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The cognitive demand of multitasking under visuo-spatial processing:

Assessment, ERPs and electrophysiology of brain networks in chronic stroke patients

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Abstract

This thesis investigates several aspects of visuo-spatial processing from a clinical, electrophysiological and neurofunctional perspective, with the aim of enriching our understanding of neurological syndromes that affect such fundamental perceptual-cognitive skill. A common thread is the use of cognitive load as a mean to study spatial awareness deficits following brain stroke. We show that increased task demands uncovers pathological spatial asymmetries both in right and left hemisphere damaged patients that performed at ceiling in standard paper-and-pencil tests. Although visuo-spatial deficits are commonly considered infrequent after left hemisphere lesions, the comparison between the two clinical populations showed that multitasking reveals patterns of neglect and extinction regardless of the affected hemisphere. A similar multitasking paradigm was then administered to young healthy participants in order to study the electrophysiological signatures of spatial monitoring, examining correct and erroneous processing of peripheral visual stimuli. Task difficulty was increased compared to the clinical version in order to obtain a consistent number of missed targets, thereby simulating patients' performance. Our results support the hypothesis that processing of visual information under multitasking is regulated by a threshold criterion: the target is successfully detected only when the electrophysiological activity reaches a critical amplitude. Finally, we conducted a resting state electroencephalographic (EEG) study in order to correlate patterns of spontaneous brain activity with neuropsychological scores and multitasking costs indices. This investigation builds on the hypothesis that cognition is not only associated with the specialization of brain regions, but also with the large-scale organization of functionally connected networks. A state-of-art methodology was used to reconstruct 14 brain networks, previously detected in fMRI studies, from electrophysiological signals in chronic stroke patients. The integration of critical clusters within each network was then examined, exploring also its correlation with behavioural measures and the contribution of specific frequency bands. Overall, this empirical work provides an original contribution to the study of the mechanisms underlying brain organization after unilateral damage and the consequent implications for cognitive performance.

Riassunto

Questo lavoro di tesi indaga diversi aspetti relativi all'elaborazione visuo-spaziale da un punto di vista clinico, elettrofisiologico e neurofunzionale, al fine di contribuire allo studio dei disturbi neurologici che comportano deficit a livello percettivo. Il filo conduttore è stato l'utilizzo del carico cognitivo per studiare deficit di consapevolezza spaziale che possono emergere a seguito di un ictus cerebrale. Abbiamo mostrato come l'aumento della difficoltà di un compito sia in grado di rilevare asimmetrie spaziali patologiche in pazienti con lesioni cerebrali all'emisfero destro o sinistro che avevano una prestazione nella norma ai classici test neuropsicologici "carta e matita". Sebbene i disturbi visuo-spaziali siano ritenuti infrequenti a seguito di lesioni emisferiche sinistre, sorprendentemente il confronto di queste due popolazioni cliniche mette in luce l'efficacia del *multitasking* nell'individuare pattern di negligenza ed estinzione indipendentemente dal lato della lesione. Una versione modificata del nostro paradigma di *multitasking* è stata inoltre somministrata ad un gruppo di giovani partecipanti sani al fine di studiare i correlati elettrofisiologici del monitoraggio spaziale, confrontando l'elaborazione corretta ed incorretta di stimoli apparsi nella periferia del campo visivo. La difficoltà del compito è stata aumentata rispetto alla versione clinica al fine di ottenere un consistente numero di stimoli non individuati e dunque di simulare la prestazione di pazienti neurologici. I nostri risultati supportano l'ipotesi che in condizione di *multitasking* l'elaborazione di informazioni visive sia regolata da un criterio di soglia. Nello specifico, la corretta percezione di uno stimolo è determinata dal raggiungimento di un'ampiezza critica dell'attività corticale. Infine, abbiamo condotto uno studio in *resting state* al fine di studiare la correlazione tra attività cerebrale spontanea e prestazione comportamentale, misurata attraverso classici indici neuropsicologici ed indici di costo al *multitasking*. Questo studio prende in considerazione l'ipotesi che la cognizione non sia associata soltanto alla specializzazione delle regioni cerebrali, ma anche all'organizzazione su larga scala di reti neuronali funzionalmente connesse. Attraverso l'utilizzo di un metodo di analisi allo stato dell'arte, 14 reti cerebrali, precedentemente studiate con tecniche di risonanza magnetica funzionale, sono state estratte dal segnale elettroencefalografico in un gruppo di pazienti con esiti di ictus in fase cronica. Inoltre, è stata analizzata l'integrazione di particolari *cluster* all'interno di ciascuna rete, indagando anche la relativa correlazione con indici comportamentali ed il contributo di specifiche bande di frequenza. In sintesi, questo lavoro

empirico offre un contributo originale allo studio dei meccanismi sottostanti l’organizzazione cerebrale a seguito di ictus e delle relative ripercussioni sulla prestazione cognitiva.

Summary

This work investigated several neurocognitive aspects related to visuo-spatial processing in chronic stroke damaged patients. In order to offer a broad view of the pathological spatial asymmetry patterns that can emerge after a brain insult, we employed a variety of data collection techniques and analysis approaches.

Brain stroke is currently one of the main causes of mortality (Feigin et al., 2014; Lozano et al., 2012), but also the cause of dramatic neurological deficits in stroke survivors. Following stroke, patients can show selective cognitive deficits that hinder the execution of common daily activities, strongly reducing the levels of independence and the possibility to explore the surrounding world. Indeed, in most everyday contexts visuo-spatial processing is a cognitive ability involved in multiple activities, such as the navigation in the space or the simple interaction with the environment. A consistent number of patients manifest visuo-spatial deficits following right hemisphere damages. Unilateral spatial neglect is a frequent consequence of stroke (Appelros, Karlsson, Seiger, & Nydevik, 2002; Buxbaum et al., 2004; Corbetta & Shulman, 2011), consisting in the inability to report or respond to stimuli presented in the contralesional side of the space (Driver & Vuilleumier, 2001; Heilman, Watson, & Valenstein, 1985). Neglect is a fascinating syndrome because of its variety of symptoms and anatomical correlates (Karnath & Rorden, 2012). Concerning the occurrence of neglect in neurological populations, many studies support the clinical observation that in post-acute phase right hemisphere stroke patients show greater severity and persistence of the deficits compared to left damaged patients, in whom spatial deficits are considered relatively infrequent (Ringman, Saver, Woolson, Clarke, & Adams, 2004; Stone, Halligan, & Greenwood, 1993).

The present thesis is composed by three chapters that explore the emergence and the severity of attentional deficits by examining the effectiveness of assessment tools, the electrophysiology of spatial monitoring, and the relation between brain networks organization and behavioural impairments. More specifically, these contributions have a common central theme: the effect of multitasking demands on visuo-spatial processing. The main purpose is to examine the allocation of spatial resources not only in the context of a simple visuo-spatial monitoring task, but also under conditions of increased attentional load.

Chapter 1 is devoted to the assessment of visuo-spatial biases in chronic stroke patients. A computerized multitasking approach that combines lateralized and not lateralized mechanisms of attention is proposed as clinical tool, in the light of its greater sensitivity in detecting spatial asymmetries compared to standard paper-and-pencil evaluations. A series of theories has been proposed to prove the specialization of the right hemisphere for visuo-spatial processes and the ability of the left hemisphere to compensate for spatial impairments (Heilman & Van Den Abell, 1979; Kinsbourne, 1987). On the other hand, the finding that the occurrence of neglect depends on assessment methodology and on task-demands (Azouvi et al., 2002) opened a discussion on the sensitivity of the clinical behavioural tests. A critical point to consider is that several domain general factors (i.e., alertness, sustained attention, increased attentional load) can modulate severity of neglect (Priftis, Bonato, Zorzi, & Umiltà, 2013; Robertson et al., 1997; Robertson, Mattingley, Rorden, & Driver, 1998). Starting from these well-established findings, a series of studies of Bonato and colleagues (2010, 2012, 2013) revealed the effectiveness of a multitasking approach in uncovering pathological spatial biases that were not detected by means of paper-and-pencils batteries for neglect. The sensitivity of this tool has been demonstrated for the right stroke population, but there was no evidence regarding patients with left hemispheric damage. To the best of our knowledge, the present results show for the first time the effect of multitasking on the visuo-spatial performance of both right and left chronic stroke patients. Interestingly, patterns of neglect and extinctions were found even if patients performed at ceiling in standard paper-and-pencil tests. A direct comparison between left and right damaged patients is presented, and theoretical and diagnostic implications of these findings are discussed.

In **Chapter 2** electrophysiological measures were used to investigate the temporal dynamics of visuo-spatial processing under multitasking condition. The visual world is rich of different types of stimuli and its exploration implicates a filtering process of the surrounding environment consisting in the suppression of the irrelevant information (Possin, 2010). Multitasking has a crucial role in the study of allocation of resources in the space, since visuo-spatial processing usually occurs concurrently with other cognitive operations (Nijboer, Borst, van Rijn, & Taatgen, 2016; Schaefer, 2014). Although we are continuously exposed to multiple sensory stimuli, we have the impression to devote the same amount of resources to the whole visual field. However, recent studies revealed an advantage in the processing of stimuli within the right hemispace during unimodal and multimodal load (Chen & Spence, 2017). Instead, other studies support the idea of a facilitation in left stimuli detection when bilateral stimuli are simultaneously presented (Holländer, Corballis, & Hamm, 2005; Verleger et al., 2010; Verleger & Śmigasiewicz, 2015). Moreover, it has been shown that the efficiency of spatial processing could be hampered by attentional demanding task (Holcombe & Chen, 2012). Although previous studies examined visuo-spatial processing under dual task conditions by means of ERPs, the cognitive and neural characteristics of spatial processing under load are not fully understood. In particular, several works investigated the electrophysiological dynamics elicited by correct targets detection, but not during misperceived trials (Handy, Soltani, & Mangun, 2001; Karnath, Himmelbach, & Rorden, 2002; O'Connell, Schneider, Hester, Mattingley, & Bellgrove, 2011; Rorden, Guerrini, Swainson, Lazzeri, & Baylis, 2008). In Chapter 2, we present a systematic investigation of the electrophysiological mechanisms associated with correct and erroneous processing of peripheral visual target(s) under load condition in a group of young healthy adults. We employed a modified version of the multitasking paradigm of Bonato, Spironelli at al. (2015) to make the processing of the spatial targets more difficult than in the clinical version, thereby increasing the number of undetected targets, in analogy to what is observed in stroke patients. Our results show a load effect on the N1 component, with a stronger modulation for the intra-modal dual task compared with both single task and cross-modal dual task. Under visual load, error responses in comparison to correct responses showed significantly lower N1 and N2 activation for the left and right visual field, respectively. Moreover, higher N1 amplitude was found for errors in the detection of bilateral targets. These results support the hypothesis that a threshold criterion is involved during the processing of visual information. They also provide an electrophysiological counterpart for the hypothesis that the allocation of cognitive resources used to detect and respond to behaviourally relevant stimuli are limited and depletable, as demonstrated by the drop in performance that almost inevitably occurs when performing concurrent tasks.

Finally, in **Chapter 3** recent advances in neuroimaging methodology are used to support the hypothesis that cognitive performance does not emerge from an ensemble of highly specialized brain regions, but rather from the dynamic organization of functionally connected networks (Park & Friston, 2013). In particular, a great deal of attention is devoted to resting state activity and to the characterization of functionally linked regions that are spatially separated (Beckmann, DeLuca, Devlin, & Smith, 2005; Damoiseaux et al., 2006; Fox et al., 2005; Fox & Raichle, 2007). In light of this new conception of the brain, the fundamental question has been to understand how large groups of neurons cooperate in the brain and which mechanisms underlie this complex assembling. Interesting, it has been demonstrated that our brain in never silent, but also at rest independent areas are connected and show high levels of ongoing functional connectivity (van den Heuvel & Hulshoff Pol, 2010). Another crucial aspect to consider is that the functional efficiency of a specific brain region depends on the connections it establishes with other distant regions (Varela, Lachaux, Rodriguez, & Martinerie, 2001). The demonstration of a well-organized system of brain networks is profoundly changing the way of thinking about pathology, as shown by the growing interest for the study of brain networks alterations in psychiatric and neurologic disorders (Baldassarre et al., 2014; Bullmore & Sporns, 2009; Greicius, 2008).

After a review of recent resting state studies, in Chapter 3 the brain-behaviour relationship is examined by considering the implications for damaged brains. fMRI investigations revealed that cognitive deficits after stroke can be predicted by the disruption of networks connectivity (Siegel et al., 2016). In particular, behavioural impairments have been associated with patterns of decreased interhemispheric communication between set of regions that are part of specific networks (Baldassarre et al., 2016; Siegel et al., 2016). The hypothesis that behavioural manifestations can be related to specific properties of human brain networks is extremely fascinating. In line with this perspective, the last study of the thesis explores the correlation between intrinsic brain activity and neuropsychological indices assessed in a group of chronic stroke patients. Moreover, though the study of brain networks is typically based on fMRI data, in this work we employed a recently proposed method for detecting resting state networks from EEG analysis (Liu, Farahibozorg, Porcaro, Wenderoth, & Mantini, 2017). For the correlation analysis classical neuropsychological batteries were considered, but also a series of indices obtained by administering our computerized multitasking paradigm to stroke patients.

The cornerstone of this work is the hypothesis that the susceptibility to multitasking can represent a sensitive clinical marker of the cognitive outcome in chronic stroke patients. By means of behavioural, electrophysiological and functional measures we carried out an in-depth analysis on the effect of the attentional load on visuo-spatial processing. Overall, our results provide a contribution to the study of the link between brain organization and behaviour, with special regard to clinical and diagnostic implications for stroke patients.

Chapter I

Assessment of pathological spatial processing: Multitasking as a clinical tool

1. Introduction

M.M., a 46-years old man, was brought to the hospital for the sudden appearance of aphasic symptoms and right hemiplegia. A Magnetic Resonance Imaging (MRI) scan showed the presence of intraparenchymal hemorrhage (internal capsule) in the left hemisphere. The man was immediately hospitalized and underwent motor rehabilitation program and logopedic treatment.

M.M., a 43-years old woman, fainted after a severe migraine episode. The Glasgow Coma Scale score was 7 out of 15. Computer Tomography (CT) revealed a right capsule hemorrhage caused by broken aneurysm of the posterior cerebral artery. After the stroke episode, the woman suffered from attentional deficits, unilateral hemianopia and left hemiparesis.

The clinical cases described above are two common examples of cognitive impairments following left rather than right hemisphere damages.

According to the Global Burden of Diseases, Injuries and Risk Factors Study, cerebral stroke has been the second cause of mortality in 2010 (Feigin et al., 2014; Lozano et al., 2012). Stroke is frequently followed by heterogeneous neurological symptoms, depending on the brain regions damaged. After a stroke insult, about 30% of patients were diagnosed with Unilateral Spatial Neglect (USN) (Appelros et al., 2002; Buxbaum et al., 2004; Corbetta & Shulman, 2011). USN is an attentional disorder commonly characterized by a lack of visuo-spatial awareness for contralesional space. Neglect patients show deficits in reporting or orienting to stimuli presented on the side contralateral to brain lesion that cannot be attributed to sensory or motor deficits (Driver & Vuilleumier, 2001; Heilman et al., 1985). Both cortical or sub-cortical lesions, in either hemispheres, can cause signs of neglect (Corbetta & Shulman, 2011; Rengachary, He, Shulman, & Corbetta, 2011), but the severity and persistence of the deficits are stronger for right brain damages in the post-acute phase (Ringman et al., 2004; Stone et al., 1993).

Over the last decades, the study of USN made a crucial contribution for understanding the link between spatial cognition and hemispheric specialization (Corbetta & Shulman, 2011). Several evidence supports the idea that neglect is a complex syndrome characterized by a variety of symptoms and anatomical correlates (Karnath & Rorden, 2012). Studies on right brain damaged patients tried to identify which areas are mainly responsible for the onset of spatial neglect. The heterogeneity of these results is rather surprising: angular gyrus (Molenberghs, Sale, & Mattingley, 2012; Mort et al., 2003), superior temporal cortex (Karnath, Berger, Küker, & Rorden, 2004; Karnath, Ferber, & Himmelbach, 2001), parahippocampus (Mort et al., 2003), temporo-parietal junction (Karnath, Himmelbach, Küker, & Kuker, 2003), inferior frontal lobe (Husain & Kennard, 1996; Rengachary et al., 2011), intra-parietal sulcus (Gillebert et al., 2011; Molenberghs, Gillebert, Peeters, & Vandenberghe, 2008), insula (Karnath et al., 2004; Rengachary et al., 2011), putamen (Karnath, Himmelbach, & Rorden, 2002; Karnath et al., 2004), caudate nucleus (Karnath et al., 2004, 2002; Medina et al., 2009), pulvinar (Karnath et al., 2002), occipital lobe (Bird et al., 2006) and fronto-parietal cortex (Bartolomeo, Thiebaut De Schotten, & Doricchi, 2007). Moreover, a recent work (Lunven & Bartolomeo, 2015) suggests that an interhemispheric disconnection could not only explain the presence of USN, but also predict the chronicity of the deficit. In particular, the fronto-parietal network, connected by the superior longitudinal fasciculus, plays a key role within the right hemisphere. Subsequently, the left hemisphere is not able to compensate for patients' impairments.

The assessment and diagnosis of neurological disorders have certainly important consequences for rehabilitation programs and recovery. For this reason, over last years, neuropsychologists carried out a heated debate in testing for USN. Cancellation tasks are the classical clinical tools used to assess the presence of spatial neglect in stroke patients (Rorden & Karnath, 2010). Despite several versions are available for clinicians (i.e., the Bells Test; the Letter Cancellation Task), patients are commonly required to identify and cancel targets on an A4 paper sheet (Azouvi et al., 2006). Nevertheless, the variability in occurrence of USN is strictly related to the assessment method. A study of Azouvi et al. (Azouvi et al., 2002) on right damaged patients showed that behavioural assessment is more sensitive than any standard paper and pencil tests. Moreover, the authors support the idea that the presence of neglect is strongly task-dependent. Specifically, the inclusion of visual components in testing seems to allow a better detection of spatial negligence. This assumption caused an interesting discussion concerning the ecological validity of classical paper-and-pencil tests (Azouvi et al., 2006), since they are used to predict the performance in daily life. Concerning left hemisphere strokes, Beis et al. (2004) assessed 80 patients and they observed neglect in less than 15% of cases when considering either cancellation or drawing tasks alone. Nevertheless, by taking the presence of neglect in any test as diagnostic criterion, the percentage of patients with some degree of neglect increased to 40%.

