performance. Differently from other NIBS techniques (e.g., transcranial Direct Current Stimulation, tDCS) it has the advantage of inducing brain *activations*, rather than cortical activity *modulation*, a feature that allows a more straightforward interpretation of experimental results and therapeutic benefits (Been et al., 2007; Lenggenhager, Lopez, & Blanke, 2007, for an example). However, not much consensus has been reached around the most appropriate parameters and setting to exploit this potential. In particular, one common concern is that the vestibular system rapidly reach sensory habituation and adaptation, potentially hampering an effective stimulation (Balter et al., 2004). In the present study we tested a newly devised protocol employing sinusoidal stimulation waveform instead of a continuous one. In this approach current intensity is not delivered at constant threshold, but changes over time following a sinusoidal trend: current intensity is negligible (close to zero) at the beginning and at the end of each cycle, whereas it peaks at its half and assumes intermediate intensities in all other phases (see Fig. 1 in Methods). In order to validate the effectiveness of this protocol, we asked 24 healthy persons to perform spatial tasks while receiving GVS with different montages (i.e., SHAM-control, Left-, and Right-anodal). The most activated hemisphere is the one contralateral to anodal stimulation (Ferrè, Longo, Fiori, & Haggard, 2013), and spatial biases are therefore seen as occurring towards the same side (Heilman & Van Den Abell, 1979). The spatial task we choose are widely used in the neuropsychological literature. We employed a Line Bisection task (LB), in which healthy subjects tend to mislocate the geometrical center of visually presented segments towards the left (Jewell & McCourt, 2000) and patients with USN towards the ipsilesional side of space (Bisiach, Bulgarelli, Sterzi, & Vallar, 1983). We then proceeded in assessing the Subjective Visual Vertical (SVV), in which participants are asked to align a segment along an imaginary vertical line; persons with vestibular disorders tend to present biases towards the side of labyrinthine dysfunction (Böhmer & Rickenmann, 1995) and patients with USN towards the contralesional side (that is, anticlockwise for a right-sided lesion, Saj, Honoré, Bernati, Coello, & Rousseaux, 2005). Finally, we assessed the Subjective Straight Ahead (SSA, proprioceptive), in which participants are asked to indicate their body midline by means of finger pointings in peripersonal space; spatial biases found in healthy persons and patients with USN are controversial, and likely not strongly lateralized (Chokron, Colliot, Atzeni, Bartolomeo, & Ohlmann, 2004; Farnè et al., 1998; Pizzamiglio et al., 2000), although this task appears particularly sensitive to assess after-effects induced by techniques such as prismatic adaptation or CVS (Karnath et al., 1994; Redding et al., 2005). While GVS has been found to effectively modulate performance of healthy participants in both LB (e.g., Ferré et al., 2013) and SVV (e.g., Zink et al., 1998), to our knowledge no study specifically explored its effects on SSA; this is surprising because the literature on the effects of CVS in SSA is very rich, and SSA has been considered the elective task to validate its effectiveness (e.g., Bottini et al., 2001; Rorden, Karnath, & Driver, 2001). For all tasks we expect to induce a spatial bias consistent with a leftward shift of spatial attention with Left-anodal and rightward with Right-anodal stimulation.

2.0 METHODS

2.1 PARTICIPANTS

Twenty-four participants were enrolled in this study, refunded for their participation with a small fee. They were all students recruited at the University of Padua, naïve to the purposes of the experiment, native Italian speakers, with no history of neurological or vestibular disorders, and normal or corrected to normal vision. They were all right-handers according to a standard screening questionnaire (M= 93.5, SD= 6.99; Oldfield, 1971). They all joined voluntarily and gave written informed consent prior to participate in the present study, after compiling a standard screening questionnaire to check for all exclusion criteria for a NIBS study (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). The study followed the Declaration of Helsinki standards and was approved by the Ethical Committee of the University of Padua. The sample (mean age= 22.62 years, SD= 2) was composed of 7 males (29%) and 17 females (71%).

2.2 APPARATUS AND STIMULI

Participants were tested in a dimly lit, quiet room, their head restrained by a chinrest, and facing a 17 In computer screen. GVS was delivered *via* a commercial, CE approved, stimulator (BrainStim, EMS, Bologna). The application of small current intensities over the mastoid bones induces very few adverse effects with stimulation up to 1.5 mA in both healthy and brain-damaged patients (Utz, Korluss, et al., 2011), although it is associated to illusion of head and body movements towards the side of anodal stimulation. Spongy electrodes (14 cm^2 area, larger than other studies as to minimize any potential discomfort), soaked with saline water and fixed in place with adhesive tape and a rubber bend were used. Stimulation was delivered only after an initial impedance check, to minimize potentially painful sensations. Three configurations were given: Left- and Right- anodal were considered active GVS conditions, inducing different (polarity dependent) effects. In these two first conditions electrodes were placed on mastoid processes symmetrically (that is, in the Left-anodal montage the cathode was placed over the right processes, and *vice versa* for the Right-anodal one). A SHAM condition was also given, with electrodes placed symmetrically about 5 cm below the mastoids, above the neck but far from trapezoidal muscles yielding proprioceptive signals (Lenggenhager et al., 2007). With this simulated GVS condition we aimed at coping with aspecific factors proper of electrical stimulation (e.g., arousal, discomfort), that are known to have an important role in modulating performance in spatial tasks, by having a reliable baseline condition. Participants performed the same behavioural tasks three times, in three different days, under each GVS condition.

As mentioned above, a sinusoidal waveform was used (see Fig. 1). Current was not continuously delivered to participants at constant intensity: current reached its intensity peak (1.5 mA) gradually, and soon declined again to zero. Each cycle of stimulation lasted 30 s, and was repeated until behavioural tasks were completed up to a maximum of 80 times. Note that in a relevant portion of each cycle current intensity was low or negligible. We divided each cycle according to an operational threshold of 1 mA, that has been often taken as a reference in other studies (e.g., Ferrè et al., 2013). For all behavioural tasks the presentation of stimuli was synched with the brain stimulator, as to have only responses provided in the 16 s time window where current intensity was above threshold.

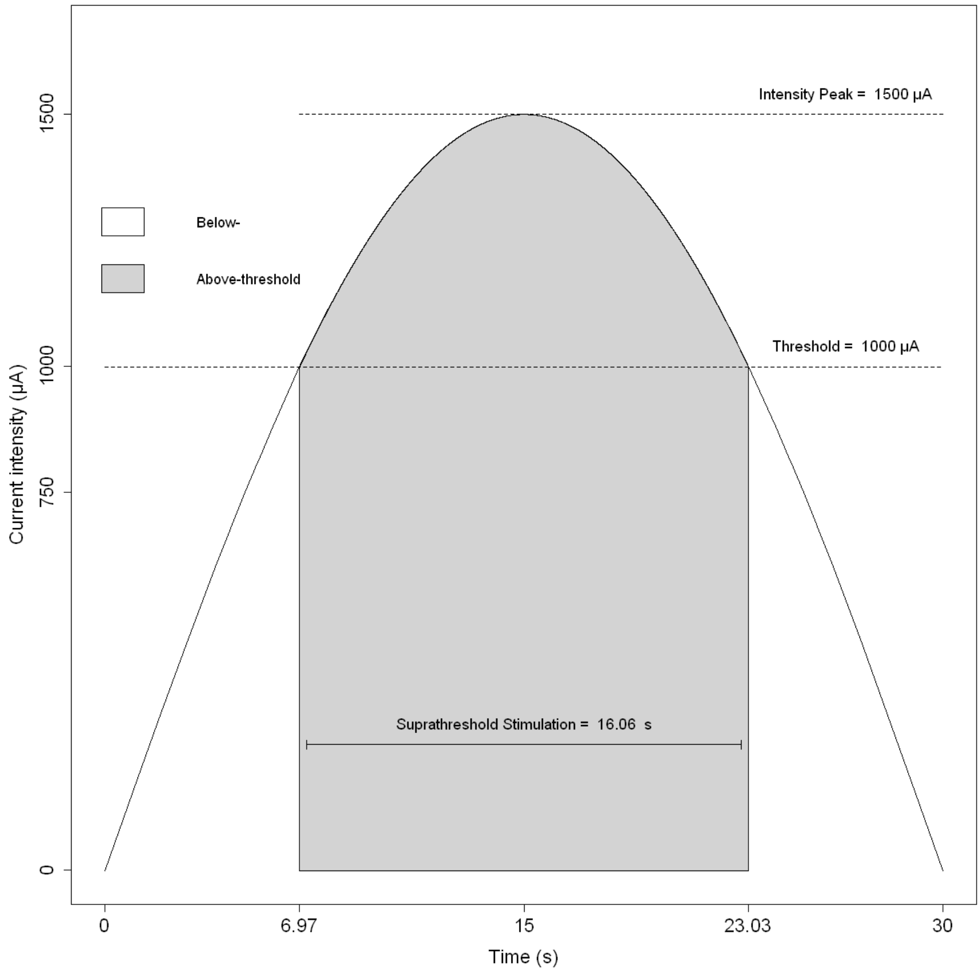

Fig. 1: Schematic depiction of the stimulation waveform employed in this study (one cycle). Current intensity was not delivered continuously but rather changed in time following a sinusoidal function. We divided each cycle using a threshold of 1mA above which stimulation was considered active and experimental stimuli were presented. Our aim was to cope with habituation and adaptation of the vestibular system and at the same time propose a viable alternative to event-related studies with a simpler protocol.

Line Bisection (LB). 30 horizontally arranged visual lines were presented on the computer screen. Lines could be 5, 10, 15, 20, 25, or 30 cm long (Length, six levels) and were always 1 mm tall. A vertical bar, 1 mm wide and 1 cm tall, appeared in a random position over the segment, the task being to align this cursor to the geometrical center of the segment. Participants, specifically, had to press two different buttons to move the cursor either left or right, and confirm their choice with the space bar. Note, hence, that this kind of line bisection task is not only perceptual but also has a strong motor component, and that response modality is not conventional. Accuracy was stressed over speed in the instructions. We used, as dependent variable, the median percent displacement for each line Length scored as in Schenkenberg, Bradford, & Ajax (1980).

Subjective Visual Vertical (SVV). Two empty dots were presented on the screen, in jittered locations as to avoid participants to use screen borders as anchoring points to perform the task. We asked participants to imagine a line joining the two dots, and to align it along the vertical plane. They used arrow keys on a standard QWERTY keyboard to rotate the imaginary line clockwise or counter clockwise and then spacebar to confirm their choice; accuracy was stressed over speed in the instructions. A total of 30 trials were given for each session. As dependent variable the median orientation of the subjective visual vertical (in degrees) was computed.

Subjective Straight Ahead (SSA). A transparent square panel (50 cm side) marked with a goniometer with lines radiating from -90° to 90° wa s placed on the table, centered on participants mid-sagittal plane (Blini et al., 2013). Participants, with eyes closed, were asked to perform pointing movements with their right upper limb, as fast and accurate as possible. Their arm was placed at the centre of the panel, the right-hand resting on the starting location near their body (and chinrest) and aligned with the mid-sagittal plane. They were instructed to indicate the subjectively estimated position of their body midline on the panel surface. On each trial, the experimenter recorded the deviation of the finger position from the true objective body midline (in degrees). 15 trials were given overall, and the median deviation was obtained and used as dependent variable.

2.3 PROCEDURE AND DATA ANALYSIS

Participants attended our laboratories in three different days, in each receiving a different GVS configuration (i.e., SHAM, Left-, and Right-anodal) and performing the same tasks. The order of GVS configuration was fully counterbalanced across subjects. SHAM GVS could be administered in either left-anodal or right-anodal configuration of electrodes (but with electrodes placed below the mastoids), counterbalanced across participants. Montage was applied at the beginning of each session and remained in place for its whole duration. After an automatic impedance check, a few seconds were given to participants in order to familiarize with electric stimulation. In case of no or minor adverse sensations (it was always the case) and after participants' consent, the experiment proceeded with tasks administration. We kept a fixed order for LB, SVV, and SSA tasks; in case of LB and SVV stimuli were randomly selected and presented to participants. In all tasks, furthermore, stimuli presentation was synched with the brain stimulator: tasks were only performed when current intensity was above 1 mA threshold, whereas a break from experimental tasks was given in the remaining part of the cycle (roughly a 14 s pause every 16 s of active stimulation). After each session, participants were given a brief questionnaire to assess and quantify any potential distress.

Collected data were trimmed, for each subject and session, at ± 3 standard deviations from the mean value, to discharge extremely deviant responses; median values for the dependent variable of each task were then submitted to repeated measures ANOVA. GVS Type (three levels: SHAM, Left-anodal, and Right-anodal, within subjects) was the only independent predictor for SVV and SSA tasks; Length (six levels: 5, 10, 15, 20, 25, and 30 cm, within subjects) was also included among predictors in LB task. For LB task only we ran analysis as in Ferrè et al. (2013). The authors ran individual regression analysis (displacement error predicted by line distance from the self, in their case, which might correspond, roughly, to line Length in our case) for each GVS session and computed intercepts and slope coefficients. These parameters might be conceptually independent, and reflect different constructs. Intercepts refer to a theoretical bias in spatial attention when line Length is ideally zero (baseline), whereas slopes reflect the rate of spatial attention shift with increasing line Length. The former was found, in Ferré et al. (2013), to be modulated in a polarity dependent fashion by GVS, whereas the latter was not; intercepts appear, then, particularly interesting to our purposes. Coefficients were submitted to planned contrasts to evaluate both polarity dependent effects (Left- vs. Right-anodal) and generic effects (average of active GVS conditions vs. SHAM). It is worth stressing, however, that while Ferré and colleagues were exploring modulation of spatial attention along the sagittal, near-to-far plane, our setting involves no depth manipulations; this substantial difference might lead to partly different results.

3.0 RESULTS

3.1 Line Bisection (LB).

We discarded 1.2% of responses exceeding, for each subject and session, 3 standard deviations from the mean percent displacement; the median percent displacement for each Type and Length was then submitted to ANOVA. As it appears clear from Fig. 2, only the main effect of Length was found to be significant ($F_{(5,115)}$= 4.32, p= 0.008, Greenhouse-Geisser corrected, η_p^2= 0.158) but with no main effect of Type ($F_{(2,46)}$= 0.56, p= 0.58) or Type by Length interaction ($F_{(10,230)}$= 0.82, p= 0.61). This reflects the tendency to gradually shift the subjective midpoint towards the leftmost end of segments with increasing line Length, with shorter lines associated to a rightward bisection error (a phenomenon described as cross-over effect, Marshall & Halligan, 1989).

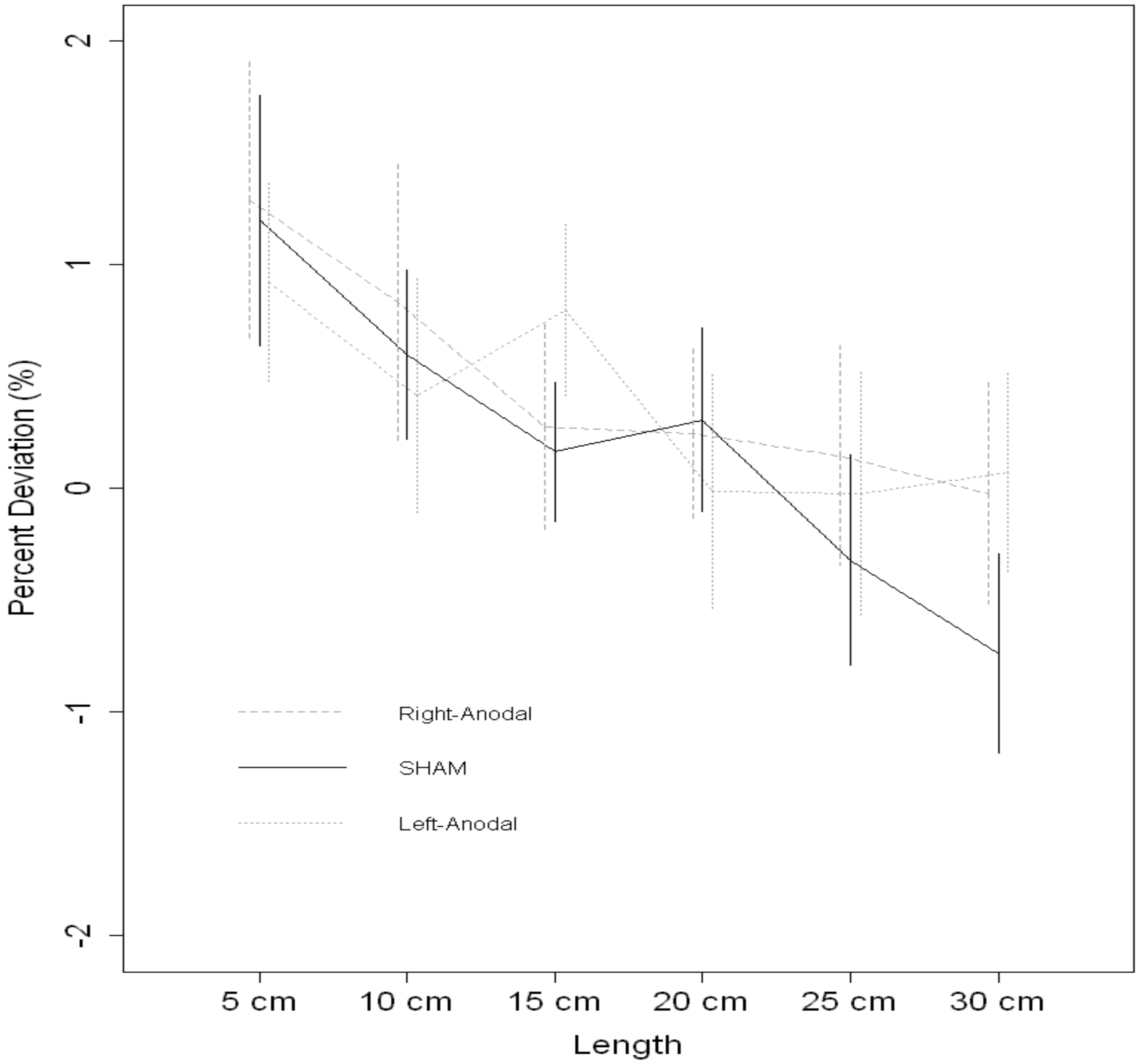

Fig. 2: LB task. The black line depicts participants' performance at baseline (SHAM condition); gray lines – dashed for Right-anodal, dotted for Left-anodal – depict active GVS conditions. GVS was not found to modulate line bisection, neither alone nor in interaction with line Length. The main effect of Length was the only significant effect observed, with shorter lines associated with a rightward bisection error gradually turning to a leftward one with increasing segments length, a phenomenon resembling the well-known cross-over effect. Error bars depict SEM.