The heterogeneity of USN has been repeatedly found (Azouvi et al., 2002; Halligan, Fink, Marshall, & Vallar, 2003) and several evidences demonstrated that non-spatial factors can strongly modulate the presence of spatial deficits (Bonato, 2012; Husain & Rorden, 2003). Severity of symptoms of USN highly depends on several domain general factors, including, among others, sustained attention (Robertson et al., 1997; Robertson, Tegnér, Tham, Lo, & Nimmo-smith, 1995), alertness (Robertson et al., 1998; Thimm, Fink, Küst, Karbe, & Sturm, 2006), increased perceptual demands (Aglioti, Smania, Barbieri, & Corbetta, 1997; Kaplan et al., 1991) and increased attentional load induced by multitasking (Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010, 2012; Bonato, Priftis, Umiltà, & Zorzi, 2013; Sarri, Greenwood, Kalra, & Driver, 2009).

Recently, a multitasking approach has been employed to investigate the presence of USN in chronic stroke patients (Bonato et al., 2010; Bonato, Priftis, et al., 2012). Although spatial impairments seem to disappear in a couple of weeks in most of cases, a consistent number of patients continue to show difficulties in every day life (Paolucci, Antonucci, Grasso, & Pizzamiglio, 2001). Starting from this evidence, a series of experiments have been carried out in order to study how the susceptibility to attentional load can modulate the presence of negligence in post-acute stroke phase. Bonato and colleagues (2010) employed a computer-based task in which patients were asked to monitor the appearance of lateralized stimuli with and without a concurrent secondary task. The main task simulated the Double Simultaneous Stimulation (DSS) test (e.g., Làdavas, 1990), consisting in reporting the position of peripheral targets (e.g., a flick of the index finger) presented on the right, on the left, or on both sides of central fixation (e.g., the nose of the experimenter). In absence of visual deficits, same patients tend to ignore targets presented in the contralesional space. In other cases, the deficit concerns the extinction of contralesional stimulus during a bilateral presentation. More specifically, in the first version of the paradigm of Bonato, the position of appearance of peripheral dot(s) had to be reported in all the conditions (Single Task, Visual

Dual Task, Auditory Dual Task). In the Single Task, patients had to ignore the additional task features. Instead, in the dual task conditions a further request was added. In the Visual Dual Task the patients reported a central letter before reporting target position. In the Auditory Dual Task the patient had to count from an auditory number before reporting target position. Multitasking paradigm (Bonato et al., 2010) is based on a top-down manipulation of attentional load (in either the visual or auditory modality), without any change of the sensory stimulation. The studies of Bonato and collaborators (Bonato et al., 2010, 2013) included cohorts of patients affected by right hemisphere damage that showed a ceiling performance in classical paper-and-pencil neuropsychological assessment. Nevertheless, the comparison between single and dual tasks showed that attentional load context elicited a strong rightward bias, proving that multitasking is a sensitive tool in detecting lateralized disorders. The additional task demands mimic a common daily situation in which people process different type of stimuli concurrently.

Successively, Bonato, Spironelli, et al., (2015) carried out an ERP study in a group of young healthy participants performing dual tasking. As expected, multitasking did not induce lateralized bias in this population, but it was able to modulate an early ERP component (P1). Moreover, regardless of the sensory modality relevant for the secondary task, attentional load also induced a deactivation of the primary visual areas. These results support the well-known theory on the limited resources of human processing systems (Marois & Ivanoff, 2005) and also suggest that multitasking is a convenient tool to investigate the allocation of attentional resources in the space.

The existence of early, sensory bottlenecks in information processing has been also confirmed by neuroimaging studies (Marois & Ivanoff, 2005), and many researchers underlined the relevance of the short-term memory limits within each modality (Linden, 2007; Marois & Ivanoff, 2005). The neural basis of this fascinating phenomenon was repeatedly investigated. Evidence showed that regions of the fronto-parietal network can limit the ability to perform multitasking (Dux, Ivanoff, Asplund, & Marois, 2006; Spence, 2008). These areas include inferior frontal junction, superior medial frontal cortex, and bilateral insula (Tombu et al., 2011). Concerning the anatomy of attentional functions, ventral regions involved in non-spatial disorders (i.e., arousal; reorienting) are characterized by a right hemispheric dominance, whereas dorsal fronto-parietal areas controlling spatial attention show a symmetric organization (Corbetta & Shulman, 2011). In other words, spatial mechanisms are fairly allocated in the brain: each hemisphere controls the contralateral side of the space. In contrast, non-spatial aspects of attention have right hemisphere predominance. Obviously, this is crucial for the study of neglect and spatial cognition processes. Therefore, Corbetta and Shulman (2011) proposed that the hemispheric asymmetry of neglect could be explained by the lateralization of non-spatial functions and by the interaction between ventral and dorsal networks.

The main purpose of this study is to prove that visuo-spatial deficits can be remarkably highlighted by means of multitasking approach. Critical for this work is the assumption that spatial awareness disorders following stroke (e.g., neglect) are strongly modulated by the interaction between spatial and non-spatial attentional processes. Another noteworthy aspect is that these interactive components require sensitive tools to assess the presence of lateralized biases. Since classical paper-and pencil tests did not provide the best measure for this goal, a computerized dual task paradigm has been proposed. Multitasking paradigm of Bonato (2010) was modified to be suitable for testing stroke patients suffering from right and left hemispheric damages. Specifically, two studies are presented. In the first one, patients affected by left-hemisphere damage (LHD) carried out a computerized monitoring task under multitasking conditions in order to clarify whether attention demands can induce spatial disorders in this clinic population. Indeed, as it is known, attentional deficits in patients with LHD are often considered infrequent (Stone et al., 1993). The purpose of this study is to clarify whether the susceptibility to multitasking is a characteristic of unilateral right-hemisphere damage (RHD), as previously showed, or whether attentional load can unveil spatial impairments regardless of the affected hemisphere. Dual task paradigm was administered to an unselected, consecutive sample of 10 LHD patients, analysed both at the group level and at the single patient level. Healthy elderly participants were also enrolled as a control group. However, given that healthy individuals typically perform at ceiling in this task (Bonato et al., 2010, 2015; Lisi, Bonato, & Zorzi, 2015), a second control group of 8 patients with diagnosis of Mild Cognitive Impairment (MCI) was included. MCI syndrome is characterized by general cognitive deficits, taking into account individual age and education, (Petersen, 2004). Previous evidence (Redel et al., 2012) revealed that MCI patients can show a subtle spatial bias (either left or right in individual cases) in conditions with bilateral targets stimulation. Due to the higher performance variability, MCI group represents a severe baseline to assess the reliability of lateralized spatial deficits in LHD patients. Moreover, the inclusion of this group of patients can clarify the relationship between spatial bias and unspecific reduction of cognitive resources.

In the second study, the same multitasking paradigm was administered both to left and right hemisphere damaged patients. Specifically, 14 consecutive chronic LHD patients, 13 consecutive chronic RHD patients and a group of 13 healthy elderly participants were tested. The direct comparison between these two groups of neurologic patients can provide convincing evidence on the allocation of spatial resources under multitasking conditions and on the occurrence rate of lateralized disorders following right rather than left hemisphere damages. Moreover, this experimental design allows to further establish whether the unaffected hemisphere can compensate for spatial disorders during increased attentional load, taking into account the specialization of the right hemisphere for spatial processing. The keystone of this investigation is to understand whether the effects of load on non-spatial attentional resources could, on one hand, increase the imbalance of interhemispheric inhibition, and, on the other hand, cause suppression of ipsilesional hemisphere activity. Interestingly, the effectiveness of multitasking paradigm in uncovering lack of awareness for contralesional hemispace in LHD and RHD patients are discussed.

2. Study 1[*]

2.1. Method

Participants

Ten consecutive stroke patients with LHD took part in the experiment. They were attending motor rehabilitation for right hemiplegia/hemiparesis and/or language therapy for aphasia at the San Camillo Neurorehabilitation Hospital (Venice-Lido, Italy). All patients were in the subacute to chronic phase (minimum time from onset: 52 days, see Tab. 1.1). Two control groups were included in the study. The first one was composed by ten healthy controls, who were on average older than LHD group (65.8 y, SD = 8.52 for Controls vs. 53.2 y, SD = 11.7 for LHD; $t_{(16.44)} = 2.75$, $p = 0.014$; Welch's t-test was used for this and the following comparisons) but did not differ for level of education (9.3 y, SD = 5.2 for Controls vs. 12.4 y, SD = 2.99 for LHD; $t_{(14.38)} = 1.64$, p = 0.12). The second control group included eight outpatients with diagnosis of MCI, who were attending cognitive stimulation protocols at San Camillo Hospital. MCI patients were also on average older than LHD patients (69 y,

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[*] This study has been published as: Blini, E., Romeo, Z., Spironelli, C., Pitteri, M., Meneghello, F., Bonato, M., & Zorzi, M. (2016). Multi-tasking uncovers right spatial neglect and extinction in chronic left-hemisphere stroke patients. *Neuropsychologia*, *92*, 147–157.

SD = 11.61; $t_{(15.2)} = 2.85$, $p = 0.012$) but did not differ from LHD for number of years of education (9.75 y, SD = 4.02; $t_{(12.62)} = 1.55$, $p = 0.145$). All participants gave written informed consent to take part in the study, in accordance to the principles of the Declaration of Helsinki. The inability to understand task instructions, and a history of other neurologic disorders or of substance abuse were considered exclusion criteria from the study. All participants were right-handed according to a standard questionnaire (Oldfield, 1971) and presented normal or corrected-to-normal vision. Detailed information is reported in Tab. 1.1 for personal data. This study was approved by the regional Ethics Committee (Comitato Etico per la Sperimentazione Clinica della Provincia di Venezia e IRCCS San Camillo; protocol n. 2014.09).

Subject/ Group	**Sex/Age/ Education (ys)**	**Lesion site**	**Etiology**	**Handedness**	**Double Simultaneous Stimulation**	**Lesional Volume (cc)**	**Time from stroke (days)**
1/LHD	M/46/11	C	H	R	-	27	115
2/LHD	F/49/13	Ta	H	R	-	15	318
3/LHD	M/60/13	Ta;C	H	R	-	5	2632
4/LHD	F/53/13	T	H	R	-	79	299
5/LHD	F/52/13	MCA	I	R	-	246	145
6/LHD	M/47/13	BG	H	R	-	79	52
7/LHD	M/64/17	F;P;T	I	R	-	165	370
8/LHD	M/41/13	T	I	R	-	46	313
9/LHD	F/41/13	T;P	H	R	+ (Contralesional omissions)	136	260
10/LHD	M/79/5	C	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. 1.1. Demographical and neurological data. LHD and MCI groups: M/F: male, female; Lesion site: F= frontal; P=parietal; T=temporal; BG=basal ganglia; C=capsula; Ta=thalamus; MCA= middle cerebral artery. R: Right-handed. LHD: I/H: ischemic, hemorrhagic; +/-: presence, absence of contralesional omissions.

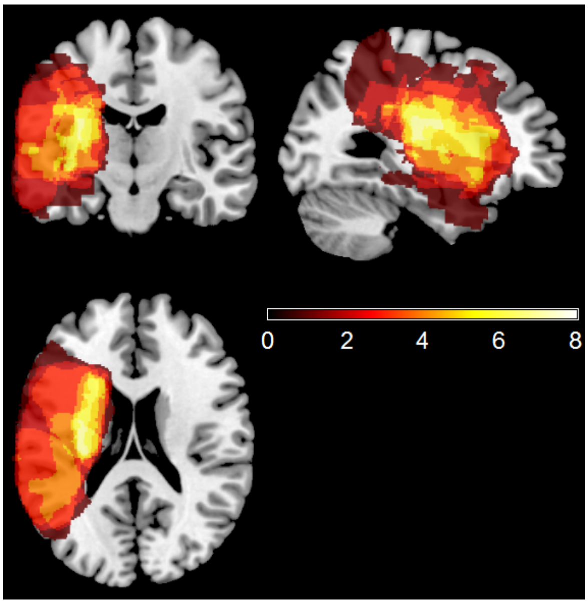


Fig. 1.1. Lesion overlays. The lesion mapping for LHD, normalized to a template of aged healthy individuals according to the procedure described in Rorden et al. (2012), is shown as an overlay on a standard template using MRIcron (Rorden & Brett, 2000). The different colors code for the number of overlapping lesions from dark red (minimal/no overlap) to white (maximal overlap).

Brain lesions for all LHD patients were manually reconstructed using MRIcron (Rorden & Brett, 2000). Individual scans (MRI or CT) were reoriented using SPM (Penny, Friston, Ashblumer, Kiebel, & Nichols, 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. 1.1. The maximal overlap (seven patients) 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).

Neuropsychological Assessment

All patients underwent an in-depth neuropsychological evaluation (see Tab. 1.2). The conventional part of the Behavioural Inattention Test (BIT, Wilson, Cockburn, & Halligan, 1987) was administered to all LHD patients in order to evaluate visuo-spatial processes. The BIT is composed by six subtests: lines, letters, and stars cancellation, line bisection, figure copy and spontaneous drawing. Each subtest was scored separately, and contributed to a global index. According to the BIT overall cut-off, no signs of negligence emerged for LHD group. Moreover, any patient was below the cut-off in all the subtests. No patient showed any hint of lateralized omissions across any subtest; scores in Table 1.2 are displayed separately for left- and right-sided targets. The average performance in the cancellation tasks was close to ceiling (Fig. 1.2).

The presence and degree of language deficits were assessed through the Aachener Aphasie Test (AAT, Luzzatti, Willmes, & De Bleser, 1996). 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).

The DSS paradigm was administered to quantify the presence of contralesional omissions/extinction. The experimenter 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 left or right index finger only, or both fingers at the same time. The participant had to report the position 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).

In order to assess a range of visuo-spatial abilities (planning, organizational, strategic abilities, visuo-perceptual and visuo-constructional functions), the Rey-Osterrieth complex figure test (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2014) was administered to all LHD patients. Both online copy and recall were assessed, and scored separately.

The Mini Mental State Examination (MMSE; (Magni, Binetti, Bianchetti, Rozzini, & Trabucchi, 1996) and Raven's progressive matrices (Carlesimo et al., 1996) were also administered to investigate overall cognitive functioning. The MMSE explores patients' spatial and temporal orientation, but also visuo-constructional abilities, working memory and long term memory; each subtest is scored separately, but a cumulative index is also computed (Magni et al., 1996).

Raven's test consists of 36 coloured matrices and it was administered to assess abstract, relatively culture-free, non-verbal reasoning abilities. Patients were asked to choose, among six options, the best element to complete an above-depicted target set. Patients had no time constraints to complete the sequences. Items were ordered in ascending difficulty order; the final score represents the overall number of correct responses.

The Rey-Osterrieth complex figure test, MMSE and Raven's test were also part of the neuropsychological evaluation of the control group of MCI patients. The diagnosis of MCI was made accordingly to criteria of Petersen (2004). All patients complained about cognitive impairments in everyday activities, and at least one relative of each patient supported this complaint. Global cognitive functioning, as assessed by means of MMSE and Raven’s matrices, was spared (see Tab. 2), whereas they showed a deficitary performance in at least one test within a standardized screening battery assessing a broader range of cognitive functions (i.e., memory, language, attention, visuo-constructional abilities).

Subject/ Group	**MMSE** Cut-off: 24	**RAVEN** Cut-off: 18.96	**ReyFig C/R** Cut-off: 28.87/9.46	**BIT** Cut-off: <130	**BIT-Barr L/R** (max 18/18)	**BIT-Star L/R** (max 27/27)	**BIT-Lett L/R** (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. 1.2. Neuropsychological assessment. MMSE (Mini Mental State Examination, (Magni et al., 1996), Raven’s progressive matrices (Carlesimo et al., 1996), and ReyFig (Rey-Osterrieth complex figure): C=Copy and R=Recall,(Caffarra et al., 2014). Across all tasks, age and education corrected scores are reported. *: performance below cut-off. BIT (Behavioural Inattention Test, (Wilson et al., 1987): global scores and raw scores at cancellation subtests (Barr= Barrage; Star= Stars cancellation; Lett=Letters cancellation) are reported separately for left (L) and right (R) hemispace. 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.

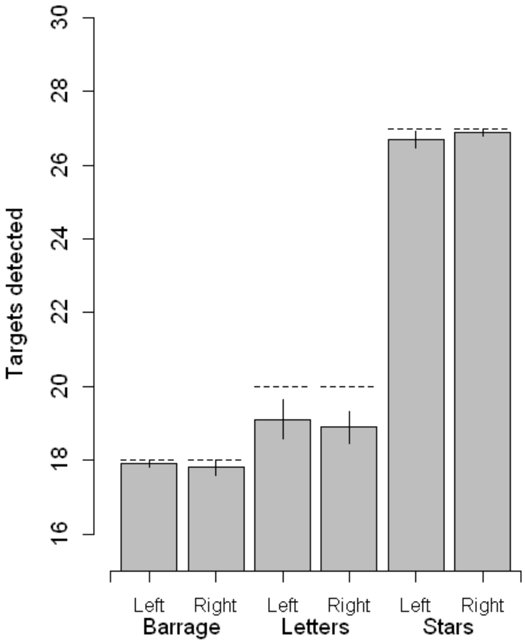


Fig. 1.2. Cancellation tasks. The mean number of target items correctly detected is shown for each BIT cancellation subtest as a function of their side on the testing sheet. Dashed lines represent the total number of targets for the specific subtest. Error bars represent SEM.

Apparatus, stimuli, and procedures

Patients were individually tested in a quiet room, sitting comfortably at a distance of about 60 cm from a 19-inch computer monitor. There were three experimental conditions: the single-task condition and two dual task conditions (visual vs. auditory) (see Fig. 1.3). Each trial started with a black screen (1000 ms), followed by a white fixation cross (about 1cm wide) that was presented in the centre 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 centre.

The lateralized visuo-spatial target was a white disk (diameter: 8mm) presented against a black background for 100ms. The target could appear unilaterally, on the right or the left side of the monitor (lateral distance from fixation: 170 mm), 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 possible spatial bias in responses. The three target locations (right, left, 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 100 ms time window elapsed, a noisy screenshot was showed 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 sound, respectively. It is important to note that the sensory stimulation was identical across all conditions. The manipulation was therefore purely top-down, based on the presence/absence of secondary 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. The experimenter coded patients’ responses using a computer keyboard. Participants were allowed to rest after each trial, if necessary. Eye movements were monitored by the experimenter and each trial started only when fixation was maintained. Trials affected by eye movements were not included in the data analyses.

The experiment consisted of 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 deficits. 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 block comprised 36 trials (9 trials for each type of lateral target). All possible combinations of shapes (3) and sounds (3) were presented within each block, balanced in frequency and with randomized order. Overall, the experiment consisted of 216 trials (3 load conditions x 4 types of target x 18 trials per cell).

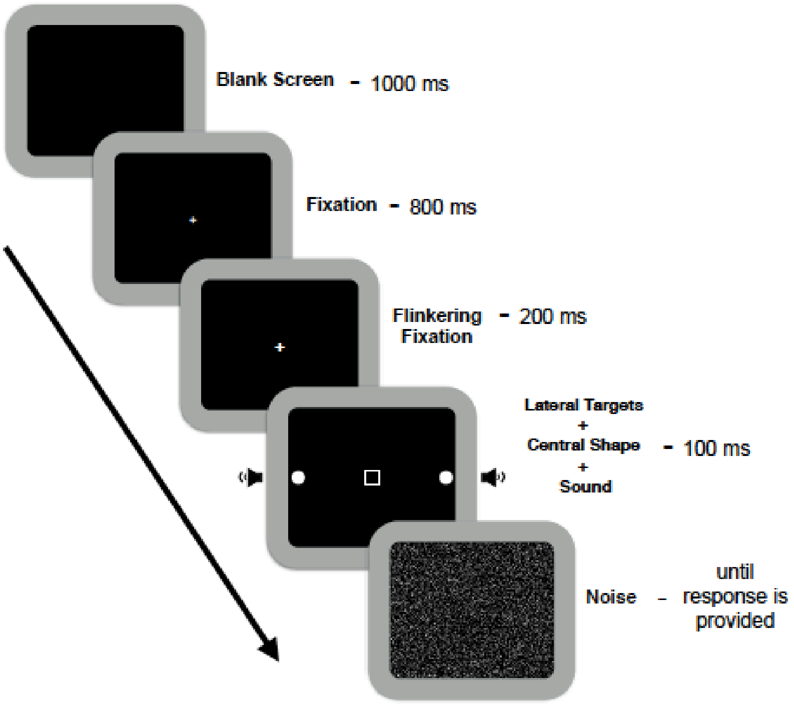


Fig. 1.3. Schematic representation of events. Physical properties of the events are identical across the three conditions, the only difference is the presence of a concurrent task in dual task conditions.

Statistical analyses

Data analyses were computed with the open-source software R (Team R Core, 2014). Practice trials and experimental trials invalidated by eye movements (<0.1%) were not included. The data were analysed at the single-trial level with *mixed-effects multiple regression models* (Baayen, Davidson, & Bates, 2008) using the lme4 package for R. Mixed models represent an interesting approach because 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). Clinical data are typically more noise that the data of healthy participants for this reason mixed models are a particularly convenient method of analysis (see (Zorzi et al., 2012), for a previous application of mixed models to neglect patients' data; also see (Goedert, Boston, & Barrett, 2013; Zorzi et al., 2012). All mixed-effects 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. The approach used for these analyses was stepwise: main effects were added before interactions, and the same log-likelihood tests were used to assess whether the improvements in the model fit were statistically significant.

2.2. Results

The Results section is organized as follows. First, analyses of spatial monitoring accuracy are reported to assess whether performance is modulated by target position and by multitasking. Second, an in-depth analysis of spatial bias was performed for LHD patients both at the group, and at the single-case levels. Finally, additional analyses of spatial monitoring accuracy that assessed potential effects of fatigue, or deficit in sustained attention are presented.

Effects of Attentional load on spatial monitoring

As a first analysis, an ANOVA, with Target Type (four levels: Left, Right, Bilateral, Catch) and Load condition (three levels: Single Task, Visual Dual Task, Auditory Dual Task) as within-subjects factors and Group (three levels: LHD, Controls, MCI) as between-subjects factor, was computed. The accuracy was arcsine transformed. Results revealed a significant three-way interaction Group by Type by Load ($F_{(12,150)} = 2.2$, $p = 0.026$, Greenhouse-Geisser corrected, $\eta_p^2 = 0.15$). The results, displayed in Figure 1.4, suggest that the multitasking conditions selectively affected performance for right-sided and bilateral targets, but only for LHD patients. Successively, mixed-effects models were fitted to the (non-transformed, single-trial) accuracy data of each group to assess the interactive effects of Target Type and Load. The random structure included Participant as random intercept and the random slopes for Load and Target type. Therefore, individual variability was accounted for both in terms of overall accuracy (intercept) and across the different experimental conditions (random slopes).

LHD. 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 ($\chi^2 = 26.38$, $p < 0.001$). Interestingly, for bilateral trials detection accuracy under load dropped from 80.4% to 65% for auditory load ($z = -2.67$, $p = 0.007$) and to 58.9% for visual load ($z = -4$, $p < 0.001$), with a significant difference also emerging between visual and auditory (z = -2.16, $p = 0.03$). Moreover, for contralesional (i.e., right only) targets accuracy dropped from 92.2% to 69.1% for auditory load (z = -3.3, $p < 0.001$) and to 62% for visual load (z = -4.6, $p < 0.001$), with a significant difference emerging also between the two dual task conditions (z = -2.24, $p = 0.025$). All the contrasts above report the Wald z value with uncorrected p value. Any load modulation emerged for ipsilesional targets and catch trials. In both conditions, performance remained high (> 96.1%). The parameters of the random and fixed effects of the final model are reported in Tab. 1.3.

Healthy Controls. Neither of the fixed main effects improved the model fit (Load: $\chi^2 = 5.32$, $p = 0.07$; Target type: $\chi^2 = 2.9$, $p = 0.4$). The fit did not improve when adding the two-way interaction ($\chi^2 = 6.63$, $p = 0.36$). However, accuracy remained high across all conditions.

MCI. Neither of the fixed main effects improved the model fit (Load: $\chi^2 = 2.39$, $p = 0.3$; Target type: $\chi^2 = 2.65$, $p = 0.45$). Moreover, the fit did not improve when adding the two-way interaction ($\chi^2 = 4.04$, $p = 0.67$) showing that accuracy remained high across load 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	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. 1.3. Details of the final mixed-effects model for LHD patients. Factors were dummy coded with left targets in the single task as reference level. The parameters of the random effects are reported in the top panel. The parameters of the fixed effects are reported in the bottom panel. Note that the b coefficient (Estimate) represents the adjustment with respect to the reference level. SD = standard deviation, SE = standard error.

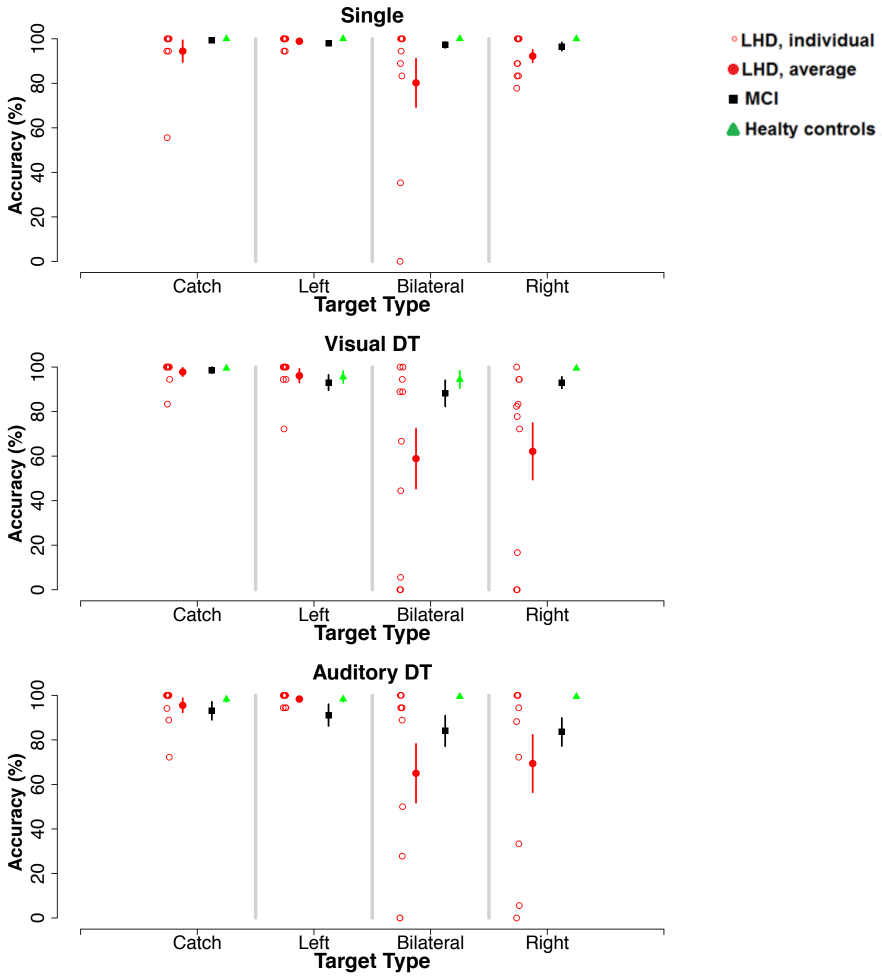


Fig. 1.4. Spatial monitoring task: global accuracy. Accuracy in the spatial monitoring task is depicted for each Load condition (single task, visual dual task, auditory dual task) as a function of Target type (left, right, bilateral, catch) and Group (LHD: filled red circles; MCI: black squares; Healthy Controls: green circles). Error bars represent SEM. Individual performance of LHD patients is shown using red empty circles.

To summarize, multitasking induced a selective impairment in reporting bilateral and contralesional targets in LHD group only, whereas the performance of healthy controls and MCI patients was unaffected.

Asymmetry Indices

Asymmetry Indices (AI) were computed for unilateral, bilateral and catch trials to explore the spatial distribution of missed targets. The AIs for bilateral and catch trials were separately computed by subtracting, for each individual, the proportion of "left" responses from the proportion of "right" responses. A negative AI reveals that "left" responses prevailed among errors, whereas positive AI indexes 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. All AI values describe the asymmetry in terms of proportion of errors. More specifically, a value of -1 indicates that all (100%) of the right targets, but none (0%) 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). As first step, it has been assessed whether each AIs significantly differed from 0 (thereby indexing spatial bias) by means of a one-sample t-test (across all Load conditions). In this case, the modulatory effect of attentional Load was assessed. Comparisons between groups could not be performed because of striking differences in variance and violation of normality. All results are plotted in Fig. 1.5.

Unilateral targets. AIs did not significantly differ from 0 both in the MCI group ($t_{(7)}$= -0.84, p = 0.43) and in the Healthy Controls group ($t_{(9)}$ = 0.61, p = 0.56). In contrast, AIs significantly differed from 0 in LHD patients ($t_{(9)}$ = -2.65, p = 0.026). One-way repeated measures ANOVA revealed an effect of Load ($F_{(2,18)}$= 5.06, p = 0.018, η_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). No differences emerged between the two dual tasks ($t_{(9)}$ = 0.24, p = 0.82).

Bilateral targets. AIs were not significantly different from 0 both in the MCI group ($t_{(7)}$= 1.5, p = 0.178) and in the Healthy Controls group ($t_{(9)}$ = -1, p = 0.34). However, AIs 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, η_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 dual tasks did not differ ($t_{(9)}$ = 2.05, p = 0.07).

Catch trials. AIs of catch trials did not significantly differ from 0 in all groups: LHD ($t_{(9)}$ = -0.8, p = 0.47); MCI ($t_{(7)}$ = 1.87, p = 0.1); Controls ($t_{(9)}$ = 0.04, p = 0.97). This result suggested that LHD patients were able to correctly report the absence of lateral targets and it allows us to exclude that the asymmetry of responses in unilateral and bilateral trials was due to a response bias (i.e., an overall tendency to respond “left”).

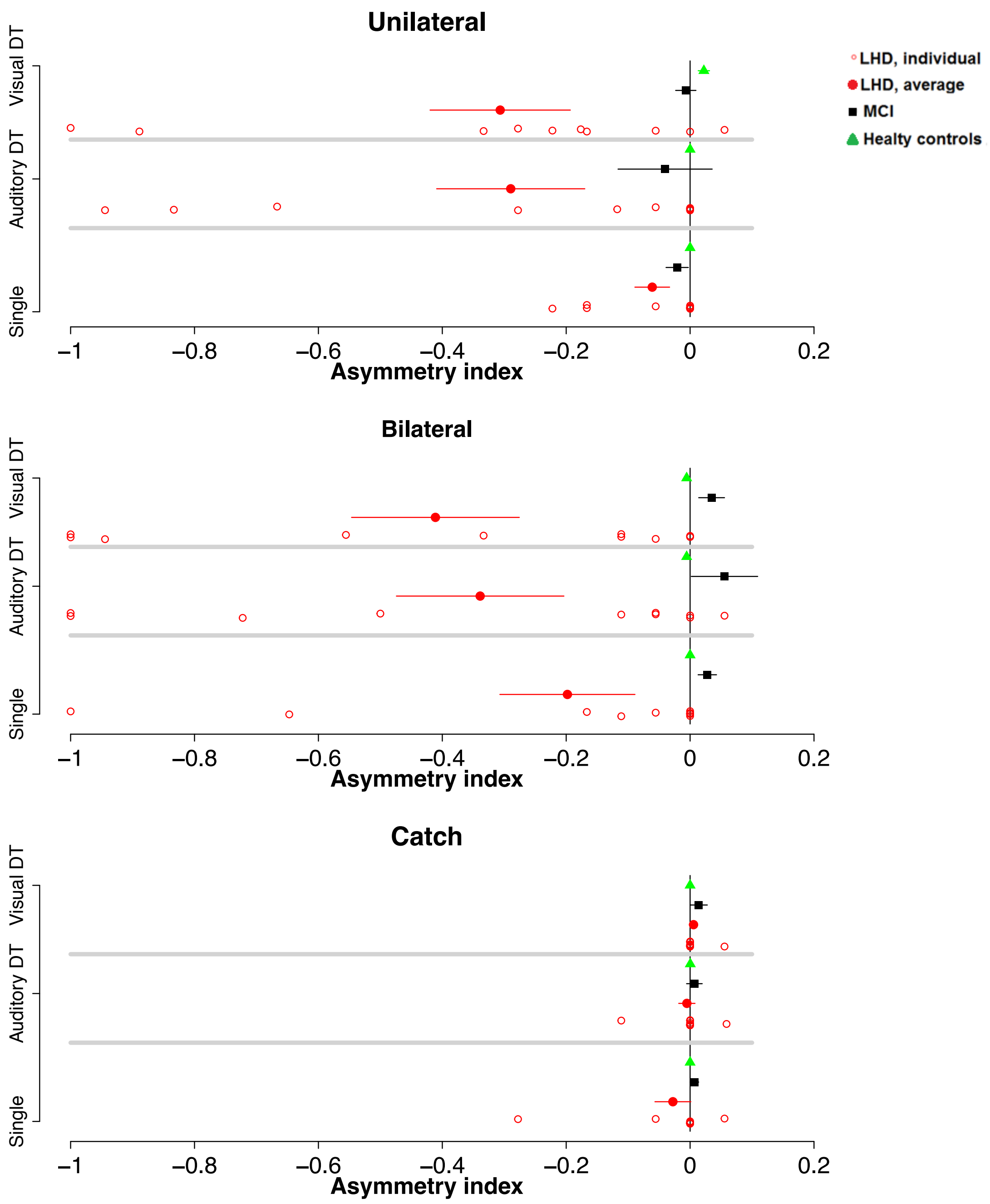


Fig. 1.5. Lateralized biases. The Asymmetry Index is depicted for each type of target (unilateral, bilateral, catch) as a function of Load condition (single task, visual dual task, auditory dual task) and Group (LHD: red circles; MCI: black squares; Healthy Controls: green circles). Note that the asymmetry is expressed in terms of proportion of errors: negative values index a leftward bias (e.g., a value of -1 means that all of the right, but none of the left targets were neglected), whereas a value of 0 indicates even distribution of omissions (or the absence of omissions). Individual values for LHD patients are shown as red empty circles. Error bars represent SEM.

Individual analysis

The ceiling performance of healthy controls group in the spatial monitoring task suggests that the multitasking paradigm employed in this experiment is well suited to uncover spatial asymmetries induced by unilateral brain damage. However, when controls' data are used to assess the presence of deficit in individual patients, ceiling effects can produce unacceptably high false positive rates (Laws, 2005). On the other hand, the group of MCI patients showed greater variability in performance than the healthy controls. Redel et al. (2012) observed subtle spatial bias in individual MCI patients, but though at the group level the direction of bias is inconsistent. For their characteristics, the MCI group represents a statistically more appropriate baseline, as well as more stringent than the one provided by healthy controls (against which almost all LHD patients would have resulted as having a pathological performance). To determine the occurrence rate of right neglect in the unilateral trials or extinction in the bilateral trials within the LHD group, individual patient AI was assessed against the MCI group as control sample (Crawford & Howell, 1998). This method uses the control sample statistics (rather than the estimated population parameters), and a t (instead of z) wider-tailed distribution to estimate probabilities. Note that this method is robust also in the case of severe violations of normality (Crawford, Garthwaite, Azzalini, Howell, & Laws, 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 ($t_{(7)} \leq -6.62$, $p < 0.001$). Moreover, the visual dual task caused spatial biases in four patients with symmetric performance in the single task [patients 2, 5, 6, and 8 ($t_{(7)} \leq -3.25$, $p \leq 0.014$)]. Therefore, while only three patients out of ten showed contralesional omissions at simple spatial monitoring, multitasking highlighted contralesional deficits in additional four cases in the visual dual task condition.

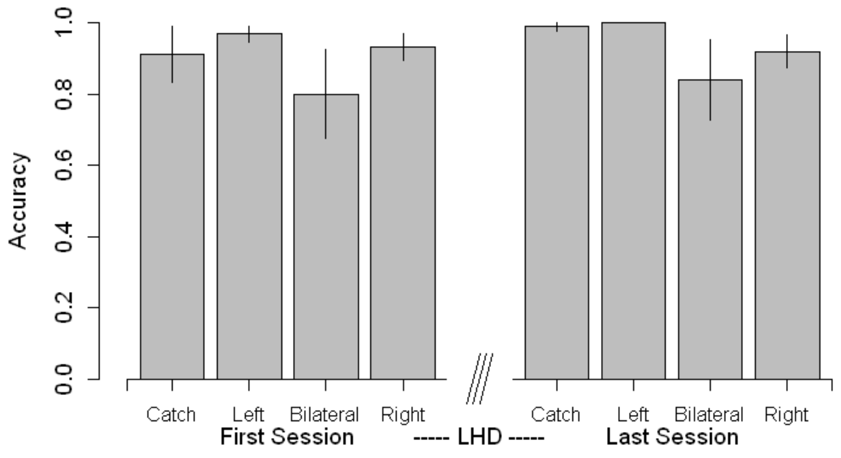
Bilateral targets. Patients 4, 5, 7 and 9 showed a significant asymmetry in the single task ($t_{(7)} \leq -3.12$, $p \leq 0.017$). The same patients consistently showed a pattern of spatial bias in both the visual ($t_{(7)} \leq -9.44$, $p(s) < 0.001$) and the auditory ($t_{(7)} \leq -3.45$, $p(s) \leq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

Correlations between AI and lesional volume

An explorative correlational analysis between AIs and lesion volume was carried out. However, the results must be taken with caution due to the small sample size. The correlation between AIs for unilateral trials (collapsed across Tasks) and lesional volume was not significant (r = -0.4, $t_{(8)} = 1.1$, $p = 0.24$). On the other hand, when AIs for bilateral trials were correlated a significant negative association emerged (r = -0.72, $t_{(8)}= 2.96$, $p = 0.018$). This was due to significant correlations for AI in Visual (r = -0.75, $t_{(8)}= 3.22$, $p = 0.012$) and Auditory (r = -0.79, $t_{(8)}= 3.7$, $p = 0.006$) dual task conditions, as opposed to a lack of correlation in the Single task (r = -0.496, $t_{(8)}= 1.61$, $p = 0.14$). All correlations were two-tailed, uncorrected, and overall show that more severe damage (wider lesion) within the left hemisphere results in stronger extinction under multitasking.