We then proceeded with computing individual regression coefficients and performing planned comparisons.

Generic vestibular input (SHAM vs. Left- and Right-anodal GVS collapsed) was not relevant in modulating spatial perception. Intercepts were overall positive at baseline (1.43%) and across active GVS conditions (1.16%), but the difference was not significant ($t_{(23)}$= 0.68, p=0.5). Slopes were overall negative (indexing a gradual leftward shift) but no difference was found across SHAM (-0.07%) and active GVS (-0.043%; $t_{(23)}$= 1.48, p=0.15).

We found no evidence for specific, polarity dependent, effects of GVS as well. Intercepts were located more rightward in the Right-anodal condition (1.3%) with respect to Left-anodal (1%), but the difference was not statistically relevant ($t_{(23)}$= 0.73, p=0.47). Slopes (-0.049% Right-, and -0.037% Left-anodal) were similar across GVS Types ($t_{(23)}$= 0.58, p=0.68).

3.2 Subjective Visual Vertical (SVV).

0.32% of extreme responses was discarded. When submitting the median SVV to ANOVA, GVS Type was not found to modulate the subjective perception of verticality ($F_{(2,46)}$= 2.96, p= 0.062, η_p^2= 0.114). However, we report a tendency for Right-Anodal GVS to shift SVV in clockwise direction with respect to our baseline SHAM condition ($t_{(23)}$= 2.2, p=0.038, paired, two-tailed, uncorrected). Results are depicted in Fig. 3.

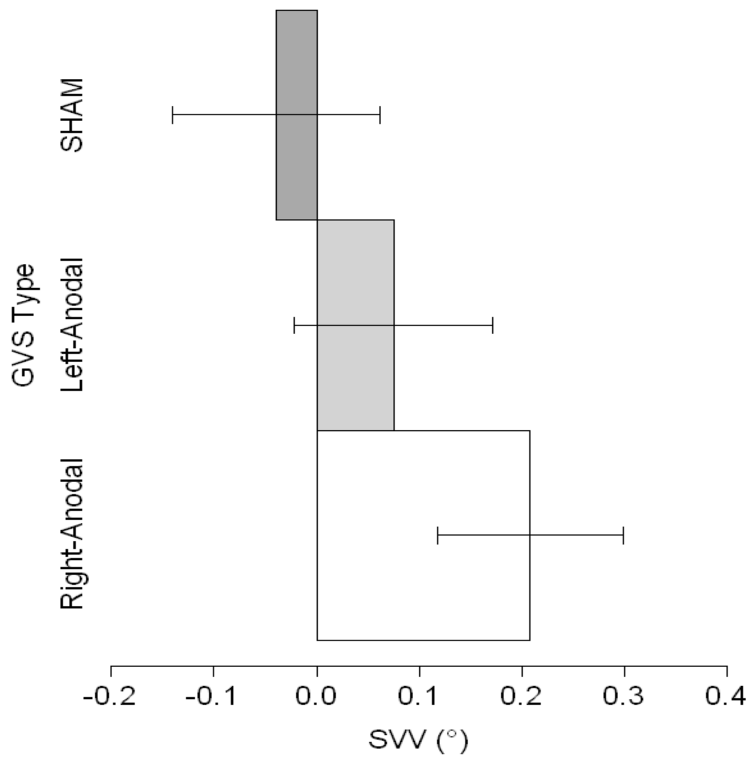

Fig. 3: SVV task. GVS was not found to modulate the subjective visual vertical, although we observed a tendency, for Right-anodal configuration only, to shift SVV clockwise (that is, towards the side of anodal stimulation) coherently with our expectations. Error bars depict SEM.

3.3 Subjective Straight Ahead (SSA).

GVS Type was found to modulate the subjective straight ahead ($F_{(2,46)}$= 3.58, p= 0.036, η_p^2= 0.135). Post-hoc t-test comparisons, corrected for false discovery rate (Benjamini & Hochberg, 1995), indicate that Right-anodal GVS Type differed from both SHAM ($t_{(23)}$= 2.48, p=0.032) and Left-anodal ($t_{(23)}$= 2.47, p=0.032), whereas the latter two did not differ ($t_{(23)}$= 0.1, p=0.91). SSA was displaced towards the anodal side only when this was placed above the right-sided mastoid processes (see Fig. 4).

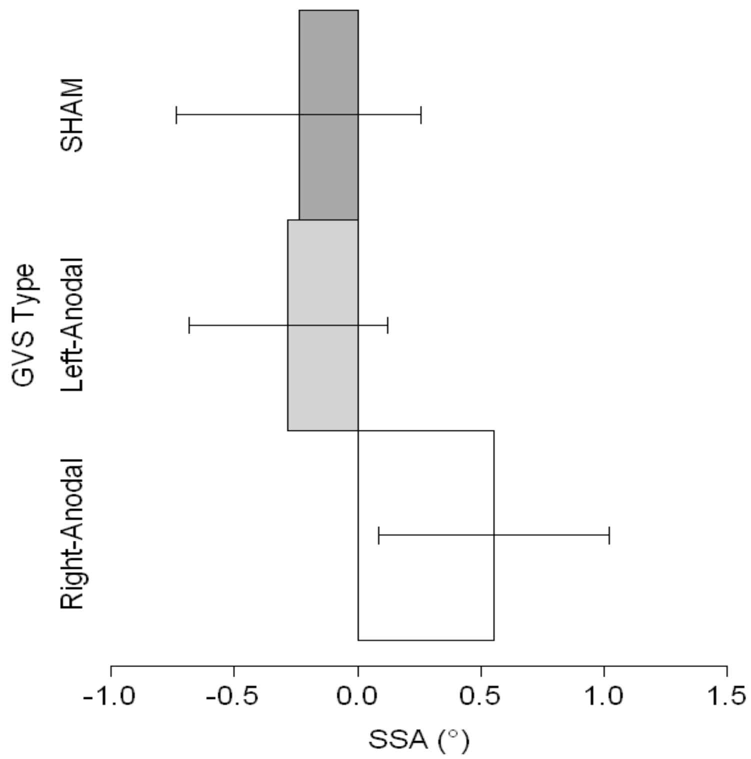

Fig. 4: SSA task. GVS modulated the subjective straight ahead in the Right-anodal condition only, leading to a displacement towards the anodal site. Error bars depict SEM.

4.0 DISCUSSION

In this study we tested the effectiveness of a novel GVS protocol: a sinusoidal stimulation waveform was employed in order to avoid habituation of the vestibular system occurring following a continuous, flat, electrical stimulation of the VIII cranial nerve. We also aimed at providing a simple and convenient alternative to event-related designs, on one hand, and new evidence concerning the effects of GVS in spatial tasks on the other hand. We choose three classic neuropsychological tests: Line Bisection (LB), Subjective Visual Vertical (SVV), and Subjective Straight Ahead (SSA). While GVS already proved to be able to modulate performance of healthy participants in the first two kinds of task (Ferré et al., 2013; Saj et al., 2006), its effects over the latter kind unknown (or conclusions were drawn by analogy with CVS).

We failed to induce a modulation of spatial perception in LB, either showing that our protocol was not effectively modulating the vestibular system or that our choice of using a complex and relatively unconventional response modality was not fully appropriate to highlight perceptual biases. However, hints over effectiveness of the protocol were obtained for SVV, task in which we observed a tendency for Right-anodal GVS in shifting clockwise participants' subjective visual vertical; Right-anodal setting also proved to effectively shift rightward their proprioceptive straight ahead when compared to both SHAM and Left-anodal conditions. At first glance, therefore, results are in line with our predictions of a spatial representational bias occurring towards the side of anodal stimulation, and suggest that the protocol presented here could represent a viable alternative to more complex event-related designs whenever those are not feasible. Note that SSA task was always performed as last, hence when putative habituation of the vestibular system should be maximal, meaning that this common concern could be successfully overcome through a sinusoidal, rather than continuous, electric stimulation pattern. It must be stressed, however, that classic and more controlled event-related designs remain the first choice, in light of some ambiguity in data presented here.