Fatigue and sustained attention

The fatigue effect or deficits in sustained attention were assessed in order to verify their influence on the impaired spatial monitoring performance of LHD patients. It is noteworthy that the single task was performed both at the beginning (i.e., first block) and at the end (i.e., last block) of the experiment. Therefore, a significant drop in performance between the two blocks would suggest that the effect of load 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. Healthy Controls were not included in the analysis because their performance in the single task was errorless (100% accuracy in both blocks). Furthermore, Block did not improve the model fit when it was entered as fixed main effect ($\chi^2 = 2.82$, $p = 0.09$) or in the two-way interaction with Group ($\chi^2 = 1.52$, $p = 0.22$). This reveals that fatigue had no effect (see Fig. 1.6). Accuracy (collapsed across Target type) lightly dropped in MCI patients (from 99.3% to 96.2%), but it lightly improved (89.6% to 93.3%) in LHD patients.



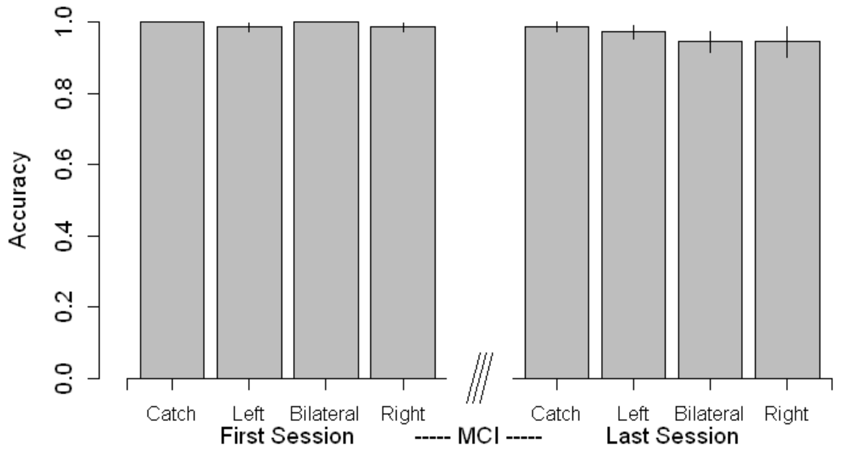


Fig. 1.6. Fatigue. Performance of LHD (top panel) and MCI (bottom panel) patients in the first block (four bars on the left) and in the last (i.e., sixth) block of the spatial monitoring task (four bars on the right). In both blocks patients only had to report target side. Error bars represent SEM.

Secondary task

The final analysis concerned the performance of the secondary tasks. This was to clarify whether accuracy in the secondary task differed as a function of Type of load (two levels: visual vs. auditory) or Group (two levels: LHD vs. MCI). Note, that the Healthy Controls group was excluded because of ceiling performance (97.5% accuracy in both secondary tasks). 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 ($\chi^2 = 4.18$, $p = 0.04$ vs. $\chi^2 = 0.52$, $p = 0.47$).

The Group by Type of load interaction did not improve the fit ($\chi^2 = 0.83$, $p = 0.36$). The visual (secondary) task was overall more difficult ($\beta = -1.12$, 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 significant differences.

2.3. Discussion

The present study investigated the effects of attentional load (i.e., multitasking) on a spatial monitoring task in a sample of chronic left hemisphere damaged patients. LHD is a clinical population in which lateralized spatial deficits are considered to be rare. Regardless of the sensory modality of attentional load (visual or auditory), simultaneous tasks demands uncover a clear pattern of contralesional stimuli omissions (right neglect and/or right extinction) despite the spatial deficits did not emerge from neuropsychological assessment. In contrast, any spatial bias was found in two groups of control participants. In detail, healthy elderly participants performed at ceiling in all conditions, whereas the patients with Mild Cognitive Impairment had a less accurate performance. However, MCI showed even (unbiased) spatial distribution of errors.

As a whole, the present results strongly confirm that the computerized multitasking paradigm is well-suited to detect asymmetries in spatial monitoring following unilateral brain damage, supporting what previously observed in chronic patients (Bonato et al., 2010). However, several changes have been introduced to the original paradigm of Bonato et al. (2010) to further improve its design and to make it more suitable for testing LHD patients, which are often characterized by linguistic impairments. First, in the version of Bonato and colleagues (2010) a letter was visually presented at fixation (to be reported in the visual dual task) and a number-word was auditory presented (for the auditory dual task), whereas in the present study all alphanumerical stimuli were deleted. Moreover, the previous version of the auditory dual task consisted in counting forward twice by two from the presented digit, whereas in the present version the only request to report the auditory stimulus minimized the demands on working memory. Second, patients were asked to always report the lateralized target first (unlike in Bonato et al., 2010), prioritizing the spatial monitoring task over the concurrent task. This allows us to exclude that spatial omissions were caused by the delayed response or by interference from the secondary task. Third, catch trials were introduced in the experimental design to exclude the presence of response biases. Fourth, the single task was administered in the first and last block of the experiment, thereby allowing us to exclude that lateralized deficits in spatial monitoring are the results of fatigue or drop in sustained attention. Although these changes were introduced, any direct comparison with previous data on RHD patients is problematic.

All LHD patients included in the study showed normal performance in a classic paper-and-pencil tests for neglect, nevertheless few of them (4 patients out of 10) exhibited pattern of extinction at baseline ("left" responses to bilateral targets in the single task), thereby revealing the high sensitivity of a test employing briefly presented stimuli which compete for awareness (Bonato & Deouell, 2013). The introduction of a secondary visual task revealed the presence of extinctions in one more patient (for a total of 5/10 cases with extinction). As expected, the multitasking paradigm revealed the absence of extinction in some LHD patients. While this absence might be veridical, another possible explanation is that in some patients non-spatial attentional resources successfully compensated spatial deficits (Bonato, 2015).

From a theoretical point of view, 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). On the other hand, the emergence of a pattern of right neglect under load context is particularly surprising. It is interesting to note that unilateral right targets are not subject to the bottom-up competition that characterizes bilateral stimuli. Our results showed a significant asymmetry in the detection of unilateral targets during the single task only in three patients, whereas under visual load the asymmetric pattern was found in seven patients out of 10. These findings allow us to conclude that subtracting non-spatial attentional resources to perform a concurrent task hinders visuo-spatial processing revealing attentional imbalances caused by the unilateral brain damage. The effect of multitasking is best understood as an interaction between spatial and non-spatial mechanisms of attention. In particular, the present data suggest that simultaneous task demands recruit non-spatial, supramodal attentional resources which are otherwise used to perform simple spatial monitoring.

Bonato, Spironelli et al. (2015) carried out an ERP study on healthy participants using a load manipulation very similar to the one employed in the present experiment. Multitasking modulated the amplitude of the first positive component (P1) and shifted its neural generators, suppressing the cortical activity in the early visual areas during both visual and auditory dual tasks. At later phase of stimulus processing, N2 contralateral components were strongly influenced by the intra-modal dual task and were related to higher activity of the right supramarginal gyrus, suggesting a great sensitivity of the right hemisphere to load manipulations. A recent work (Lisi et al., 2015) showed that the top-down allocation of supramodal attentional resources in a similar multitasking paradigm are able to modulate pupil dilation. It has been demonstrated that the locus coeruleus–noradrenergic neuromodulatory system has a central role in the functional integration of the attentional networks (Corbetta, Patel, & Shulman, 2008). Interestingly, the cognitively-related pupil dilation has been associated to this neurotransmitter system (Aston-Jones & Cohen, 2005).

Classically, theories concerning the brain asymmetries in spatial processing (Heilman & Van Den Abell, 1979) or in interhemispheric inhibition (i.e., stronger inhibition by the right hemisphere; Kinsbourne, 1987) successfully explained the much higher prevalence of spatial neglect after right hemisphere compared to left hemisphere lesions. However, the pathological leftward bias observed in LHD patients suggests that the unaffected right hemisphere is unable to compensate for the left hemisphere damage, at least under multitasking. Convincingly, the present findings are supported by the interhemispheric inhibition model. The hypothesis is that increasing attentional load boosts non-spatial, right-lateralized mechanisms, thereby increasing the imbalance in interhemispheric inhibition and causing stronger suppression of left hemisphere activity. However, the pathological leftward bias observed here does not reflect an exacerbation of the subtle leftward bias described in healthy participants (i.e., pseudoneglect; (Jewell & McCourt, 2000). Indeed, increased cognitive load can change the leftward bias in healthy participants in to a rightward bias (Dodds et al., 2008; Peers, Cusack, & Duncan, 2006). Therefore, one interesting explanation of these results is that neural activity in the bilateral dorsal fronto-parietal network, which has symmetrical distribution in the healthy brain (Corbetta & Shulman, 2011), becomes heavily asymmetrical under the combined influence of left hemisphere damage and increased ipsilesional hemisphere inhibition induced by multitasking.

The interhemispheric competition theory is also supported by recent neuroimaging study: fMRI-guided TMS over the left intraparietal sulcus elicits a leftward spatial bias in healthy participants (Szczepanski & Kastner, 2013). The present results can be also explained considering the 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 mechanisms are determinants in several cognitive processes, including perception and spatial awareness, but typically their contribution in healthy participants is related to the modulation of response times. In presence of neurological deficits, the structural limits can be emphasized. Consequently, more striking behavioural effects can be manifested, such as the inability to perceive a lateralized target. This particular case is often observed in patients with USN, where the co-occurrence of core lateralized impairments and of non-spatial deficits (Husain & Rorden, 2003) determine the complex clinical manifestations of USN.

Generally, LHD patients do not show attentional disorders, although previous evidence suggests the presence of this type of deficit is not rare (Peers et al., 2005; Timpert, Weiss, Vossel, Dovern, & Fink, 2015), especially in the subacute phase (Ringman, Saver, Wooison, Clarke, & Adams, 2004). This difference could be a consequence of exclusion of patients with severe linguistic disorders from the samples since they could fail to comply with task instructions. At the same time, this allows to observe only selected and overall less impaired patients (Bonato, Sella, Berteletti, & Umiltà, 2012). In a study on 80 unselected LHD patients, Beis and colleagues (2004) found neglect in less than 15% of patients by considering either cancellation or drawing tasks alone. Interestingly, if 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 the presence of lateralized attentional disorders might be revealed in a substantial proportion of LHD patients using a comprehensive screening tests and a less strict diagnostic criterion.

This study has amply demonstrated that multitasking can reveal marked lateralized spatial deficits in a consistent proportion of LHD patients who do not show attentional deficits at paper-and-pencil battery, which is the gold standard for neglect diagnosis. Given the ubiquity of multitasking in everyday activities, the multitasking tool can certainly provide clinically relevant information (see Bonato et al., 2012, for a practical example). Finally, as a next step, a large-scale study should directly compare, using the same tasks, the rate of occurrence of lateralized disorders in RHD and LHD patients. A larger sample will also help in understanding the anatomical correlates of the spatial deficits.

3. Study 2

3.1. Method

Participants

Two groups of consecutive patients with unilateral brain damage were included in the study. All patients underwent a personalized neurorehabilitation program at the San Camillo

Hospital (Venice-Lido, Italy). All patients were in the subacute to chronic stage (minimum time from onset: 52 days, see Tab.1.4). The first experimental group included 14 LHD patients (mean age= 53.57 years, SD = 11.61; mean education= 12.35 years, SD = 3.38), whereas the second one included 13 RHD patients (mean age= 62.07 years, SD = 10.14; mean education= 10.92 years, SD = 3.68). Thirteen healthy participants (mean age= 65.84 years, SD = 7.34; mean education= 9.69 years, SD = 5.64) took part in the study as a control group. RHD patients and controls did not differ for age and for level education ($t_{(21.87)}$= -1.08, $p >$ 0.05 and $t_{(20.64)}$= 0.65, $p >$ 0.05, respectively). The LHD group was on average younger than both the control group ($t_{(22.16)}$= -3.30, p = < 0.05) and the RHD group ($t_{(24.91)}$= -2.03, p = 0.05). However, the three groups did not differ for the level of education (LHD vs. RHD: $t_{(24.37)}$= 1.05, $p >$ 0.05; LHD vs. controls: $t_{(19.36)}$= 1.47, $p >$ 0.05). Welch's t-test was used for all comparisons. All participants gave their written informed consent to take part in the study, in accordance to the principles of the Declaration of Helsinki. Exclusion criteria were the presence of neglect assessed by neuropsychological battery (global score at Behavioural Inattention Test), 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. 1.4 for personal data and in Tab. 1.5 for neuropsychological assessment.

Subject/ Group	**Sex/Age/ Education (ys)**	**Lesion site**	**Etiology**	**Handedness**	**Double Simultaneous Stimulation**	**Lesional Volume (cc)**	**Time from stroke (days)**
1/LHD	M/46/8	C	H	R	-	32	115
2/LHD	F/49/13	Ta	H	R	-	8	318
3/LHD	M/60/13	Ta;C	H	R	-	7	2632
4/LHD	F/53/13	T	H	R	-	66	299
5/LHD	F/52/13	MCA	I	R	-	374	145
6/LHD	M/47/13	BG	H	R	-	55	52
7/LHD	M/64/17	F;P;T	I	R	-	290	370
8/LHD	M/41/13	T	I	R	-	32	313
9/LHD	F/41/13	T;P	H	R	+ (Contralesional omissions)	n.a.	260
10/LHD	M/79/5	C	H	R	-	2	57
11/LHD	M/42/18	T;I	I	R	-	52	738

12/LHD	M/69/8	Ta;C	I	R	-	7	76
13/LHD	M/45/13	T;P	H	R	-	73	312
14/LHD	M/62/13	T	I	R	-	98	148
1/RHD	M/65/17	Pu	H	R	-	31	399
2/RHD	M/47/8	F;P	I	R	-	n.a.	1266
3/RHD	F/68/5	C	H	R	-	11	97
4/RHD	M/56/13	T;C	I	R	-	n.a.	63
5/RHD	M/72/13	C	H	R	-	7	64
6/RHD	M/59/13	F;T	H	R	-	77	2497
7/RHD	M/62/13	C	I	R	-	n.a.	79
8/RHD	M/51/13	T;C	I	R	-	n.a.	70
9/RHD	M/49/8	BG	H	R	-	35	100
10/RHD	M/79/5	O	I	R	-	2	344
11/RHD	M/56/8	F;P	I	R	-	n.a.	106
12/RHD	M/68/13	P	I	R	-	130	1286
13/RHD	M/75/13	P	I	R	-	62	103

Tab. 1.4. Demographical and neurological data. LHD and RHD groups: M/F: male, female; Lesion site: F= frontal; O=occipital; P =parietal; T=temporal; BG=basal ganglia; C=capsula; I=insula; MCA= middle cerebral artery; Pu=putamen; Ta=thalamus. I/H: ischemic, hemorrhagic; R: Right-handed. +/-: presence, absence of contralesional omissions. n.a.: data not available.

Brain lesions for 13 LHD and 8 RHD patients were automatically segmented using the Lesion Identification with Neighbourhood Data Analysis software (LINDA) (Pustina et al., 2016). LINDA software adopts hierarchical improvements of lesion estimation from low to high resolution. This method takes in to account the signal at single voxel and neighbourhood-voxels levels. Individual lesion masks were visually checked and eventually manually modified using ITK-snap software. Individual scans (MRI or CT) were reoriented and then normalized to an age-appropriate template brain using FSL. Lesion overlays are depicted in Fig.1.8. For LHD group, the maximal overlap (10 patients) occurred in the white matter adjacent to the putamen (MNI: X= -27, Y= -12, Z= 16). For RHD group, the maximal overlap (8 patients) was found in the white matter adjacent to putamen (MNI: X= 26, Y= -12, Z= 11). Scans for 1 LHD and 5 RHD patients were not available because of incompatibility with MRI examination.

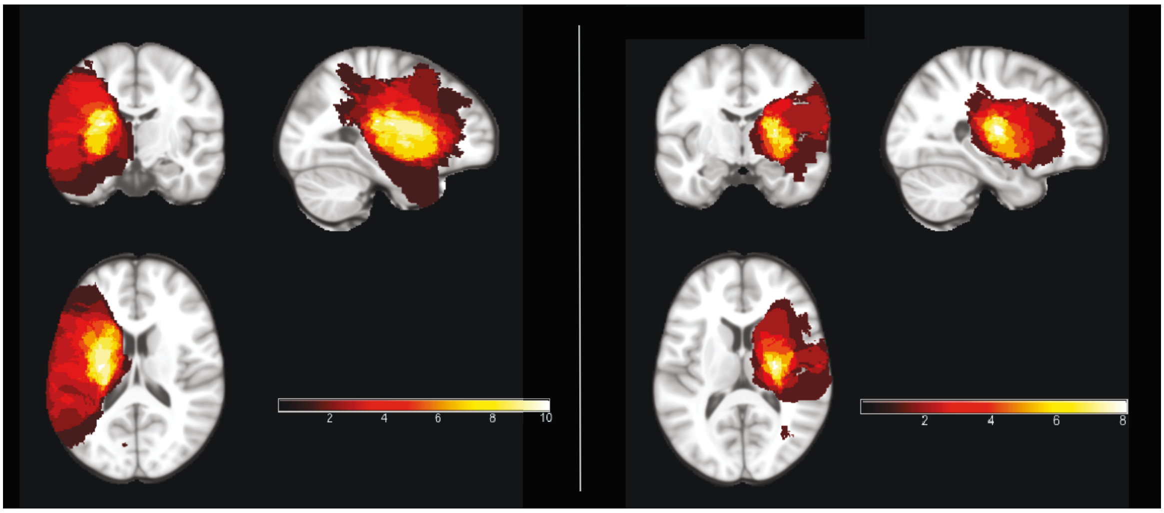


Fig. 1.8. Lesion overlays. The lesion mapping for LHD (left panel) and RHD (right panel), normalized to a template of aged healthy individuals, is shown as an overlay on a standard template using MRIcron (Rorden & Brett, 2000). The different colors code for the number of overlapping lesions from dark red (minimal/no overlap) to white (maximal overlap).