For example, Right-anodal configuration was found to be more effective than the Left-anodal one. This is surprising, given that the most activated hemisphere is the one contralateral to the anode site, but the right hemisphere appears dominant for vestibular (Dieterich et al., 2003) and spatial attentional processing (Heilman & Van Den Abell, 1979). For these reasons, Left-anodal GVS should activate right-hemisphere vestibular areas comparatively more strongly that Right-anodal GVS left-hemisphere ones, and behavioural effects should be more evident with the first configuration. One might object that it is generally easier to reduce a pre-existing leftward attentional bias, instead of exaggerating it (e.g., Ranzini et al., 2014), especially in a sample of healthy individuals with no compromising of monitoring/control resources (also see Chapter 1); however, the effect of Right-anodal GVS was strong enough, in this study, to induce rightward biases in SVV and SSA in face of a leftward bias at baseline (that is, the observed biases crossed the central visual or proprioceptive meridian), casting the doubt that this effect might be more deeply rooted. One prominent model accounting for the very different prevalence of USN after right- vs- left-hemispheric damage claims that, while the left hemisphere would be mainly or solely activated by contralateral stimuli, the right hemisphere would be activated equally by both left- and right-sided ones (Heilman & Abell, 1980); a right-sided lesion would damage this latter, dominant system, causing the leftward one to prevail and rightward biases to occur, whereas a damage to the left hemisphere would leave the right hemisphere spared and more or less able to orient attention along the whole visual scene. Keeping in mind that GVS-induced activations are actually mostly bilateral (Brandt et al., 2012), we can speculate that the results seem to corroborate this view: Right-anodal GVS, mainly tapping on the left hemisphere, seems the condition more prone to enhance attentional processing in a lateralized way.

It is important to stress, finally, that evidences for a distortion of metric properties of space do not imply a bias in spatial unawareness or inattention. For example, Rorden, Karnath, & Driver (2001) found that CVS and neck proprioceptive stimulation, while producing a spatial bias in healthy subjects asked to indicate their body midline, had no effects in a Temporal Order Judgment task, in which the performance reflects possible asymmetries in the allocation of spatial attentional resources (Casarotti et al., 2007; Rorden, Mattingley, Karnath, & Driver, 1997; Shore, Spence, & Klein, 2001; Stelmach & Herdman, 1991). These arguments raise the question of whether the consequences of a vestibular dysfunction or stimulation are confined to a disturbed perception of spatial dimensions or actually extend to the search for and the perception of stimuli in outer space. Indeed, an interesting attempt at clarifying this issue has been made recently by Choi et al. (2013): the authors assessed several paper and pencil tasks (i.e., bisection, cancellation and drawing tasks) in 25 individuals with vestibular neuritis, and found clinical signs of USN in about 1/3 of the group. To be precise, however, 32% of the patients showed a deficitary performance in line bisection while only 1 patient (4%) also showed neglect in one cancellation task, and none in drawing tasks. This may be attributed either to a lack of sensitivity of the standard cancellation tasks in detecting sub-clinical forms of USN (see Chapters I and II), or rather to a mere distortion of spatial metric not extending to spatial inattention. The discussed similarities between USN, vestibular disorders, and vestibular stimulations should be better framed in these terms.

The complex interactions that are seen between the multisensory parieto-insular network and primary areas in the brain, as assessed *via* tasks requiring the computation of spatial dimensions, are certainly intriguing. This can be appreciated by reviewing the literature concerning the SSA (e.g., Bartolomeo & Chokron, 1999; Biguer, Donaldson, Hein, & Jeannerod, 1988; Karnath et al., 1991). SSA assesses the presence of a shift in the perceived body midline and thus of egocentric spatial coordinates, and it is affected by a number of peripheral stimulations like CVS (Bottini et al., 2001; Karnath et al., 1994), neck-vibratory stimulation (Biguer et al., 1988; Karnath et al., 1994; Strupp, Arbusow, Borges Pereira, Dieterich, & Brandt, 1999), sensorimotor painful stimulation (Bouffard, Gagne, & Mercier, 2013), prismatic adaptation (Fortis, Ronchi, Calzolari, Gallucci, & Vallar, 2013; Harris, 1974; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002; Redding, Rossetti, & Wallace, 2005; Rossetti et al., 1998; Sarri et al., 2008) and optokinetic stimulation (Karnath, 1996; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1995), as well as a number of different medical conditions like torticollis (Anastasopoulos et al., 1998), complex regional pain syndrome (CRPS; Sumitani et al., 2007), hemianopia (Ferber & Karnath, 1999; Saj, Honoré, Richard, Bernati, & Rousseaux, 2010), vestibular neuritis (Hamann et al., 2009; Saj et al., 2013) and so on. However, despite those results could help our understanding of the complex interactions between sensory modalities (and brain areas not confined to the parietal lobe) and the egocentric representation of space (Ferber & Karnath, 1999), results are often contradictory (e.g., Saj et al., 2010, found that the rightward SSA shift of USN patients was worsened by a concomitant hemianopia, while Ferber & Karnath, 1999, found that hemianopia somehow restored this bias), and, most importantly, a deficitary performance in this task does not imply the presence of USN and, conversely, the presence of USN does not imply a shift in the perceived body midline (Bartolomeo & Chokron, 1999; Chokron & Bartolomeo, 1997; Farnè et al., 1998; Pizzamiglio et al., 2000), although an enhanced variability in responses may suggest an increased uncertainty and thus a non-directional impairment in body-centred coordinates (L Pizzamiglio et al., 2000). The same arguments hold for LB, traditionally indexing a bias in the allocentric frame of reference, that is also known to be affected by several experimental manipulations like GVS (Ferrè, Longo, Fiori, & Haggard, 2013; Utz et al., 2011), optokinetic stimulation (Pizzamiglio et al., 1990) and prismatic adaptation (Colent, Pisella, Bernieri, Rode, & Rossetti, 2000; Pisella et al., 2002; Rossetti et al., 1998; Schintu et al., 2014) medical conditions like hemianopia (Barton, Behrmann, & Black, 1998;

Barton & Black, 1998) or schizophrenia (Barnett, 2006; McCourt, Shpaner, Javitt, & Foxe, 2008; Ribolsi et al., 2013), cultural factors like the scanning direction in reading habits (Chokron, Bartolomeo, Perenin, Helft, & Imbert, 1998; Chokron & Imbert, 1993), contextual factors like the concurrent processing of magnitude information (Blini, Cattaneo, & Vallar, 2013; Cattaneo, Fantino, Tinti, Silvanto, & Vecchi, 2010; Ishihara, Jacquin-Courtois, Rode, Farnè, & Rossetti, 2013), or simply which hand is used (Brodie & Pettigrew, 1996; also see Ferber & Karnath, 2001).

In summary, straight ahead and line bisection tests are very useful in the clinical (given the correlation of a defective performance with the presence of USN) and experimental practice (given the sensibility to brain asymmetries or certain spatial manipulations or procedures), but many other factors like disturbances of sensory or cognitive processes may affect the performance, suggesting that these measures are not highly specific for hemispatial inattention (Chokron et al., 2007; Ferber & Karnath, 2001). It is therefore important, when exploring the close link or similarity between a given disorder (e.g., vestibular neuritis, or CPRS) and USN, to assess these two task together with higher construct validity tests (i.e., cancellation or detection tasks). As Ferber and Karnath (2001) stressed, cancellation or detection tests directly reflect the core deficit and definition of USN, consisting in the failure to search for or respond to stimuli in the contralesional side of space (Heilman, Watson & Valenstein, 1985), while the straight ahead and line bisection tasks are neither specific nor sensitive (Ferber & Karnath, 2001) and therefore may reflect a spatial bias not referrable to USN-like features. As a second point, another important characteristic of a clinical test is its sensitivity, which allows a reliable detection even of small attentional asymmetries: classic paper and pencil tasks are designed for a neurological population of patients, where USN is often behaviourally evident, and may not be suitable for sub-clinical forms (Bonato et al., 2013); this is probably the case of patients suffering for a vestibular loss. Finally, the straight ahead and line bisection tests are commonly believed to reflect the role of two different frames of reference (i.e., egocentric vs. allocentric), requiring different cognitive operations and neural networks (Galati et al., 2000); given that USN is known to affect different reference frames in a doubly dissociated fashion (Halligan et al., 2003), both egocentric and allocentric tasks should be assessed together, as to explore the presence of a spatial bias in different conditions. Our results, indeed, seem to indicate that a task exploiting an egocentric frame of reference might be more prone to be modulated by a vestibular stimulation technique such as GVS. We argued in favour of sensitivity and specificity of a diagnostic test before in this work (Chapters I and II); now we argue that the task previously described should be administered to a range of clinical populations (e.g., patients with vestibular disorders), complemented by tasks assessing ego- and allo-centric spatial representations, in order to test whether such disturbances are confined to a distortion of spatial metric (e.g., Borel et al., 2008) or rather extend to spatial inattention (e.g., Karnath & Dieterich, 2006).