Neuropsychological assessment

All patients included in the study underwent a neuropsychological testing. The Mini Mental State Examination (MMSE, (Magni et al., 1996) and Raven's progressive matrices (Carlesimo et al., 1996) were administered to both LHD and RHD patients in order to assess the global cognitive functioning. The presence of visuo-spatial deficits was assessed using the conventional part of the Behavioural Inattention Test (BIT, Wilson, Cockburn, & Halligan, 1987), with their six subtests. As displayed in Tab. 1.5, any patient was below the cut-off in any BIT subtests. Moreover, patients did not show hint of lateralized omissions across any subtest; scores are displayed separately for left- and right-sided stimuli. The average performance in the cancellation tasks was close to ceiling for both RHD and LHD groups (Fig. 1.9). The presence of contralateral omissions and extinctions was monitored administering the DDS test to all patients. The Rey-Osterrieth complex figure test (Caffarra et al., 2014) was also used to investigate strategic, visuo-perceptual and visuo-constructional abilities. Finally, in the LHD group, the Aachener Aphasie Test (AAT, Luzzatti, Willmes, & De Bleser, 1996) was administered to quantify the presence of language deficits and to ascertain that the comprehension was not impaired.

Subject/ Group	MMSE Cut-off: 24	RAVEN Cut-off: 18.96	BIT Cut-off: <130	BIT-Barr L/R (max 18/18)	BIT-Star L/R (max 27/27)	BIT-Lett L/R (max 20/20)	AAT Comprehension
1/LHD	30	30.8	142	18/18	27/27	20/18	9
2/LHD	27.9	31.8	146	18/18	27/27	20/20	9
3/LHD	27.5	29.8	138	18/18	25/26	20/20	8
4/LHD	n.a.	25.3	144	18/18	27/27	20/20	6
5/LHD	n.a.	32.8	140	18/16	27/27	19/18	4
6/LHD	24.9	26.3	136	18/18	26/27	16/16	2*
7/LHD	n.a.	22.6	145	18/18	27/27	20/20	7
8/LHD	25.9	31.8	145	18/18	27/27	20/19	9
9/LHD	n.a.	30.8	145	18/18	27/27	20/20	4
10/LHD	20.7*	19*	132	17/18	27/27	16/18	-
11/LHD	26.2	36	142	18/18	27/27	19/18	9
12/LHD	24	35.6	144	18/18	27/27	20/19	9
13/LHD	23.2	31.3	145	18/18	27/27	20/20	7
14/LHD	n.a.	29.8	145	18/18	27/27	20/20	7
1/RHD	24.2	31.7	136	18/18	23/27	20/20	
2/RHD	n.a.	32.8	143	18/18	27/27	19/19	
3/RHD	26.9	38.9	143	18/18	27/27	20/20	
4/RHD	n.a.	30.3	142	18/18	27/27	18/20	
5/RHD	26.7	33.2	138	18/18	27/27	18/17	
6/RHD	26.2	21.5	144	18/18	26/25	19/19	
7/RHD	n.a.	36.3	145	18/18	27/27	20/20	
8/RHD	24.2	28.1	145	18/18	26/27	20/20	
9/RHD	30	30.3	143	18/18	27/27	20/19	
10/RHD	23.7	22	137	18/18	25/26	20/20	
11/RHD	28	28.8	141	18/18	27/27	20/20	
12/RHD	30	31.1	141	18/18	27/27	20/20	
13/RHD	30	24.8	139	18/17	26/26	20/20	

Tab. 1.5. Neuropsychological assessment. MMSE (Mini Mental State Examination, (Magni et al., 1996), Raven's progressive matrices (Carlesimo et al., 1996). Across all tasks, age and education corrected scores are reported. *: performance below cut-off. BIT (Behavioural Inattention Test, (Wilson et al., 1987): global scores and raw scores at cancellation subtests (Barr= Barrage; Star= Stars cancellation; Lett=Letters cancellation) are reported separately for left (L) and right (R) hemispace. 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.

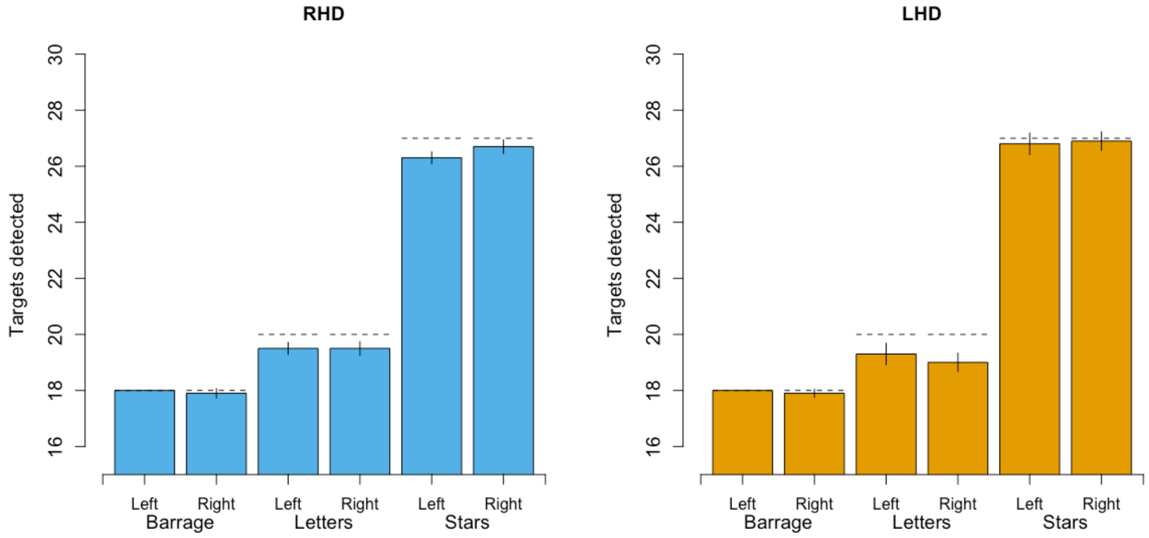


Fig. 1.9. Cancellation tasks. The mean number of target items correctly detected is shown for each BIT cancellation subtest as a function of their side on the testing sheet. Dashed lines represent the total number of targets for the specific subtest. Error bars represent SEM. On the left RHD group in blue, on the right LHD group in orange.

Apparatus, Stimuli and procedures

All participants were asked to perform the multitasking paradigm of Blini et al. (2016). Task, setting and procedures were exactly the same described in the Study 1 of this chapter.

Statistical analysis

Data were analysed using the open-source software R. Practice and experimental trials invalidated by eye movements (0.2%) were dismissed. All experimental conditions were analysed by means of repeated measures analysis of variance (ANOVA) (ez package). Accuracy data were arcsine transformed. According to Mauchly test, the Greenhouse-Geisser (GG) correction was applied in the case of violation of sphericity. Accuracy data were analysed as follow. Given that the main purpose of this study was to understand how load modulates peripheral targets detection in different groups of patients, a preliminary omnibus ANOVA was performed in order to verify the presence of a significant interaction between Load (three levels: Single Task, Visual Dual Task, Auditory Dual Task), Target Type (four levels: Left, Right, Bilateral, Catch) and Group (three levels: LHD, RHD, Controls). If such effect would emerge, further analyses would be performed within each group in order to ascertain the load effect. If in a group a significant interaction would emerge between Load and Target Type, four separate ANOVA would be computed within each type of target to highlight which stimuli are selectively affected by increased attentional load.

3.2. Results

The Results section is organized as follows. The first analysis concerns accuracy to spatial monitoring task in order to investigate how targets position and attentional load can modulate participants' performance at group level. Then, an in-depth analysis of spatial bias has been carried out to assess how omissions were spatially distributed in both LHD and RHD patients, exploring also the differences between groups. Finally, as last analysis, potential effects of fatigue or sustained attention on spatial monitoring task were explored.

Effect of attentional load on spatial monitoring

As first analysis, an omnibus ANOVA has been carried out, including Target Type (four levels: Left, Right, Bilateral, Catch) and Load condition (three levels: Single Task, Visual Dual Task, Auditory Dual Task) as within-subjects factors and Group (three levels: LHD, RHD, Controls) as between-subjects factor. This analysis revealed a significant three-way interaction Group by Load by Type ($F_{(12,222)}= 2.76$, $p < 0.01$). This interaction, plotted in Fig. 1.10, suggests a different effect of multitasking, with greater accuracy for Single than Dual Task conditions across the three groups. Load selectively affected performance for bilateral and contralateral targets, but only for LHD and RHD patients. Given that a three-way interaction emerged, an ANOVA with Target Type (four levels: Left, Right, Bilateral, Catch) and Load condition (three levels: Single Task, Visual Dual Task, Auditory Dual Task) was performed separately for each group. For Controls only a Load main effect emerged ($F_{(2,24)}= 6.35$, $p < 0.01$), that revealed greater accuracy for Single compared to Auditory Dual Task ($t_{(12)}= 2.99$, $p < 0.05$) and Visual Dual Task ($t_{(12)}= 2.62$, $p < 0.05$). In contrast, a significant interaction Load by Target position was found for both LHD ($F_{(6,78)}= 4.78$, $p < 0.001$) and RHD patients ($F_{(6,72)}= 2.61$, $p < 0.05$). Multitasking strikingly affected LHD performance with a significant accuracy decrease from Single to Auditory ($t_{(13)}= 3.04$, $p < 0.01$) and to Visual Task ($t_{(13)}= 4.17$, $p < 0.01$). Accuracy was higher for auditory than visual load ($t_{(13)}= 2.79$, $p < 0.05$). Within RHD group, accuracy dropped from Single to both Dual Task conditions ($t_{(12)}= 3.61$, $p < 0.01$ and $t_{(12)}= 3.73$, $p < 0.01$, respectively). No differences emerged between Auditory and Visual Dual Task.

To follow up the Load by Target Type interaction found in both patients groups, four one-way ANOVAs were separately performed within LHD and RHD to assess the effect of multitasking on each stimulus position. Each analysis included Type of Target (four levels: Left or Right or Bilateral or Catch) and Load condition (three levels: Single Task, Visual Dual Task and Auditory Dual Task) as within-subjects factors (LHD or RHD).

Left targets. The one-way repeated measures ANOVA carried out within LHD group did not reveal an effect of multitasking for left stimuli ($p > 0.05$). However, load selectively affected the performance of the RHD group ($F_{(2,24)}$=6.008, $p < 0.05$, Greenhouse-Geisser corrected, $\eta_p^2 = 0.333$). In detail, accuracy dropped from 92.68% in Single Task to 79.83% in Auditory ($t_{(12)}$= 3.13, $p < 0.01$) and to 64.95% in Visual Dual Task ($t_{(12)}$= 2.78, $p < 0.05$). Auditory and Visual Dual Tasks did not differ ($t_{(13)}$= 1.47, $p > 0.05$).

Right targets. The ANOVA performed within LHD group suggested that multitasking strongly affected the detection of right stimuli ($F_{(2,26)}$= 9.52, $p < 0.001$). Fig 1.10 shows a clear decline of performance from Single Task (90.87%) to Auditory Dual Task (70.19%) ($t_{(13)}$= 2.21, $p < 0.05$) and to visual load (62.23%) ($t_{(13)}$= 3.96, $p < 0.01$). Moreover, a significant difference emerged also between Auditory and Visual Dual Tasks ($t_{(13)}$= 2.68, $p < 0.05$). No significant effects were found for RHD group (p > 0.05).

Bilateral targets. The analyses carried out on bilateral stimuli showed an effect of multitasking for both LHD ($F_{(2,26)}$= 11.40, $p < 0.001$) and RHD patients ($F_{(2,24)}$= 8.34, $p < 0.01$). LHD performance decreased from 84.26% (Single Task) to 69.25% (Auditory Dual Task) ($t_{(13)}$= 3.58, $p < 0.01$) and to 61.90% (Visual Dual Task) ($t_{(13)}$= 3.85, $p < 0.01$). No difference emerged between the two dual tasks conditions ($t_{(13)}$= 1.57, $p > 0.05$). RHD group also showed a greater accuracy in Single Task (89.74%) compared to both Auditory (74.81%) ($t_{(12)}$= 2.58, $p < 0.05$) and Visual Tasks (58.97%) ($t_{(12)}$= 3.41, $p < 0.01$). No difference emerged between the two dual tasks conditions ($t_{(12)}$= 2.01 $p > 0.05$).

Catch trials. No load modulation emerged from the analyses carried out within the two groups (all ps > 0.05). These results demonstrated that patients reported correctly the absence of stimuli in the periphery of the visual field, excluding potential bias effect in the responses.

Given that load specifically affected contralateral targets (i.e., left targets for RHD and left targets for LHD), the last analysis assessed, by recoding target position as contra- or ipsi-lesional, whether this selective drop in accuracy was similar or different between groups. An ANOVA, with Load (three levels: Single Task, Visual Dual Task and Auditory Dual Task) and Type of Target (three levels: contralateral, ipsilateral and bilateral targets) as within-subjects factors and Group (two levels: LHD, RHD) as between-subjects factors, showed a significant Type by Load interaction ($F_{(4,100)}$= 5.08, p < 0.001) but no differences across the two groups (p > 0.05). This further confirms that the presence of contralesional omissions and sensitivity to the effect of load did not differ between LHD and RHD.

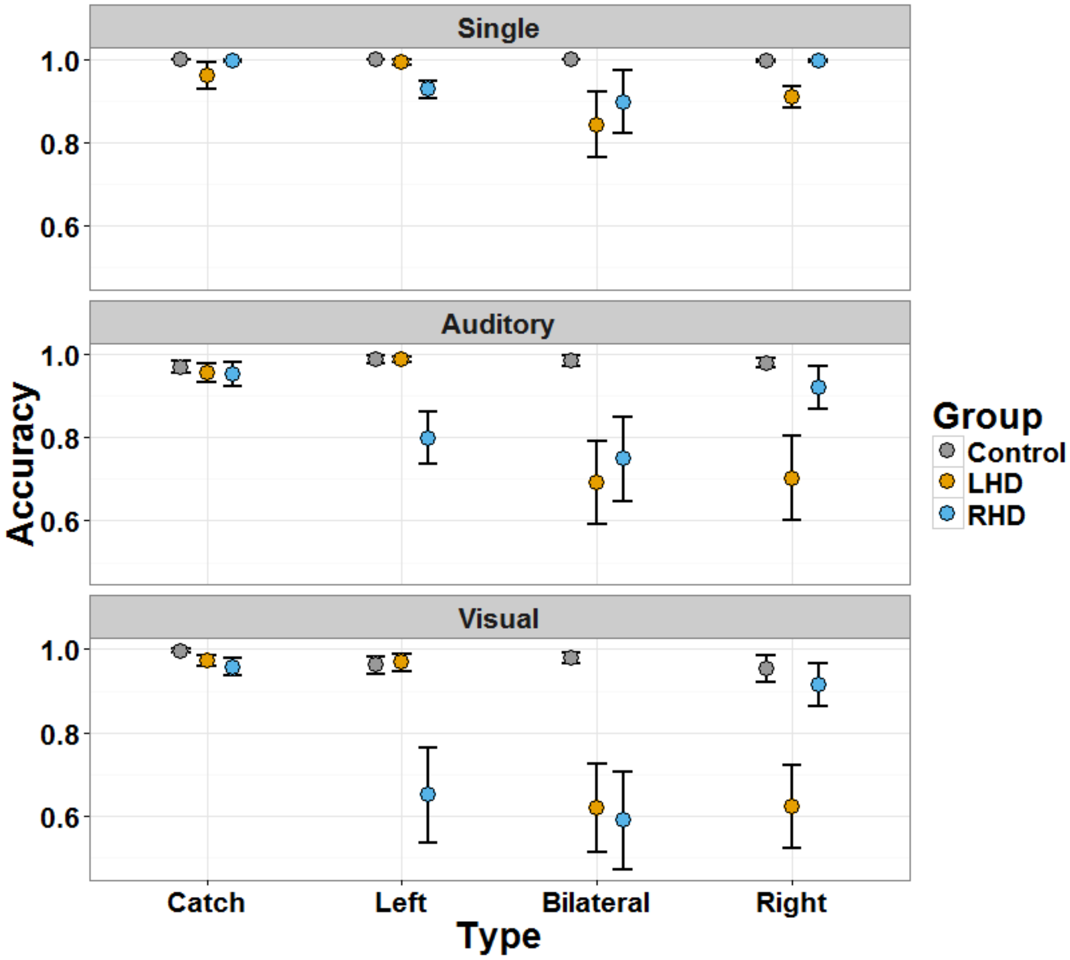


Fig. 1.10. Spatial monitoring task: global accuracy. Accuracy in the spatial monitoring task is depicted for each Load condition (single task, visual dual task, auditory dual task) as a function of Target type (left, right, bilateral, catch) and Group (LHD: orange circles; RHD: blue circles; Healthy Controls: grey circles). Error bars represent SEM.

Asymmetry indices

To assess the spatial distribution of the omissions Asymmetry indices (AI) were computed separately for unilateral, bilateral and catch trials. AIs were computed as in Blini et al. (2016), whereby negative values index a higher proportion of “left” responses (i.e. right omissions being more frequent) and positive ones index a higher proportion of “right” responses (i.e. left omissions). When the presence of spatial bias was assessed (i.e., significant difference from 0), the effect of Load was investigated within each group due to the differences in variances and violation of normality.

Unilateral targets

AIs significantly differed from 0 for both LHD ($t_{(13)}$= -3.41, $p < 0.01$) and RHD groups ($t_{(12)}$= 2.88, $p < 0.05$). In contrast, AIs did not differ from 0 in the healthy Controls Group ($t_{(12)}$= -0.74, $p > 0.05$) (see Fig. 1.11). One-way repeated measures ANOVA revealed a Load effect ($F_{(2,26)}$= 7.49, $p < 0.01$) for LHD group. AIs significantly decreased from -0.07 during Single Task condition to -0.26 during Auditory Dual Task ($t_{(13)}$= 2.69, $p < 0.05$) and to -0.31 under Visual Dual Task ($t_{(13)}$= 3.42, $p < 0.01$). No differences emerged between auditory and visual conditions ($t_{(13)}$= -0.86, $p > 0.05$). Multitasking affected also RHD group during unilateral targets processing ($F_{(2,24)}$= 4.72, $p < 0.05$), with AI increasing from Single Task (0.06) to Auditory (0.14) to Visual Dual Tasks (0.29). AIs were significantly greater for Visual than Single Task ($t_{(12)}$= -2.39, $p < 0.05$). No other differences emerged.