5.0 ACKNOWLEDGMENTS

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CHAPTER VI

Temptations in the Brain: Resting State Neural Predictors of Value-Driven Attentional Capture

ABSTRACT

Intrinsically rewarding stimuli strongly capture humans' attention, this effect being magnified in several addiction behaviours. We devised a visual search task in which 30 healthy participants had to detect and act over a little dot appearing more or less distant from high- or low-value distracters. We found that performance was affected by the position of high-reward ones (HRD), being better when they were in close proximity of (or overlapping) the target and gradually decreasing as HRD appeared farther away. Participants were previously scanned to collect resting-state fMRI data: we sought to predict their performance in the reward task from connectivity indices obtained through graph theoretical analysis. Preliminary results seem to firmly indicate a major role of the Cingulate-Opercular Network (CON), known to play a relevant role in core reward-related processes, in driving this effect. The mean clustering coefficient (CC) of CON could predict individual performances in our task, being lower in participants with stronger effects. A lower CC for the CON, pointing to a bias in global as opposed to local efficiency, suggests that signals processed in CON areas are more likely to reach nodes that are far away (pervasiveness). Results fit nicely with the literature concerning addiction disorders; future perspectives and directions, starting from these first encouraging preliminary data, are discussed.

1.0 INTRODUCTION

Prof. Brown is attending a tedious talk, stuck in the center of a crowded theatre. He's just arrived in town, after a long and difficult journey because of which he missed to lunch. Now he's so famished he could eat an entire horse. In the meanwhile, to the sides of the theatre, peoples in charge of the catering are finally finishing preparing the generous buffet, and long tables full of delicacies run along the theatre's sidewalls.

In this scenario Prof. Brown has very clear "priority maps" (Awh, Belopolsky, & Theeuwes, 2012; Itti & Koch, 2001; Serences, 2008), and while he's trying to maintain a socially convenient behavior he is also deeply tempted by all the goodies in his peripheral visual field. There is a chance that, while his hunger grows higher and his stomach starts to growl, he may start peeking at all those tasty sandwiches, just to snap immediately back to the old speaker's soporific voice. What happens in this moment? And most importantly, what happens to Prof. Brown's brain while the food exerts such a magnetic attraction to him, and grabs his eyes?

This is more than an intriguing question: this is likely to be a crucial one if we consider that the extreme deviation from this widely spread behavior, i.e. an aberrant and excessive attraction for intrinsically rewarding distracters, seems to be a recurrent feature of a variety of addiction disorders. Indeed, cocaine (Bonson et al., 2002; Hester, Dixon, & Garavan, 2006; Hester & Garavan, 2009), alcohol (Field, Mogg, Zetteler, & Bradley, 2004; Noël et al., 2006), nicotine (Bradley, Field, Mogg, & De Houwer, 2004; Field, Mogg, & Bradley, 2003), food (Castellanos et al., 2009; Werthmann et al., 2011) users and abusers are known to present drug-related attentional biases, such that any cue concerning their addiction exerts an aberrant attentional capture (AC). The degree of AC is sometimes found to be a good predictor of a successful treatment or relapse from therapy (Garland, Franken, & Howard, 2011; Marissen et al., 2006; Waters et al., 2003).

The vast majority of studies focused on monetary reward (a secondary need) because it is easier to manipulate parametrically and does not depend on temporary states. Here, a growing number of studies showed that distracters that were associated with rewards in the past keep on influencing the performance of healthy humans engaged in a variety of tasks (Anderson, Laurent, & Yantis, 2011; Anderson & Yantis, 2012; Chelazzi, Perlato, Santandrea, & Della Libera, 2013;

Della Libera & Chelazzi, 2006; Hickey, Chelazzi, & Theeuwes, 2010), and that the effects of monetary rewards may be also highlighted during on-line tasks (Engelmann & Pessoa, 2014; Theeuwes & Belopolsky, 2012). Yet, the physiology of this phenomenon is rather poorly understood, and the cognitive classification better defined only during the last few years. Several authors recently complained that the classical exogenous/endogenous dichotomy is probably over-simplified, and that value-driven AC (VDAC) may sometimes hamper our current goal-directed behaviour without being tied to particular features of the stimulus itself (Awh et al., 2012). Indeed, the effects of reward and attention are sometimes hard to discriminate in experimental designs (Maunsell, 2004); for instance, participants may be more likely to deploy attention towards more rewarding targets, as part of a proper goal-directed behaviour, if this is not controlled for. On the other hand, animal studies addressing the role of the dopaminergic system within the reward circuitry have clearly established its primary role in driving attention and behaviour (Berridge & Robinson, 1998; Schultz, 2002; Schultz, Dayan, & Montague, 1997; Wise, 2004).

What may ascribed to the reward circuit in the brain, more specifically, is a wide and complex network of interacting brain areas and chemicals (Grabenhorst & Rolls, 2011; Hoebel, 1985), with every node being in charge of different cognitive operations. Among the highly relevant nodes, key functions are covered by the OrbitoFrontal Cortex (OFC), that seems to encode the perceived value and magnitude of rewards (Wallis, 2007) together with other abstract representations, mostly independent from visuospatial or motor factors (Gottfried, O'Doherty, & Dolan, 2003; Padoa-Schioppa & Assad, 2006); the Amygdala (Am) is from a long time known to have a major role in negative affect processing and fear conditioning (Davis, 1992), but it was more recently found to be relevant for stimulus-reward learning (Baxter & Murray, 2002) and conditioned reinforcement as well (Cador, Robbins, & Everitt, 1989; Gottfried et al., 2003), in concert with the Striatum and the Basal Ganglia (BG), where the expectation of predictable rewarding events is likely to be coded (Apicella, Scarnati, Ljungberg, & Schultz, 1992; Schultz, Apicella, Scarnati, & Ljungberg, 1992; Schultz, Tremblay, & Hollerman, 2000) and reinforcement learning is likely to occur (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; O'Doherty et al., 2004); the Insula (In), moreover, is activated during risk prediction and avoidance (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; Preuschoff, Quartz, & Bossaerts, 2008; Xue, Lu, Levin, & Bechara, 2010) and may integrate interoceptive states for decision-making processes that involve uncertainty, risk and reward aspects (Naqvi & Bechara, 2009, 2010). But the reward circuitry is definitely not confined to these areas, because it requires several additional structures joined in complex networks. More relevant for our purposes, because strictly tied to attentional aspects, the Anterior Cingulate Cortex (ACC) also has an established role in monitoring outcomes as to select the most appropriate and rewarding choice for future events (Botvinick, Cohen, & Carter, 2004; Bush et al., 2002; Hadland, Rushworth, Gaffan, & Passingham, 2003; Rushworth, Walton, Kennerley, & Bannerman, 2004) and reward learning (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006; Lecce et al., 2015). It also appears crucial for the allocation of attentional resources towards rewarding stimuli in space (Hickey et al., 2010; Lecce et al., 2015; Mesulam, 1999), perhaps supported by the Superior Parietal/Temporo Parietal circuitry and the Temporo Parietal Junction (TPJ), in charge of shifting attentional resources towards relevant stimuli in space (Corbetta & Shulman, 2002) also accordingly to motivational states (Bisley & Goldberg, 2010; Mohanty, Gitelman, Small, & Mesulam, 2008).

In the present study we capitalize on the growing number of studies outlining the structure and organization of brain networks (Baldassarre et al., 2014; Fox et al., 2005; Hacker et al., 2013; Mantini, Perrucci, Gratta, Romani, & Corbetta, 2007) in order to search for brain connectivity predictors of the degree of attentional capture induced by distracting, task-irrelevant, monetary rewards. When healthy individuals are scanned without any active task to perform, free to wander with their mind, several brain areas present highly correlated hemodynamic activity over time (that is, those areas are functionally connected). Through several different techniques (e.g., Principal Component Analysis) a consistent topographical classification of these areas into intrinsic brain networks, each associated with specific cognitive processes, has been found.

We first scanned 30 healthy subjects for structural and resting-state fMRI, and then administered them a visual search task in which a small dot could appear in one of ten random positions over a standard PC monitor, the goal being to move the mouse cursor over the corresponding box and click over it. Critically, each position was linked, on a trial-by-trial basis and in a completely random fashion, to a more or less valuable reward outcome. Results suggests that the performance of participants was modulated by the amount of potential reward, being better when high rewards were allotted for a correct response and progressively being less efficient the more high rewards were distant in space from the target (see Fig. 1, top panel). The individual regression slope coefficients, representing the degree of attentional capture shown by each volunteer (Fig. 1, bottom panel), were then used as dependent variables in a model where individual connectivity indices were used as predictors.

2.0 METHODS

2.1 PARTICIPANTS

Thirty healthy volunteers (11 men, 19 women, 20 to 31 years old) were enrolled in the study, refunded for their participation. All volunteers fulfilled the inclusion criteria suggested by the Italian Society of Medical Radiology; none had a history of neurological, major medical, or psychiatric disorders. Experimental procedures and scanning protocols were approved by the University of Padua Ethics Committee and conducted in accordance with the Declaration of Helsinki. All participants gave their informed written consent in order to participate in the study.

2.2 BEHAVIOURAL DATA

An exemplificative depiction of the paradigm is reported in the top panel of Fig. 1. 10 empty boxes, arranged in two columns, appeared on the screen for a duration of 1000 ms; the mouse cursor was dragged in the center of the screen. Then, all boxes were filled with images of coins, but only one with a small black dot; the task was to detect and click over the small dot, in the example appearing in the rightmost central square. Participants only had 1500 ms to produce a response. Time limit was calibrated to reach an overall accuracy of about 80%, as to avoid ceiling performance. After a response was provided or 1500 ms elapsed, a feedback text was presented for 1000 ms. Participants, in case of a correct and speeded response, could “win” an amount of money equal to the value of the coin that was presented under the target dot. Feedback text was presented in green after a valid response, red after an invalid one, and reported both the amount earned during the last trial and the overall gain from the beginning of the experiment (practice excluded). Note, hence, that rewards were task-irrelevant distracters, the task only concerning the black dots. 360 trials (plus 20 familiarization trials), divided in three blocks, were given; the square in which dots were presented and their Distance from HRD were balanced and randomly presented. The critical manipulation, indeed, was the distance at which target was presented from the coins with higher value (HRD, that is, 50 cents). We expected better performance when HDR and target were overlapping, and gradually less efficient performance the more HDR was farther away, in light of attentional capture occurring farther from the task-relevant stimulus. Indeed, as shown in bottom panel of Fig. 1, this was highlighted when individual regression analysis was applied, allowing to quantify the rate of decrease in efficiency (computed as a ratio between accuracy and squared reaction times, collapsed across all 10 squares) as a function of the Distance between target and HDR. This effect is indexed by the overall negative regression slopes computed for each participant (M= -0.007, SE= 0.002, BF= 13.89, one-sample Bayesian t-test). We therefore assume that the steepness of the regression line, obtained for each subject, reflects the individual sensitivity to our manipulation: we used this variable as dependent variable in a model where neural networks' properties were introduced as predictors. Note that, as to ease interpretation of the results, we changed the sign of this slope in subsequent analyses, so that a positive value for this index reflects an enhanced sensitivity to reward.

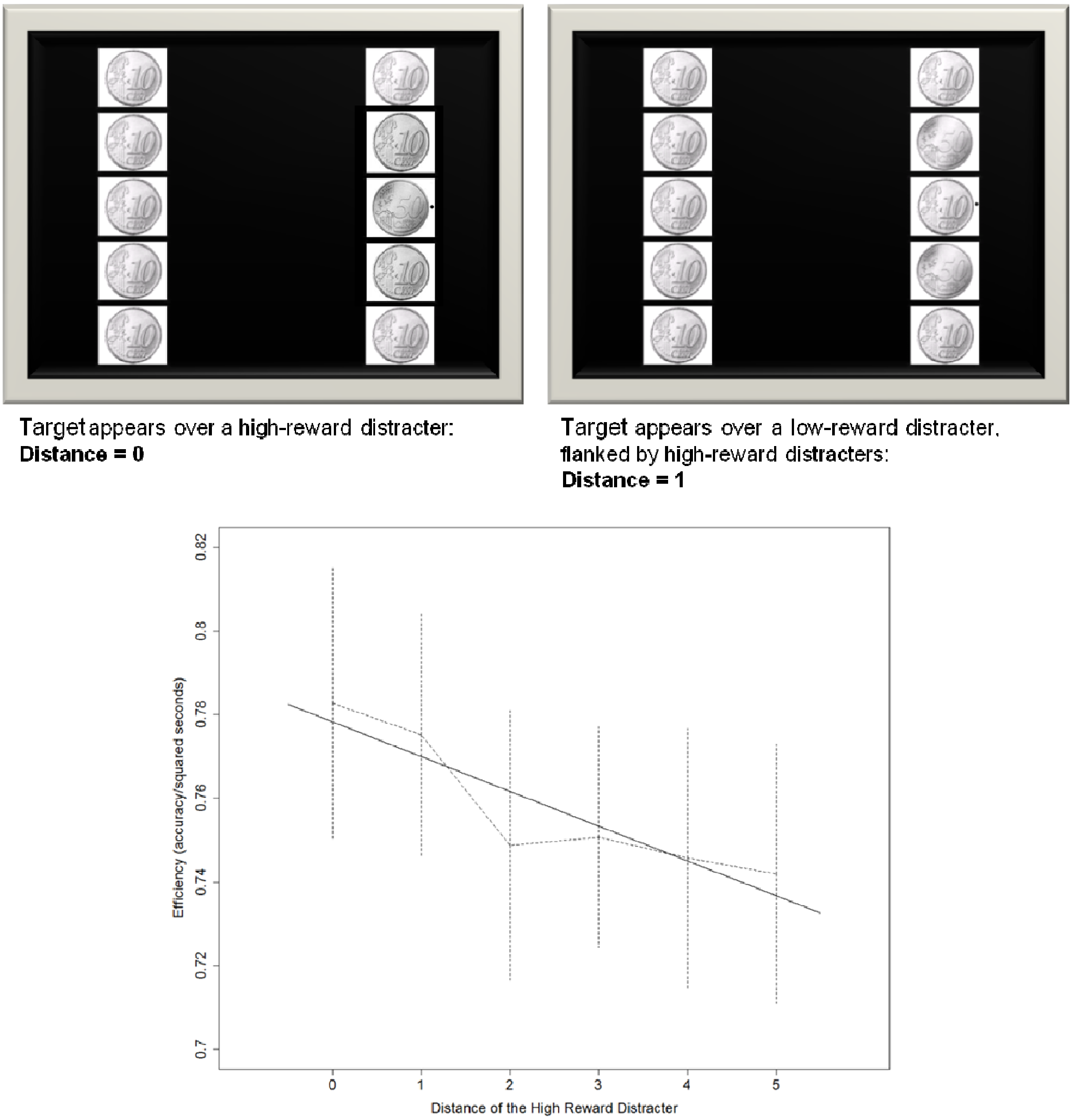

Fig. 1: An exemplificative depiction of the paradigm is reported in the top panel. The best performance was when HDR and target were overlapping; performance was gradually less efficient the more HDR was farther away, possibly in light of attentional capture occurring farther from the task-relevant stimulus. The bottom panel reports results from individual regression analysis (SEM).

2.3 fMRI DATA

Data acquisition. The experiment was carried out on a whole body 1.5 T scanner (Siemens Avanto) equipped with a standard Siemens eight channels coil. Functional images were acquired with a gradient-echo, echo-planar (EPI) T2*-weighted sequence in order to measure blood oxygenation level-dependent (BOLD) contrast throughout the whole brain (37 contiguous axial slices acquired with descending interleaved sequence, 56 × 64 voxels, 3.5 mm × 3.5 mm × 4.0 mm resolution, FOV = 196 mm × 224 mm, flip angle = 90◦, TE = 49 ms). Volumes were acquired continuously for each run with a repetition time (TR) of 3 s; 260 volumes were collected, resulting in a single functional run of 13 min duration. High-resolution T1-weighted image were acquired for each subject (3DMP-RAGE, 176 axial slices, no interslice gap, data matrix 256 × 256, 1 mm isotropic voxels, TR = 1900 ms, TE = 2.91 ms, flip angle=15◦). Participants were asked to keep their eyes open throughout all the scanning session.

Preprocessing. Data preprocessing was performed using SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB 10.2a environment (MathWorks, Natick, MA, USA). ArtRepair toolbox (ArtRepair software Package, for SPM2) was adopted in order to correct for possible images corruption due to signal spikes induced by head motion. Motion correction was carried out by realigning and unwarping data. Structural images were segmented; the gray matter image was then co-registered with all the functional images. Structural and functional images were normalized through the template provided by the Montréal Neurological Institute (MNI) implemented in SPM8. We did not use spatial smoothing. Spatial smoothing can dramatically increase the probability of false positives (Stelzer, Lohmann, Mueller, Buschmann, & Turner, 2014) and potentially cancel out differences within anatomically adjacent, but functionally distinct, brain areas.

Graph theoretical analysis. Resting-state fMRI measures spontaneous low-frequency fluctuations in the BOLD signal to investigate the functional architecture of the brain. Application of this technique has allowed the identification of various Resting State Networks (RSNs), namely spatially distinct areas of the brain that demonstrate synchronous BOLD fluctuations at rest. Various methods exist for analyzing resting-state data, including seed-based approaches, independent component analysis, graph methods, clustering algorithms, neural networks, and pattern classifiers (see Lee, Smyser, & Shimony, 2013, for review).