Bilateral targets

The analysis of AIs showed overall negative scores in LHD ($t_{(13)}$= -3.03, $p < 0.001$) and overall positive scores in RHD ($t_{(12)}$= 2.56, $p < 0.05$). For LHD, one-way ANOVA showed an effect of Load ($F_{(2,26)=}$ 8.59, p <0.01, Greenhouse-Geisser corrected, η_p^2 =0.415), with AI decreasing from -0.15 in the single task to -0.29 in the auditory ($t_{(13)}$= 2.59, $p < 0.05$) and to -0.38 in the visual task ($t_{(13)}$= 3.18, $p < 0.01$). The difference between auditory and visual tasks was also significant ($t_{(13)}$= -2.56, $p < 0.05$). Also in RHD group load strongly modulated AIs ($F_{(2,24)=}$ 7.36, $p < 0.05$, Greenhouse-Geisser corrected, η_p^2= 0.380). In particular, spatial asymmetry increased from Single Task (0.09) to Auditory (0.15) ($t_{(12)}$= -2 , $p > 0.05$) and significantly to Visual Dual Task (0.35) ($t_{(12)}$= -2.85, $p < 0.05$). Moreover, AIs were higher during intra-modal than cross-modal load ($t_{(12)}$= 2.60, $p < 0.05$). AIs were not significantly different from 0 in Healthy Control group ($t_{(12)}$= -1, $p > 0.05$).

Catch targets

AIs did not significantly differ from 0 in all groups: LHD ($t_{(13)}$= -1.42, $p > 0.05$); RHD ($t_{(12)}$= 1.42, $p > 0.05$); Controls ($t_{(12)}$= 0.57, $p > 0.05$). The correct report of catch trials proved the absence of responses bias during spatial monitoring task.

To investigate whether the spatial bias induced by load context was more prominent for a patient group compared to the other one, a separate ANOVA was computed with Type of AIs (two levels: Unilateral; Bilateral) and multitasking condition (two levels: Auditory Dual task or Visual Dual Task) as within-subjects factors and Group (two levels: LHD, RHD) as between-subjects factors. Given that LHD patients always presented negative scores while RHD positive indices, all these last analyses considered absolute values for each group. This allowed us to obtain a measure of the AI across tasks conditions regardless of bias direction, making possible groups comparisons. The results further confirmed that multitasking induced similar level of spatial asymmetry in both LHD and RHD groups when a concurrent visual or auditory secondary task was performed (all *p*s > 0.05).

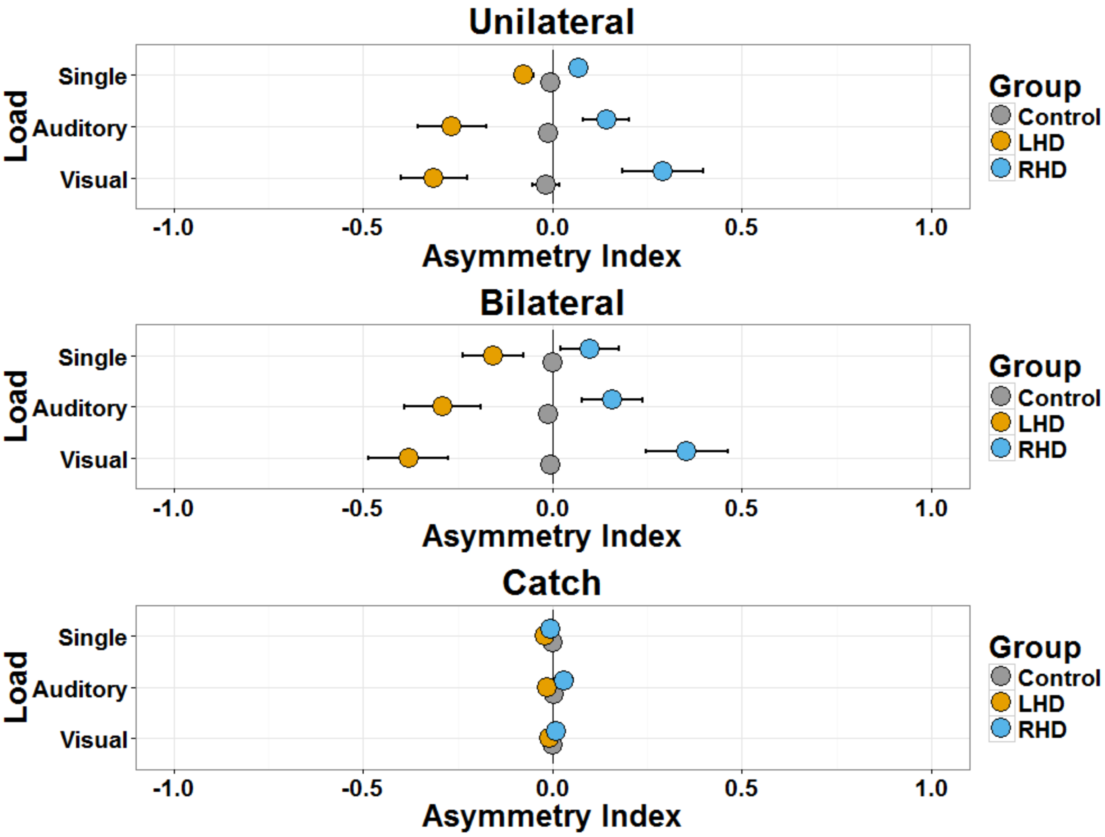


Fig. 1.11. Lateralized biases. The Asymmetry Index is depicted for each type of target (unilateral, bilateral, catch) as a function of Load condition (single task, visual dual task, auditory dual task) and Group (LHD: orange circles; RHD: blue circles; Healthy Controls: grey circles). Note that the asymmetry is expressed in terms of proportion of errors: negative values index a leftward bias (e.g., a value of -1 means that all of the right but none of the left targets were neglected), whereas a value of 0 indicates even distribution of omissions (or the absence of omissions). Error bars represent SEM.

Correlations between AI and lesional volume

We carried out an explorative correlational analysis between AIs and lesion volume, including both LHD and RHD in the same group and considering absolute values for all indices. When AIs for unilateral trials were correlated with lesional volume, no significant correlation emerged. (Single Tasks: r= 0.03, $t_{(19)}$= 0.14, p > 0.05; Visual Dual Task: r= -0.03, $t_{(19)}$= -0.11, p > 0.05 ; Auditory Dual Task: r= 0.21, $t_{(19)}$= 0.98, p >0.05). With respect to bilateral targets, we found a positive correlation between AIs in Auditory Dual task and lesion volume (r= 0.49, $t_{(19)}$= 2.45, p < 0.05). No significant correlations were found for Single (r= 0.27, $t_{(19)}$= 1.26, p > 0.05) and Visual Dual Task (r= 0.30, $t_{(19)}$= 1.39, p > 0.05). All correlations were two-tailed, uncorrected and the results suggest that the larger the lesion the more contralesional targets were extinguished under auditory load. However, because of the small sample size these results must be taken with caution.

Fatigue and sustained attention

A repeated measures ANOVA was performed in order to assess whether fatigue or deficits of sustained attention influenced spatial monitoring performance. Session (two levels: first Single Task block; second Single Task block) and Type of Target (four levels: Left, Right, Bilateral, Catch) were included as within-subjects factors and Group (two levels: LHD, RHD) as between-subjects factor. Note that Single Task was administered as first and last block. Healthy Controls group was not included in the analysis because of their ceiling performance (100% accuracy during first block; 99.78% accuracy during second block). From the ANOVA analysis only a Type of Target main effect emerged ($F_{(3,75)}$= 3.06, p < 0.05, Greenhouse-Geisser corrected, η_p^2= 0.123), indexing a significant difference in the detection of bilateral targets compared to catch trials ($t_{(26)}$= 2.48, p < 0.05). Patients' performance did not differ between the first and the last session, proving that the previously described pattern is due to the genuine effect of multitasking and suggesting the absence of fatigue effect across all experimental conditions. Mean values for first and last block were 91.6% and 93.6% in LHD patients and 96.1 % and 94.6% in RHD patients, respectively (Fig. 1.12).

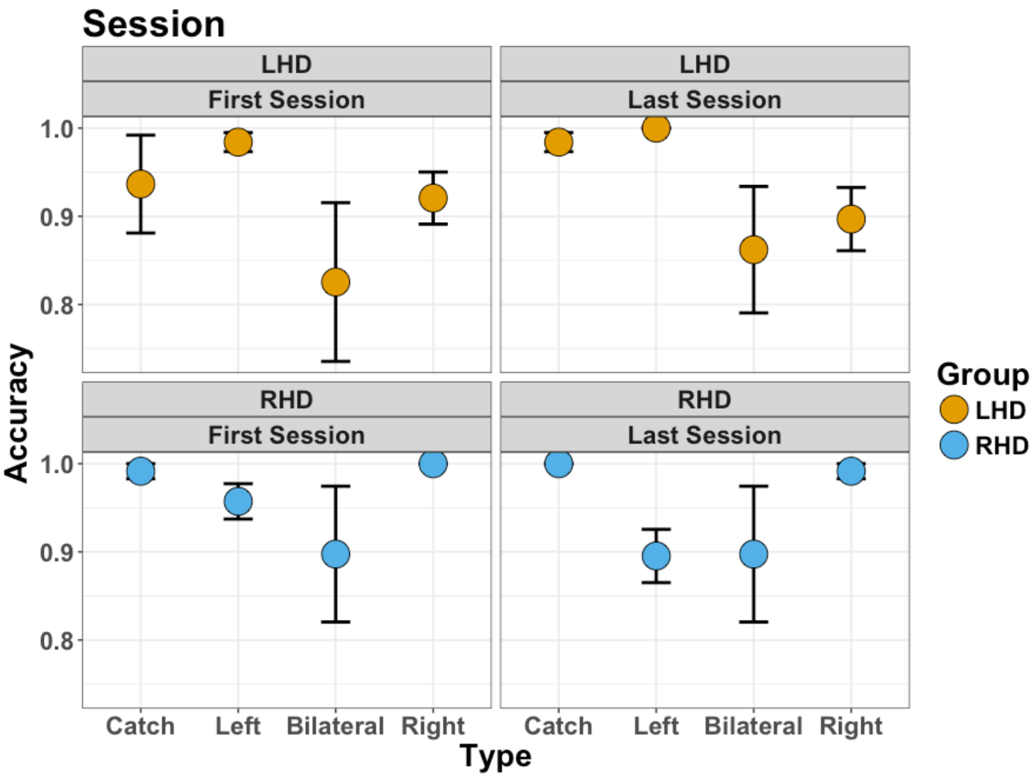


Fig 1.12. Fatigue. Performance of LHD (top panel) and RHD (bottom panel) patients in the first block (four circles on the left) and in the last (i.e., sixth) block of the spatial monitoring task (four circles on the right). In both blocks patients only had to report target side. Error bars represent SEM.

Secondary task

As last analysis, the effect of Load on accuracy in the secondary task (Visual Dual Task vs. Auditory Dual Task) was explored. Due the ceiling performances, Control group was excluded from this analysis. The ANOVA included Type of Load (two levels: visual, auditory) and Type of Target (four levels: Left, Right, Bilateral, Catch) as within-subjects factors and Group (two levels: LHD, RHD) as between-subjects factor. The results revealed a Load main effect ($F_{(1,37)}$= 10.11, $p < 0.01$) and a Group main effect ($F_{(1,25)}$= 8.84, $p < 0.01$). Accuracy was significant greater for auditory than visual secondary task ($t_{(26)}$= 3.22, $p <$ 0.01). Moreover, accuracy was higher for RHD compared to LHD group ($t_{(18.56)}$= -3.04, $p <$ 0.01). However, note that in the visual secondary task, the less accurate condition, overall accuracy was higher than 70% for LHD and 90% for RHD group.

3.3. Discussion

The main purpose of this work was to validate the effectiveness of a multitasking paradigm in unveiling pathological spatial asymmetry comparing two groups of chronic stroke patients suffering from left rather than right hemisphere damage. Once ascertained the presence of spatial bias in these two clinical populations, the aim was to establish whether the degree of impairment showed similar occurrence or whether the deficit was more emphasized in one of the two patients' groups (LHD vs. RHD). Although several studies (Blini et al., 2016; Bonato et al., 2010, 2013) considerably demonstrated the sensitivity of this assessment tool, the present work is the first one in which a direct comparison between LHD and RHD patients, performing exactly the same task, has been proposed. The findings confirmed the selective effect of load during visuo-spatial processing of stimuli presented in the periphery of the visual field. In particular, performance of RHD patients dramatically decreased during dual task conditions, but only when bilateral and left-side stimuli had to be reported. This selective impairment for contralateral and bilateral targets emerged also in LHD group. Under multitasking, accuracy dropped for right-side stimuli, with stronger modulation when a concurrent visual secondary task was performed. Moreover, bilateral targets perception is affected regardless of the sensory modality of attentional load (visual or auditory). Interestingly, when the performance of the two patients' groups was compared, considering contralateral, ipsilateral and bilateral targets detection, any difference emerged. This result shows that during the most complex conditions (i.e., detection of bilateral targets or stimuli located in the contralateral side of the visual field) the two groups showed similar amount of errors. The most interesting result concerns the clear pattern of pathological spatial asymmetry emerged from the analysis of missed targets. As reported in the first study of this chapter, contralesional targets omission (right neglect and/or right extinction) was found in LHD group. Similar pattern of spatial bias emerged also in RHD group (left neglect and/or left extinction). Nevertheless, any neuropsychological test was able to assess the presence of lateralized disorders in any patient included in the study. As expected, multitasking did not induce lateralized bias in healthy control group. Overall, these findings clearly remark that asymmetry in spatial monitoring can be uncovered by means of multitasking approach and, interestingly, reveal that the bias size induced by load was similar for LHD and RHD patients. This is confirmed by the comparison between the two groups in AIs computed for unilateral and bilateral targets. Undoubtedly, the present study has considerable theoretical and practical consequences. First of all, these findings proved that multitasking approach represents a convenient tool to investigate visuo-spatial disorders after both right and left brain damages, supporting previous evidence (Blini et al., 2016; Bonato et al., 2010; Bonato, Priftis, et al., 2012). Second, given that patients showed similar pathological asymmetry patterns, regardless of the damaged hemisphere, we suggest that any compensation process becomes possible under high cognitive effort. As previously discussed, Kinsbourne's model (1987) can be extended to both left and right spatial bias phenomena induced by task demands. More specifically, increasing attentional load requires the employment of non-spatial resources that, inevitably, elicit an activity inhibition of the damaged hemisphere. Therefore, it is possible to conclude that this mechanism of inhibition, caused by multitasking, can equally affect both hemispheres. Concerning clinical aspects, despite all patients had normal performance in classic paper-and-pencil tests, evidence for contralesional spatial unawareness were found when multitasking was required. These findings suggest that a test being able to assess both lateralized and non-lateralized deficits, together with their interaction, might add precious clinical and empirical information to neuropsychological evaluations. Right-sided neglect is believed to be uncommon, but its occurrence might dramatically change when attentional load is introduced, confirming the hypothesis of a task-dependent occurrence of neglect (Azouvi et al., 2002). Tapping on right lateralized (aspecific) resources unveils lateralized biases that might otherwise remain undetected, shedding light on possible explanations for the very different prevalence of USN after right vs. left hemispheric stroke. The relevance of multitasking in everyday life is uncontested, for this reason the possibility to use a sensitive clinical tool that take into account spatial and no-spatial aspects of attention can significantly enrich the diagnostic process and the planning of effective rehabilitation programs.

Chapter II

Temporal dynamics of spatial processing under multitasking

1. Introduction

When we enter in a room, are we able to process all the details around us? And if, at some point, the telephone starts to ring or someone talks to us, what happens to our attentional systems?

During everyday life, we continuously explore the visual world to detect behaviourally-relvant stimuli. Depending on our goals, when we interact with the surrounding space, we automatically suppress the irrelevant information in favour of the salient ones (Possin, 2010). The filtering process of the environment certainly represents a crucial step in visual perception (Karnath, 2015). This fascinating phenomenon almost never occurs in isolation but, in most of the cases, while simultaneously with other ones (Nijboer et al., 2016; Schaefer, 2014). Consider, for example, how many times people are used to perform different concurrent cognitive tasks during the day. The concept of multitasking certainly has a key role in the study of the allocation of the cognitive resources and it has also important theoretical and pratical implications (Burgess, Veitch, de Lacy Costello, & Shallice, 2000; Logie, Trawley, & Law, 2011). It has been repeatedly shown that the cognitive performance drops under multitasking conditions (Al-Hashimi, Zanto, & Gazzaley, 2015) and this load-related decline is often explained in term of a limited amount of depletable resources (Marois & Ivanoff, 2005; Pashler, 1994). Futhermore, from a neurofunctional framework, the signatures of multitasking (Al-Hashimi et al., 2015) are closely entwined with the cognitive characteristis of the task at hand (Sasai, Boly, Mensen, & Tononi, 2016).

Spatial processing is a crucial cognitive mechanism involved in most everyday context: it is fundamental to safely navigate in the space and to successfully interact with the sourronding environment. Although the spatial ability is often considered strongly automatic in the common experience, it could be heavily affected by concurrect tasks execution. Several evidences showed that the efficiency of our spatial processing could be impaired under certain circumstances, such as the attentional demanding task (Holcombe & Chen, 2012) or in presence of neurological impairments (Lundin-Olsson, Nyberg, & Gustafson, 1997). Recently, both approaches were used to study how multitasking affects the processing of the contralesional space following unilateral brain damage. In particular, Bonato and colleagues (2013, 2010) used their well established multitasking paradigm to distinguish, in chronic stroke patients, those who were compensating for their spatial deficits from those who were not. Patients were asked to perform one primary spatial monitoring task (reporting the position of appearance of lateralized target(s)) with and without a concurrent – visual or auditory – task. Note that all patients included in these studies had normal performance in classic assessment for neglect. Interestingly, the request to monitor concurrently for the appearance of spatial targets and for the presentation of an auditory number – or a visual letter at fixation – unveiled patterns of neglect and extinction (Bonato, Priftis, et al., 2012; Bonato et al., 2013).

More recently, Blini and collaborators (2016), using a multitasking paradigm, showed the presence of contralesional omissions also in an unselected sample of chronic left hemisphere damaged patients, a clinical population in which spatial attention deficits are rarely observed (Ringman et al., 2004). All these findings support the idea that multitasking is a surprisingly sensitive instrument to unveil the presence of subtle biases in the spatial allocation of processing resources. Moreover, multitasking allows us to detect core deficits in spatial processing that are otherwise compensated in less demanding tasks. The same multitasking paradigm was also adapted to investigate spatial processing in healthy participants (Bonato, Spironelli et al., 2015; Lisi et al., 2015).