Here we focused on graph methods. Graph theoretical analysis is commonly applied to study properties of functional and structural brain networks and compare the differences among these complex networks (Bullmore & Sporns, 2009; Stam & Reijneveld, 2007). Graph theory is the natural framework for the mathematical representation of complex networks. Formally, a complex network can be represented as a graph by G(N, K), with N denoting the number of nodes and K the number of edges in graph G. Graphs can be classified as directed or undirected based on whether the edges have sense of direction information. Likewise, graphs can also be divided into unweighted (binary) graphs if every edge in the graph has an equal weight of 1 or weighted graphs if its edges are assigned with different strengths. In this study, we focused on undirected and weighted graphs. For an undirected and weighted graph G(N, K), the connectivity pattern can be completely described by an N×N symmetric square matrix named adjacency matrix A whose entry a_{ij} (i, j=1,…,N) is settled to a connectivity value computed using a specific measure of functional connectivity (e.g., Pearson correlation, mutual information, coherence) between node i and j. Typically, in fMRI resting state studies, the set of nodes correspond to specific regions of interest (ROI) extracted from the brain, and edges. A network graph is usually characterized by some topological parameters, among which the clustering coefficient and the shortest path length are two crucial parameters for characterising the so-called ‘‘small-world’’ network topology. This parameter is crucial for pruning the adjacency matrix A, selecting a subset of K edges from the initial ((NxN)-N)/2 edges of the adjacency matrix, in order to construct the final graph G(N,K). Moreover, a lot of parameters have been proposed for describing in a quantitative way the network topology and its structural/functional organization (Rubinov & Sporns, 2010). Finally, statistical analyses can be performed on the network parameters in order to investigate connectivity changes across different populations, experimental conditions, or for predicting individual performance (for a review see Lee et al., 2013).

Node construction. For the adjacency matrix construction we selected a subset of nodes corresponding to 169 distinct ROIs used in Baldassarre et al. (2014).

Connectivity measures. Here we used a single-subject-connectivity-matrix approach, as suggested by Langer, Pedroni, & Jäncke (2013). Thus, for each participant we computed a connectivity matrix using mutual information (MI) as a measure of statistical dependence among node pairs. Mutual information indexes the reduction in uncertainty about one random variable given knowledge of another. High values of MI indicate a large reduction in uncertainty; low values of MI indicate a small reduction; and zero value of MI between two random variables indicates that the variables are independent.

Adjacence matrix thresholding. After obtaining the connectivity map, a critical point for the construction of the graph is the choice of a threshold for pruning the adjacence matrices. In order to compare functional networks among different groups or perform a statistical test on the graph population, it is crucial to maintain graphs with the same density, that is having the same mean edge number (i.e., the mean degree of the graph). Thus, we used the proportional thresholding method, which ranks the connections (i.e., MI edge values) in a descendent order and selects a certain percentage of the top ranked connections, expressed by a specific threshold. Networks of so-called "small-world" topology represent a good compromise between efficient information transmissions among distant nodes, and efficient local information processing (Bullmore & Sporns, 2009). Thus, even if at the moment there is no standard way to choose a threshold for the graph construction, a recent proposal of Langer, Pedroni, and Jäncke (2013) is to select a threshold that maximises the mean clustering coefficient and minimises the mean path length. The small-word parameter encode information related to both clustering and path length parameters: according to the formulation of Humphries & Gurney (2008), a network with a small world topology has the small-word parameter larger than 1. Here, we adopted a procedure based on controlling the small-word parameter as function of the network threshold. Thus, at each of the selected thresholds (i.e., 10-90 %, with step of 10%) we computed the small-word parameter for each participant, and selected the larger threshold that preserved the small word network topology (i.e., the mean small-word parameter > 1): this allowed us to maintain a more conservative version of the connected graph without including spurious correlations, and discard the more defragmented graphs.

Connectivity indices. To obtain connectivity indices, we therefore applied graph theoretical analysis (Bullmore & Sporns, 2009) over 169 brain areas (nodes) previously identified by Baldassarre and colleagues (2014) as forming 10 distinct brain networks. Graph theoretical analysis is a formal way to describe complex interactions among several objects, and is applied here to assess – beside functional connectivity itself – many other descriptive properties of the connections. In this work we focus on results obtained when analyzing the mean Clustering Coefficient (CC) of the 10 networks (see Fig. 2). CC is obtained for each node, and it reflects the proportion of neighboring nodes (that is, nodes to which one area is directly functionally connected) that are also mutually connected. CC ranges between 0 – case in which no neighboring area is mutually connected – to 1, case in which all neighboring areas are connected (see Fig. 2). It is generally assumed that high CC reflects high segregation of a brain area, whereas low CC reflects a more distributed pattern of connections among neighboring nodes and hence towards brain areas beyond them. In other words, an high CC reflects a bias towards an enhanced local efficiency as opposed to a more global/distributed information processing.

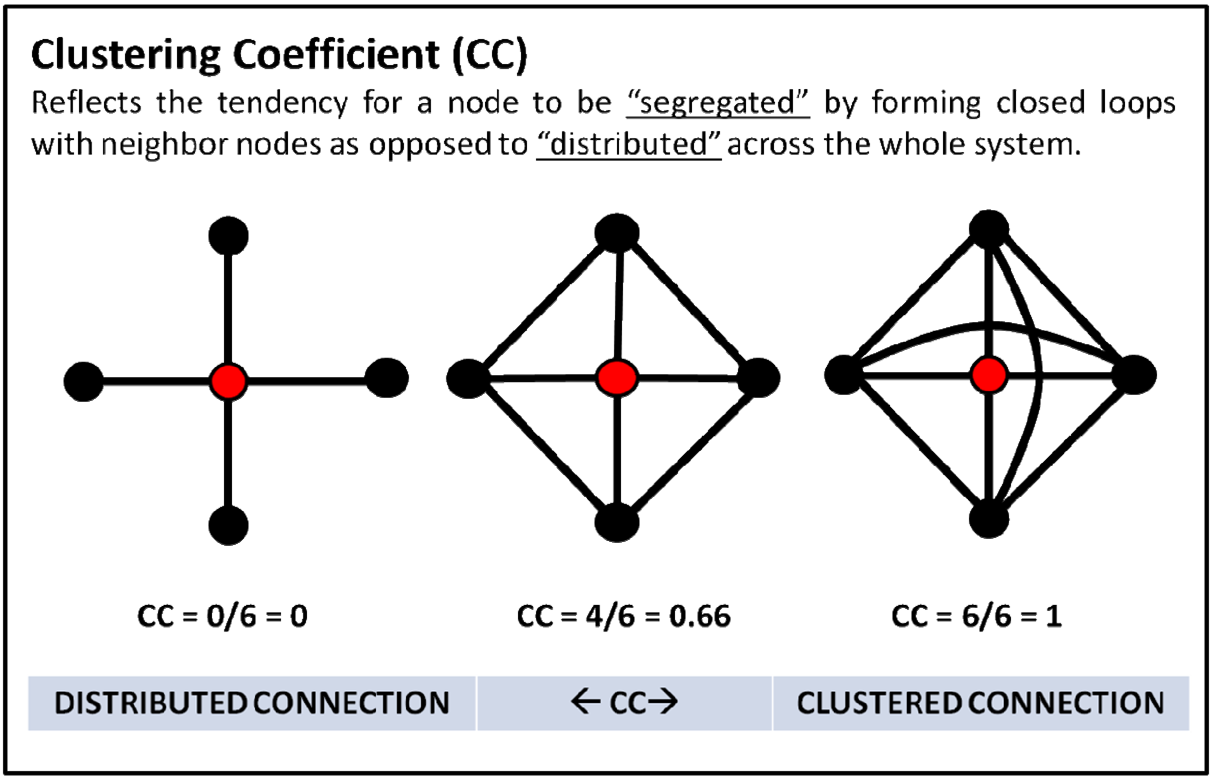

Fig. 2: Graph theory offers several parameters for describing the topology of a network and its structural and functional organization (Rubinov & Sporns, 2010). In this work we focus on the Clustering Coefficient (CC), that is computed locally as the fraction of triangles around each individual node. A schematic depiction is reported, representing three nodes (central-red) and their connectivity pattern. In the example each node is functionally connected to four neighbor nodes (peripheral-black); the connectivity pattern among these neighboring nodes, however, is markedly different. In the leftmost example black nodes are not mutually connected, whereas in the rightmost one all possible combinations are present (that is, each neighboring node is connected to all other neighboring nodes). The former is thought to represent a more distributed configuration, information being more prone to reach nodes beyond neighboring ones, whereas the latter is thought to reflect clustered and segregated connectivity. The mean CC, as a global connectivity measure for the network, reflects the prevalence of clustered connectivity around individual nodes within the network itself.

3.0 RESULTS

In light of the aforementioned properties of the CC and the literature review over brain areas particularly involved in the reward loop, we hypothesized that a more pervasive role of cingulated cortices, as indexed by lower CCs, might be predictive of an enhanced sensitivity to reward because, instead of being confined in this specific network, effects of reward might be more prone to reach more distant areas (e.g., visual, motor), all together contributing to the effect that we observed in a complex visuo-perceptual and motor task. As can be seen from Tab. 1, this is clearly the case. Results are also depicted in Fig. 3: the main result is that a higher segregation of the Cingulate Opercular Network (CON) predicts a minor value-driven attentional capture, whereas effects of reward are more pronounced in case of distributed connections within the CON.