By measuring pupil dilation, Lisi et al., (2015) differentiated the multitasking effects due to the number of features that have to be kept in mind to respond correctly from the perceptual difficulty of extracting the correct response. From an electrophysiological perspective, Bonato, Spironelli et al., (2015) studied the ERP correlates of dual task processing, by administering non-masked targets to be detected either in isolation (single task) or while processing another task feature. Early effects included a modulation of the P1 component together with a deactivation of the primary visual areas, but also later components were affected by task load. In detail, left-side stimuli elicited greater activation of the supramarginal gyrus during visual dual task. This effect was found on the N2 component and located in the right posterior regions underlining not only the crucial role of the right hemisphere in spatial resources allocation, but also its susceptibility to load manipulations.

It has been consistently showed that the processing of items occurring within the right hemispace is facilitated, under both unimodal and multimodal load (Chen & Spence, 2017). Other studies have reported an advantage for the left visual field when left and right hemispaces have to be simultaneously attended (Holländer et al., 2005; Verleger et al., 2010; Verleger & Śmigasiewicz, 2015). A recent experiment (Verleger & Śmigasiewicz, 2015) used a rapid stream visual presentation paradigm in which two streams of stimuli, consisting of consecutive letters, were concurrently presented in both left and right visual fields at three different intervals. When spatial resources were heavily recruited and split across hemispaces to monitor in parallel for the appearance of a target, the left visual field showed a clear advantage. Does this widely replicated effect index a right hemispheric supremacy in spatial processing? Can such a finding be generally extended to all experimental contexts requiring to concurrently monitor for the appearance of lateralized stimuli?

While very informative for understanding the factors mediating the interference of distracters, the leading theory of the link between visual processing and the amount of processing resources available (Lavie, 1995, 2005) does not speak to the influence of performing additional tasks while processing space. According to Lavie's load theory, peripheral visual distracters do not affect performance when tasks are characterized by high perceptual load at fixation, because all resources are allocated on stimulus processing. In contrast, low load conditions do not exhaust all available resources and allow the processing of irrelevant information. Some theories explain the various performance across hemispaces as due to hemispheric rivalry. For instance, the interhemispheric inhibition theory of Kinsbourne (Kinsbourne, 1970, 1987) has been used to explain asymmetries in perception as deriving from brain asymmetries. This model is based on the notion of an imbalance in the activation of the cerebral hemispheres. In particular, it postulates that when we have to orient our attention to the contralateral hemifield, a mechanism of mutual inhibition between the hemispheres occurs, and this inhibition is stronger for the right hemisphere.

The present work address the study of the correlates of dual tasking -as revealed by electrophysiological measures- while performing spatial processing. Previous ERP studies on spatial processing under multitasking (Handy et al., 2001; O'Connell et al., 2011; Rorden et al., 2008) mainly focused on the electrophysiological correlates found after successful processing of targets, i.e., when participants can respond correctly to target stimuli. More specifically, Rorden and colleagues (2008) observed greater amplitudes for peripheral stimuli presented as targets (i.e., task-relevant) and a reduction of activity for peripheral stimuli presented as distracters (i.e., task-irrelevant). Handy et al. (2001) used task-irrelevant peripheral distracters and showed that increasing attentional load at fixation produced a decrease of amplitude on the P1 component. These results suggest that task demands can elicit different effects depending on whether the peripheral stimuli are considered relevant or irrelevant.

However, what happens in a healthy brain when stimulus processing leads to incorrect responses is much less known. By manipulating endogenous and exogenous forms of attention, Chica and colleagues (2012, 2010) carried out a series of ERP studies to clarify the relationship between attention and conscious perception. The results of the first study (Chica et al., 2010) showed that seen targets elicited a greater P300 component compared to the unseen ones. In this experiment, exogenous peripheral cues were presented before the target appearance, and a cue-related analysis revealed an higher P100 activation, located in the occipito-parietal areas, for seen targets when the cue was valid (same location as the stimulus). In addition, Chica and collaborators (2012) combined endogenous and exogenous orienting of attention using central and peripheral cues. A larger P100 activation for seen *vs.* unseen targets emerged only in the case of peripheral cues and endogenously invalid (i.e., appearing at the non cued position) targets. A difference in N100 component was also found in the parieto-occipital areas: when the endogenously trials were valid, unseen targets elicited higher negativity compared to consciously perceived targets, but when they were invalid, the N100 was larger for seen targets.

To the best of our knowledge, no electrophysiological works have been carried out to highlight the cortical mechanisms associated with the modulation of awareness of lateralized targets elicited by a purely top-down/multitasking approach, which keeps the stimuli constant across different tasks. With the aim of filling this gap, in the present study a main analysis of early ERP components associated with correct target detection (i.e., P1, N1 and N2 components) was carried out in a sample of young healthy adults using a multitasking paradigm (e.g., Bonato, Spironelli et al., 2015) previously-validated with supra-threshold visual stimuli. Here the threshold was carefully manipulated in order to induce omissions of the lateralized target(s), simulating a response pattern similar to that observed in brain damaged patients. The duration of the target was determined according to average group performance, and a visual mask was added to the stimuli to make the processing of the spatial targets more difficult. This experimental manipulation allowed us to contrast the electrophysiological correlates of correct vs. incorrect responses within a sub-sample of participants showing a significant number of errors on their behavioural performance. The same ERP components analysed in the main analysis (i.e., in the whole group) were also investigated by contrasting the electrophysiological pattern of activation elicited by correct and error trials, with the aim of clearly detecting how and when visual information processing leads to different behavioural responses. With respect to this critical issue, two possible mechanisms are foreseen: (a) both correct and incorrect responses elicit similar ERP components, but the latter show an amplitude significantly over- or under-threshold with respect to the correct ones; (b) considering the whole process of visual target analysis, correct and incorrect responses reveal different patterns of activation at a certain time point of the processing stream (e.g., early or late ERP components).

2. Materials and methods

Participants

Twenty undergraduates (8 males; mean age: 23.68 years) took part in the study. The experiment was carried out at the Department of General Psychology of the University of Padova. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971, average score > 96%) and had normal or corrected-to-normal vision. All participants gave their written informed consent to take part in the experiment, according to the Declaration of Helsinki. The experimental procedure was approved by the Ethics Committee of the Department of General Psychology, University of Padova.

Stimuli, tasks, and procedure

Participants sat at a distance of about 60 cm from a 38 x 30.5 cm computer monitor. The task was programmed and administered using E-Prime (Psychology Software Tools, Pennsylvania, USA, http://www.pstnet.com).

Stimuli and procedure resembled those used by Bonato, Spironelli et al. (2015) with three important differences: i) target duration was determined by means of a calibration procedure (carried out in a separate session); ii) the presence of masking; iii) a different response mapping.

There were three experimental tasks (Fig. 2.1): one single-task condition and two dual task conditions (visual vs. auditory). Each trial started with a black screen (1000 ms). A black background was present through the whole experiment. Then, a white fixation cross was centrally-presented for 1000 ms. A white dot target (approximately 0.8° of visual angle) was then presented, in equal proportion, on the left side, on the right side, or bilaterally for 67 ms, at a lateral distance of about 16° of visual angle from the centre of the screen. Therefore, either a single target (left-sided or right-sided) or bilateral targets (left- and right-sided) were presented. The duration of the lateralized targets, which was the same for all participants, has been determined by a calibration procedure (36 trials) implemented in a separate session, carried out two weeks before the ERP experimental task. In the calibration phase, stimuli and response modality were the same of the experimental task, while the duration of the targets was determined by participants' accuracy to bilateral targets. A correct response led to a decreased presentation time (one refresh period) in the following trials. Errors led to increased presentation time (three refresh periods). Also omissions led to increased presentation time (two refresh periods) for the subsequent trials. The average duration for the last 24 trials of the procedure was taken as final outcome. The aim of this procedure was to find out an average duration that would have resulted in a relatively high number of errors/omissions and, at the same time, to maintain an equal temporal sequence for all participants. This was the best and possibly only option to then perform stimulus-locked ERP analyses. Target presentation time for the experimental task was then determined by subtracting one standard deviation from the mean target duration (measured by the number of refresh periods). Synchronously with the lateral target(s), a geometric shape (square, circle, or diamond, in equal proportion, about 1.1° of visual angle) was presented at fixation and a pure tone (high frequency ≈ 800 Hz, medium ≈ 450 Hz, or low ≈ 255 Hz, in equal proportion) was binaurally presented by means of earphones. After the offset of sound (100 ms), two masks, made by four white dots (arranged like the face of a die), were presented bilaterally. Note that the masks were not present in the task used by Bonato, Spironelli and colleagues (2015).

In the Single task, participants had to report the position of the target(s) (i.e., “right”, “left”, or “both” sides), while ignoring the central shape and the auditory tone. Participants were required to respond as fast and as accurately as possible by pressing a button on a standard QWERTY keyboard (left index (d key) for left target, right index (k key) for right target). In case of bilateral targets they had to press both buttons at the same time. Absence of response before the end of the trial (2 sec) was considered as an omission. In both Dual tasks, the display and the sequence of events were identical to that of the Single task. In the Visual Dual task, after having responded (keyboard) participants had to respond (using the keyboard) to the position of the lateral visual target(s) and then verbally classify the centrally presented shape. In the Auditory Dual task, participants had to respond (keyboard) to the position of the lateral visual target(s) and then to verbally classify the sound pitch as high, medium or low.

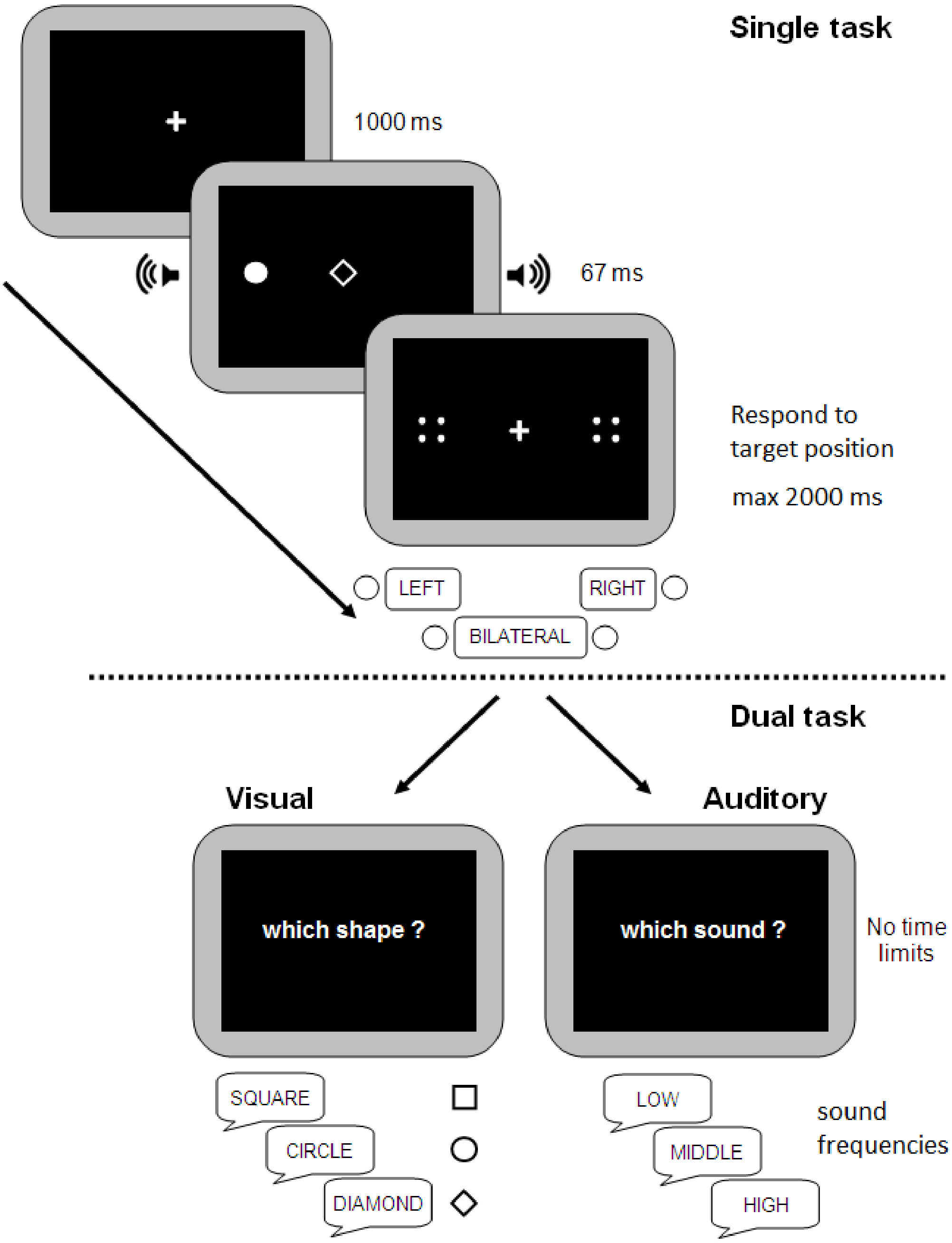


Fig 2.1. Trial structure of the Single task (top panel) and of Dual tasks (bottom panel). Across all tasks the same stimuli were presented: lateralized dot(s), a central form and a binaurally presented sound, followed by two four-dot-die masks on left and right lateralized dot(s) position. In the Single task participants only had to report the position of the dot. In Dual tasks after the response to dot(s) position, participants had to report the identity of the central shape (Visual Dual task: left side, bottom panel) or the pitch of the sound (Auditory Dual task: right side, bottom panel).

The experimenter coded participants' oral responses to the identity of the centrally presented shape (in the Visual Dual task) or to the sound pitch (in the Auditory Dual task). There were no time limits to respond to the secondary tasks.

Each task comprised 162 trials, equally distributed in three blocks (3 repetitions x 3 sounds x 3 shapes x 3 spatial positions), for each task. Participants performed the Single task first, and then the Dual tasks (Visual vs. Auditory) in a counterbalanced order. The importance of maintaining gaze at fixation was stressed before each block.

Data acquisition and analysis

EEG cortical activity was recorded by 32 tin electrodes, 30 mounted on an elastic cap (ElectroCap) according to the International 10-20 system (Oostenveld and Praamstra, 2001), and the other two applied on mastoids (M1, M2). Electro-oculogram, allowing the detection of eye movements, was recorded with a bipolar montage using two additional electrodes placed below the right eye (Io1) and on the left canthium (F9), respectively. All cortical sites were on-line referred to M1. Data were stored using the Micromed software (System Plus, Micromed, Mogliano Veneto, Italy). Data were recorded with a 0.2-30 Hz bandwidth; the sampling rate was set at 512 Hz and the impedance was kept below 5 kΩ.

EEG was continuously recorded in the AC mode and stored for later analysis. Data were off-line re-referenced to the average reference (including the activity of both mastoids). Signal analyses were carried out using the Brain Vision Analyzer system (Brain Products GmbH, Germany). Eye movement artifact components (i.e., vertical and horizontal movements, and blinking) were corrected by applying the Independent Component Analysis (ICA) transformation to the EEG signal. Raw data were therefore segmented in epochs of 1.5-s intervals, including 0.5 s before and 1 s after target onset, and a 100-ms baseline preceding target onset was subtracted from the whole trial epoch. Each trial was then visually inspected for any residual artifacts (e.g., head movements or muscular activity) and, for the main analysis, trials corresponding to errors to target position, form/sound type or both, were discarded. All accepted trials within a specific experimental condition (on average, 92.25% of trials available after discarding errors, with no differences between conditions) were averaged. Thus, this rate of averaged epochs included all artifact-free trials for which participants provided correct responses to both the target and, for Dual tasks only, the secondary task (shape or sound classification). In any case, the performance to the secondary task was always good, with average accuracy rates greater than 85% (mean accuracy to Visual task: 95.65%, range 89-100%; mean accuracy to Auditory task: 88.90%, range 74-98%). For the error analysis, carried out on the sub-sample of participants that showed a sufficient number of error responses to behavioural performance, we visually inspected only the trials in which participants made a mistake to target position, whereas we discarded the stimuli corresponding to correct responses as well as those with a error response to form/sound type[†]. All trials within a specific experimental condition that fulfilled the above-mentioned criteria (on average, 83.44%, with no differences between conditions) were therefore averaged. This rate of averaged epochs included all artifact-free trials for which participants provided error responses to the target and correct responses for the secondary task (shape or sound classification). We selected to limit the analysis of error responses to the target in view of correct responses to the secondary task to have a direct comparison between the main, "standard" analyses carried out on correct responses and those carried out on the errors, while maintaining the load effect (depending on a good performance to the secondary task) fixed.

On the basis of grand-mean waveforms (Fig. 2.2), we analysed the time-windows centred on P1, N1 and N2 peaks (i.e., 99.80-111.53 ms, 176.04-195.59 ms and 281.22-300.77 ms, respectively). The Kolmogorov-Smirnov test was applied to ensure that every ERP component was normally distributed (all ds ≤ 0.308, *ps* > 0.20). For statistical analysis, electrodes were clustered into two posterior quadrants/regions of interest: Left Hemisphere (LH: TP7, P7, O1), Right Hemisphere (RH: TP8, P8, O2). Thus, the mean amplitude values of the ERP measured in cortical sites with the same polarity were averaged.

[†] We established the minimum number of error responses necessary to include a participant in this sub-sample following two main criteria: (a) since we have a general good performance to secondary tasks (>85%), the minimum number of available stimuli for the primary task was 46, of which (b) at least 55% (i.e., 25 stimuli) was accurate (for the main analysis on the whole group). These criteria leaved possibly about 20 stimuli to error analyses.