We ran stepwise multiple regression modeling using the mean CC for each of the 10 networks described in Baldassarre et al. (2014) as regressors, and the slope coefficients previously introduced (see Fig. 1) as dependent variable. Model selection was performed using the Akaike's Information Criterion, to evaluate both goodness of fit and complexity of the to-be-tested models; a Bayesian approach, using the Bayes Factor (BF) as criterion, was also performed to complement analysis.

Both approaches yielded support for the model including 4 networks: Cingulate Opercular (CON), Linguistic (LN), Visual Peripheral (VPN), and Visual Foveal (VFN). It must be said that the 4 networks model (BF= 13.73) was only slightly preferred to the model where VFN was not included (BF= 10.7) and to the model where no visual network was included (BF= 8.74); indeed, when top-down testing was performed, the CON was found to have by far the major role (BF_{01}= 40.35), followed by LN (BF_{01}= 3.92), but with visual networks showing only a marginal role in model's goodness of fit. In top-down testing BF is obtained for models in which one variable at a time is dropped from the full model (composed of 4 networks), against the full model itself (therefore taken as a reference); BFs are base 1 because each model created in this fashion is by design less informative than the reference / full one by a factor equal to the so-obtained BF. Though we only have anecdotal evidence for a role of visual networks, when considered individually, we also observed a massive drop in explained variance when these two networks were omitted (from 45% to 31%), suggesting that deeper analysis should be envisaged.

Network	Full Name	Beta	SE	BF_{01}
CON	Cingulate Opercular Network	-0.1	0.028	40.35
LN	Linguistic Network	0.1	0.04	3.92
VPN	Visual Peripheral Network	-0.073	0.038	1.67
VFN	Visual Foveal Network	-0.06	0.034	1.36
Fit:	$F_{(4,25)} = 5.19$, $R^2 = 0.454$, BF = 13.73			

Tab. 1: Results of the stepwise multiple regression modeling using the mean CC for each of the 10 networks described in Baldassarre et al. (2014) as regressors, and the slope coefficients previously introduced as dependent variable. The CON was found to have by far the major role (BF_{01}= 40.35), followed by LN (BF_{01}= 3.92), but with visual networks showing only a marginal role in model's goodness of fit.

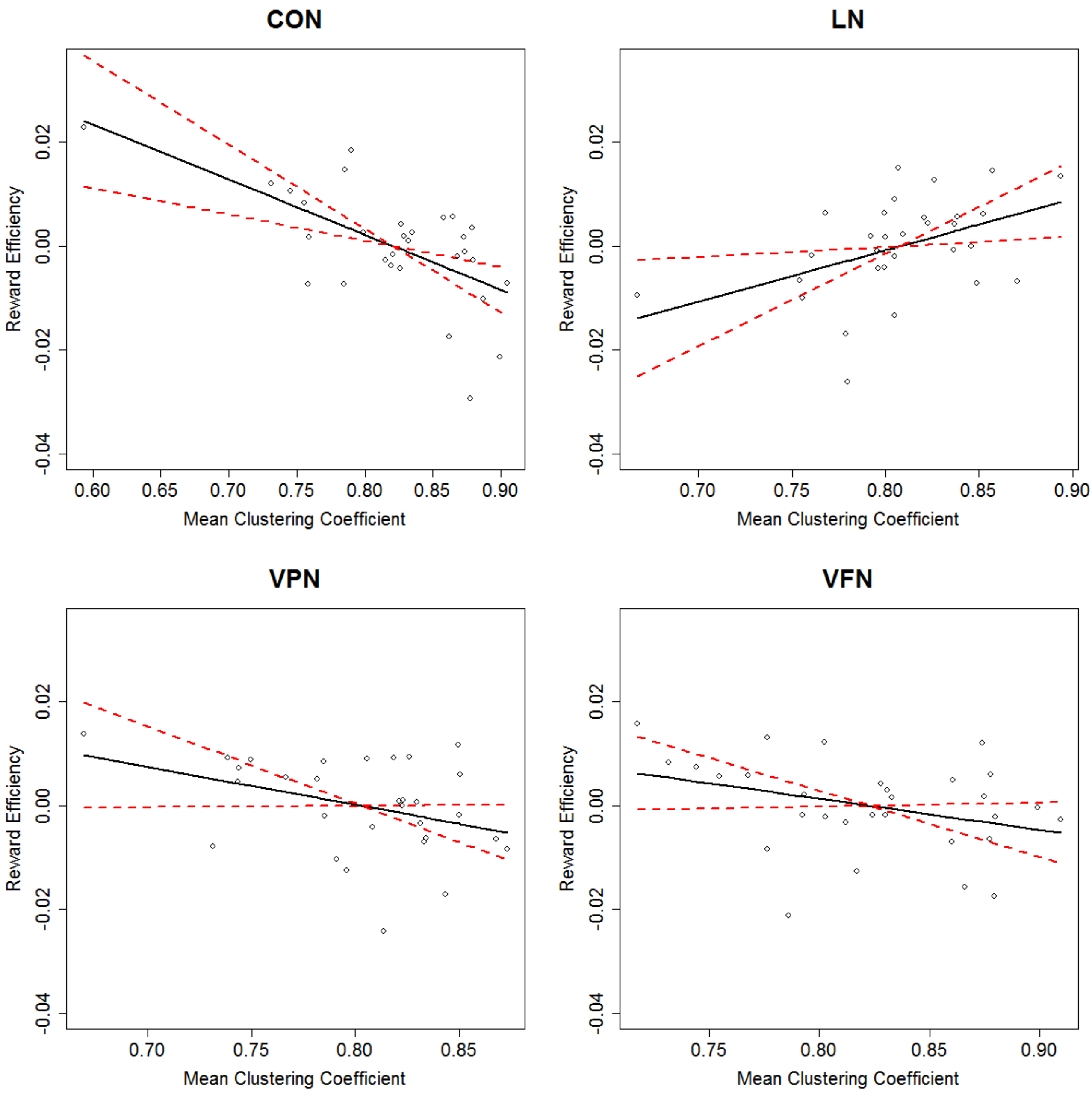

Fig. 3: Results of the multiple regression modeling (Tab. 1) are depicted. The degree of segregation shown by the Cingulate Opercular Network (CON) was by far the most informative index when trying to predict the effects of reward in our visual search task; specifically, stronger value-driven attentional capture was seen the more CON connections were distributed across the whole brain (lower clustering coefficient). We also found weak evidence for a role of Linguistic network, in the opposite direction, and ambiguous evidence for a role of visual ones. Black lines' steepness represent beta coefficients, and red dashed lines their pointwise standard errors; dots depict the residuals. No evidence for multicollinearity (assessed through VIFs) amongst observations or highly influential observations (assessed through Cook's distances) was found.

4.0 DISCUSSION

Results fit nicely with the idea of a cingulate network, including the ACC, that would be in charge of allocating attentional resources in space accordingly to motivational needs (Hickey et al., 2010; Lecce et al., 2015; Mesulam, 1999). We found that reward-induced effects were stronger the more CON was open to connections with distant areas, suggesting to further explore its functional connectivity; indeed, although we have hints concerning a more pervasive role of the CON, further analysis (e.g., seed-based) are necessary to characterize this role, and test whether specific connections (e.g., with visual, attentional, or motor areas) are driving this effect or rather the whole network activity remains more informative. The same argument holds for the role of the Linguistic network, that we found having a similar, although weaker, role in VDAC: LN includes brain areas with rather heterogeneous functions, including areas with both language-specific and aspecific motor programming functions (e.g., Broca's area, Fadiga, Craighero, & D'Ausilio, 2009; Nishitani, Schürmann, Amunts, & Hari, 2005), and thus an in-depth analysis could shed light on its contribution.

A fascinating parallel can be made with respect to imaging literature over addiction behaviours, that points to a dysfunction of core reward-related mesolimbic networks (Goldstein & Volkow, 2002; Goldstein et al., 2007; Ma et al., 2010; Sutherland, McHugh, Pariyadath, & Stein, 2012). One recent study (Tschernegg et al., 2013) reported a reduced clustering coefficient in a population of pathological gamblers (Potenza, 2008) with respect to a control group of healthy individuals; their results, thus, closely resemble preliminary data reported in this chapter. Tschernegg et al. (2013), specifically, found a bias towards global (as opposed to local) efficiency in areas included in the CON, especially in the left paracingulate and supplementary motor areas, together with their increased centrality and integration. Interestingly, a tendency in a decreased centrality of the left inferior frontal gyrus (increased for the caudate) was also found (Tschernegg et al., 2013), confirming that our results about the role of LN deserve to be assessed thoroughly. Behavioural addictions are complex clinical entities, and shall not be reduced only to reward-related aspects; however, it is certainly intriguing to speculate about a possible continuum in sensitivity to reward, stemming from acceptable physiological levels and proceeding towards aberrant and excessive ones, ultimately leading to problematic behaviours (Dawe, Gullo, & Loxton, 2004). A possible neural marker of this tendency, predictive of stronger behavioural effects in cognitive tasks (as in this chapter) and frankly reduced in clinical populations (Tschernegg et al., 2013), might be the lack of segregation of CON areas, pointing to an enhanced pervasiveness of this system.

5.0 ACKNOWLEDGMENTS

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