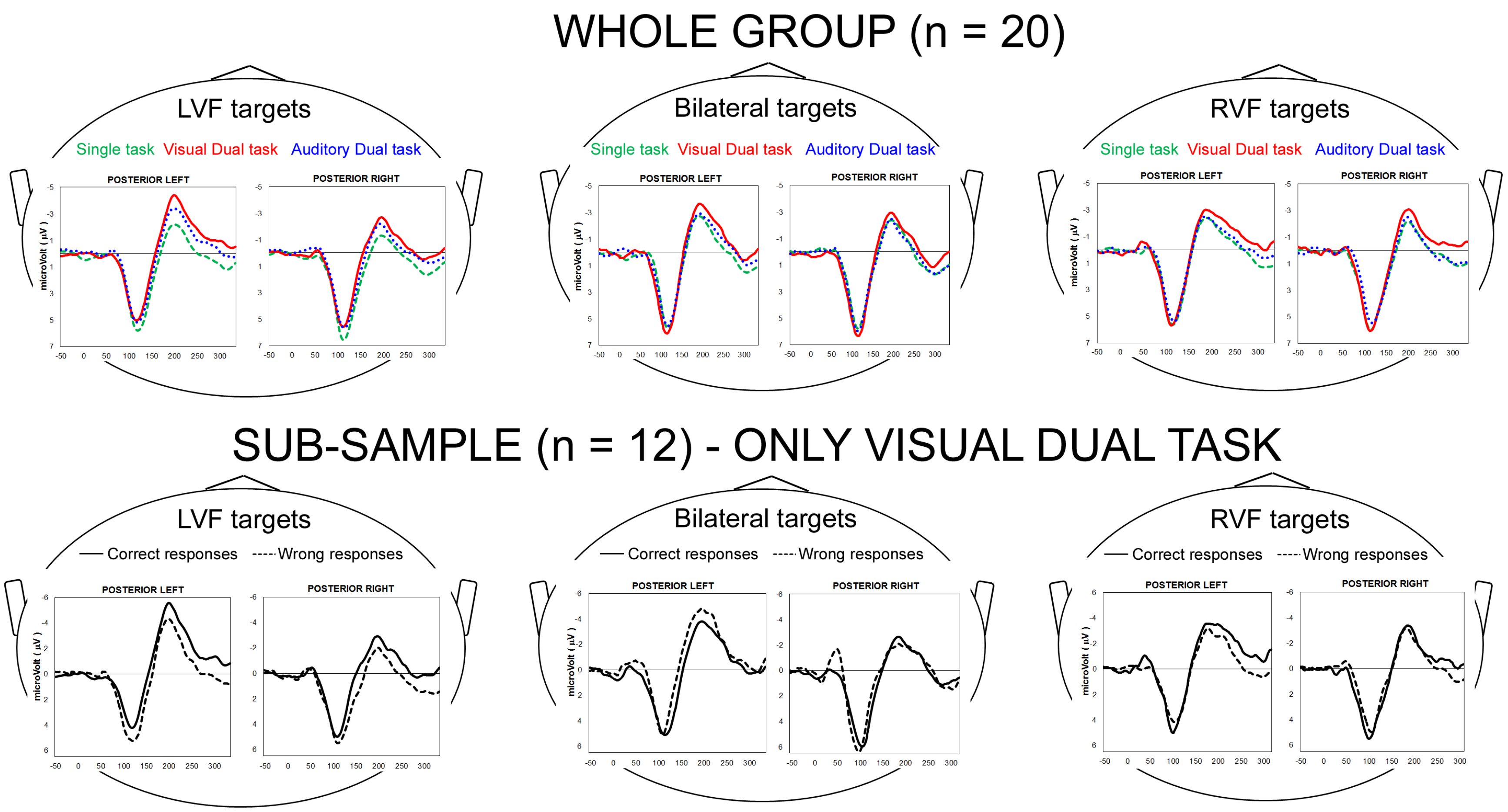


Fig 2.2. Left Visual Field: Grand mean average potential of correct targets (Top) and correct/error responses (Bottom). (Top) P1, N1 and N2 components of the whole group (n = 20), showing LVF, Bilateral and RVF stimuli during Single (green lines), Visual Dual (red lines) and Auditory Dual task (blue lines). (Bottom) P1, N1 and N2 components of the sub-sample (n = 12), showing correct (full line) and error (dashed lines) responses elicited by LVF, Bilateral and RVF stimuli during Visual Dual (Negativity is shown upwards.

3. Results

Both behavioural and ERP data were analysed using repeated measures analysis of variance (ANOVA). The Greenhouse-Geisser (GG) correction was applied in the case of violation of sphericity (in these cases, we report uncorrected degrees of freedom, epsilon values, and corrected probability levels). Post-hoc comparisons were computed using the Newman-Keuls test ($p < 0.05$).

All analyses have been carried out using the Statistica software (Statsoft Italy, 6.1 version). Only significant main effects or interactions are reported.

3.1. Behavioural Results

Reaction times were analysed by means of a two-way ANOVA with Load (three levels: Single vs. Visual Dual vs. Auditory Dual) and Target Position (three levels: Left Visual Field [LVF] vs. Bilateral vs. Right Visual Field [RVF]) as within-subjects factors. RTs were faster in the Single task (551 ms) compared with those measured in both Dual tasks (Visual: 726 ms, Auditory: 667ms; all ps < 0.001; due to a main effect of load on the target detection task: $F_{(2,38)}= 23.64$, $p < 0.001$, GG $\varepsilon = 0.91$). A main effect of Target Position was also found ($F_{(2,38)}= 3.57$, $p < 0.05$, GG $\varepsilon = 0.72$), RTs being faster for LVF (618 ms) compared with Bilateral (676 ms, $p < 0.05$), but not RVF (552 ms) targets.

Accuracy data were analysed using another two-way ANOVA with Load and Target Position as within-subjects factors. As for RTs, the Load main effect was significant also considering accuracy ($F_{(2,38)}= 10.67$, $p < 0.001$, GG $\varepsilon = 0.80$). Accuracy decreased from 67.23% of Single Task and 66.13% of Auditory Dual Task ($p > 0.05$) to 57.25% of Visual Dual Task (all ps < 0.001). In addition, accuracy was higher for LVF (74.03%) compared with Bilateral (54.45%, p < 0.05) but not RVF (62.13%) targets (Target Position main effect ($F_{(2,38)}= 3.81$, $p < 0.05$, GG $\varepsilon = 0.83$). A significant two-way interaction was also found ($F_{(4,76)}= 3.29$, $p < 0.05$, GG $\varepsilon = 0.68$), suggesting that the accuracy was higher for LVF compared to Bilateral targets in all tasks, whereas for RVF accurate responses were more frequent than Bilateral in the Single Task condition only.

3.2. ERP results

Analyses of ERP components of correct targets (whole group)

As a first step, we analysed the results of the whole sample (20 participants). This analysis included the correct responses only. We performed separate three-way ANOVAs on P1, N1 and N2 time-intervals with the following factors: Load (three levels: Single vs. Dual Visual vs. Dual Auditory), Target Position (three levels: LVF vs. Bilateral vs. RVF) and Laterality (two levels: Left vs. Right hemisphere).

P1 component

The ANOVA carried out in the early time interval corresponding to the P1 component (100-112ms after target onset) revealed a Load by Target Position interaction ($F_{(4,76)}= 2.71$, $p < 0.05$, GG ε = 0.77). However, post hoc analysis did not reveal significant differences among conditions. The significant interaction Target Position by Laterality ($F_{(2,38)}= 5.12$, $p < 0.01$, GG ε = 0.85) showed that LVF targets elicited greater right than left positivity ($p < 0.001$), whereas Bilateral and RVF targets evoked similar, bilateral activation (Fig. 2.3).

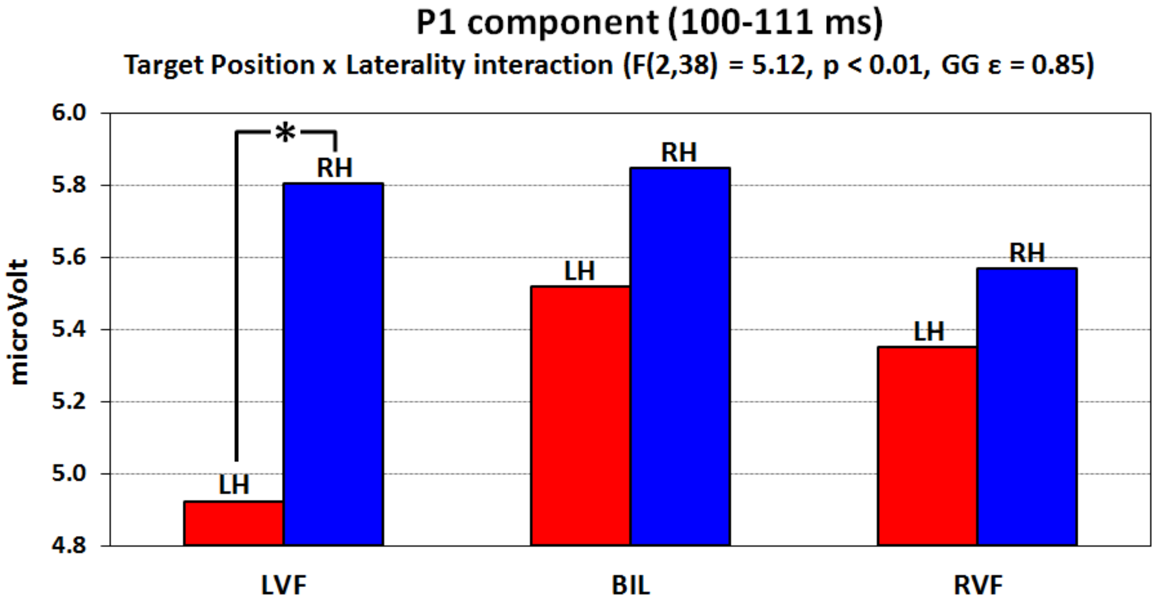


Fig. 2.3. P1 component elicited on posterior sites. Target Position by Laterality interaction. LH = Left Hemisphere; RH = Right Hemisphere; LVF = Left Visual Field targets; BIL = Bilateral targets; RVF = Right Visual Field targets.
* significant post-hoc comparisons.

When considering within-hemispheres differences, greater positivity was measured, in the left hemisphere only, for Bilateral than for LVF targets ($p < 0.01$). No other main effect or interaction was significant.

N1 component

The ANOVA carried out in the time interval corresponding to the N1 component (176-196 ms after target onset) showed a main effect of Load ($F_{(2,38)}= 4.07$, $p < 0.05$, GG $\varepsilon = 0.78$). We found a greater negativity under the Visual Dual Task (-3.10 μV) than under the Single task (-2.04 μV, $p < 0.05$), whereas no differences were found considering the Auditory Dual task (-2.48 μV). The ANOVA also revealed a significant Target Position by Laterality interaction ($F_{(2,38)}= 4.13$, $p < 0.05$, GG $\varepsilon = 0.85$), with increased amplitude for LVF and Bilateral targets in the Left vs. Right hemisphere ($p < 0.001$ and $p < 0.05$, respectively), and a bilateral pattern of activation for RVF targets (Fig. 2.4).

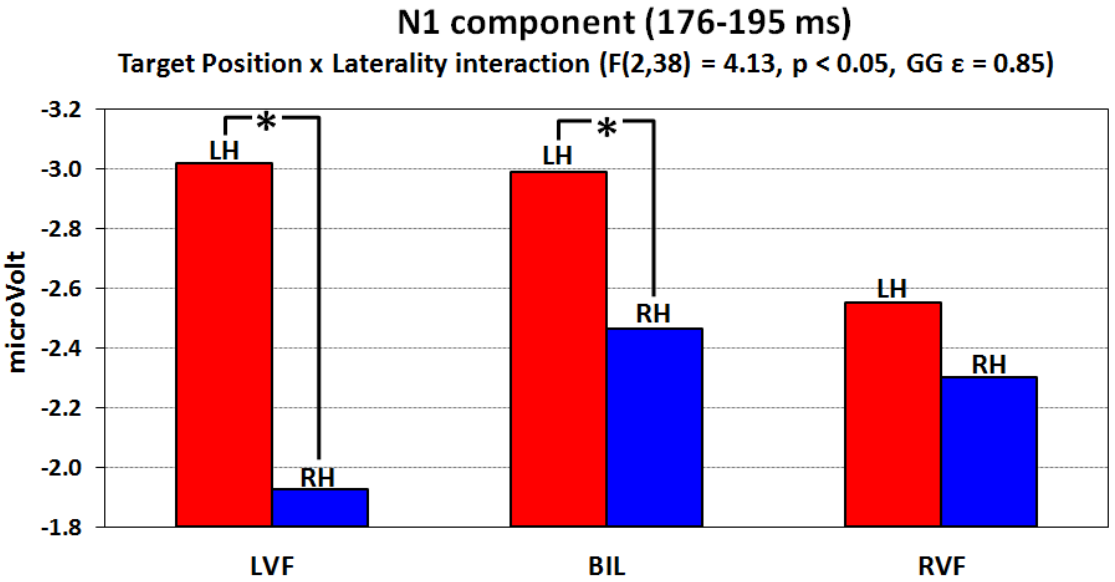


Fig. 2.4. N1 component elicited on posterior sites. Target Position by Laterality interaction. LH = Left Hemisphere; RH = Right Hemisphere; LVF = Left Visual Field targets; BIL = Bilateral targets; RVF = Right Visual Field targets.
* significant post-hoc comparisons.

When considering within-hemispheres differences, greater negativity was measured, in the Left hemisphere, for Bilateral and LVF stimuli compared with RVF targets ($p < 0.05$), and, in the Right hemisphere, for Bilateral stimuli compared with LVF targets ($p < 0.05$).

N2 component

The ANOVA carried out in the time interval corresponding to the late N2 component (281-301 ms after target onset) showed main effects for Load and Target Position ($F_{(2,38)}$= 50.30, $p < 0.001$, GG ε = 0.93, and $F_{(2,38)}$= 3.73, $p < 0.05$, GG ε = 0.80, respectively). Relatively greater negativity was found under Visual Dual (0.05 μV) than Single task (1.26 μV, $p < 0.05$), which, in turn, had significantly greater relative negativity than Auditory Dual task (4.97 μV, all *ps* < 0.001). Moreover, LVF and RVF stimuli (1.94 and 1.88 μV, respectively) elicited relatively higher negative amplitude compared with bilateral targets (2.45 μV, all *ps* < 0.05). In addition, the significant Target Position by Laterality interaction ($F_{(2,38)}$= 5.87, $p < 0.01$, GG ε = 0.89) revealed increased amplitude for LVF and Bilateral targets in the Left vs. Right hemisphere ($p < 0.001$ and $p < 0.05$, respectively), and a bilateral pattern of activation for RVF targets (Fig. 2.5).

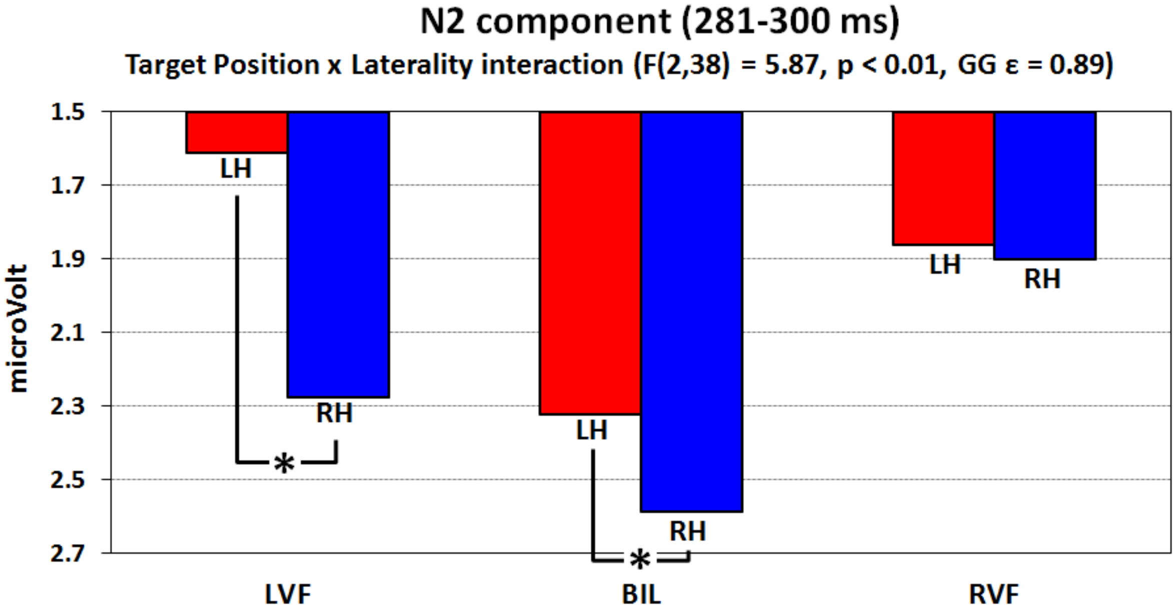


Fig. 2.5. N2 component elicited on posterior sites. Target Position by Laterality interaction. LH = Left Hemisphere; RH = Right Hemisphere; LVF = Left Visual Field targets; BIL = Bilateral targets; RVF = Right Visual Field targets.
* significant post-hoc comparisons.

When considering within-hemispheres differences, greater negativity was measured, in the Left hemisphere, for Bilateral compared with LVF and RVF targets ($p < 0.001$ and $p < 0.01$, respectively), and, in the Right hemisphere, for LVF and Bilateral stimuli compared with RVF targets ($p < 0.01$ and $p < 0.001$, respectively).

Comparison of ERP components for correct vs. error responses to target position (sub-sample of participants)

In these second analyses, we focused on the way visual information has been processed when errors occurred at behavioural level. A sub-sample of twelve participants showed a sufficient number of errors to allow analysing the error responses to targets for the three previously described ERP components (whole group). On the basis of the Load main effect on Accuracy, these analyses only focused on the Visual Dual task, because this was the condition that elicited the greater error rates compared with both Single and Auditory Dual tasks.

Therefore, we carried out three separate three-way ANOVAs on P1, N1 and N2 time-intervals, with the following factors: Target position (three levels: LVF vs. Bilateral vs. RVF), Response (two levels: Correct vs. Error) and Laterality (two levels: Left vs. Right hemisphere).

P1 component

The ANOVA carried out in the early time interval corresponding to the P1 component (100-112 ms after target onset) showed a Target Position main effect ($F_{(2,22)}= 5.48$, $p < 0.01$, GG $\varepsilon = 0.98$). Regardless of whether the response was correct or incorrect, bilateral targets (5.44 μV) elicited greater positivity compared with LVF and RVF stimuli (4.75 and 4.73 μV, respectively; all *ps* < 0.05). In addition, a significant Response by Target Position interaction was found ($F_{(2,22)}= 3.38$, $p = 0.05$). However, post hoc analysis did not reveal significant differences among conditions.

N1 component

The ANOVA carried out in the time interval corresponding to the N1 component (176-196 ms after target onset) revealed a significant Response by Target Position by Laterality interaction ($F_{(2,22)}= 4.76$, $p < 0.05$, GG $\varepsilon = 0.97$). As already seen for the whole group analysis, for correct responses a significant greater negativity in Left than Right hemisphere was present for both LVF and Bilateral targets ($p < 0.001$ and $p < 0.05$, respectively), whereas RVF stimuli elicited a bilateral pattern of activation (Fig. 2.6, red and blue columns). This pattern characterized also error responses (all *ps* < 0.001; Fig. 2.6, red and blue striped columns). However, considering within-hemisphere differences, significantly greater right negativity was found for Correct compared with Error LVF responses in both Left ($p < 0.01$)

and Right hemisphere ($p < 0.05$), and for Error compared with Correct Bilateral response in the Left hemisphere only ($p < 0.01$). Instead, no differences were found for the RVF targets.

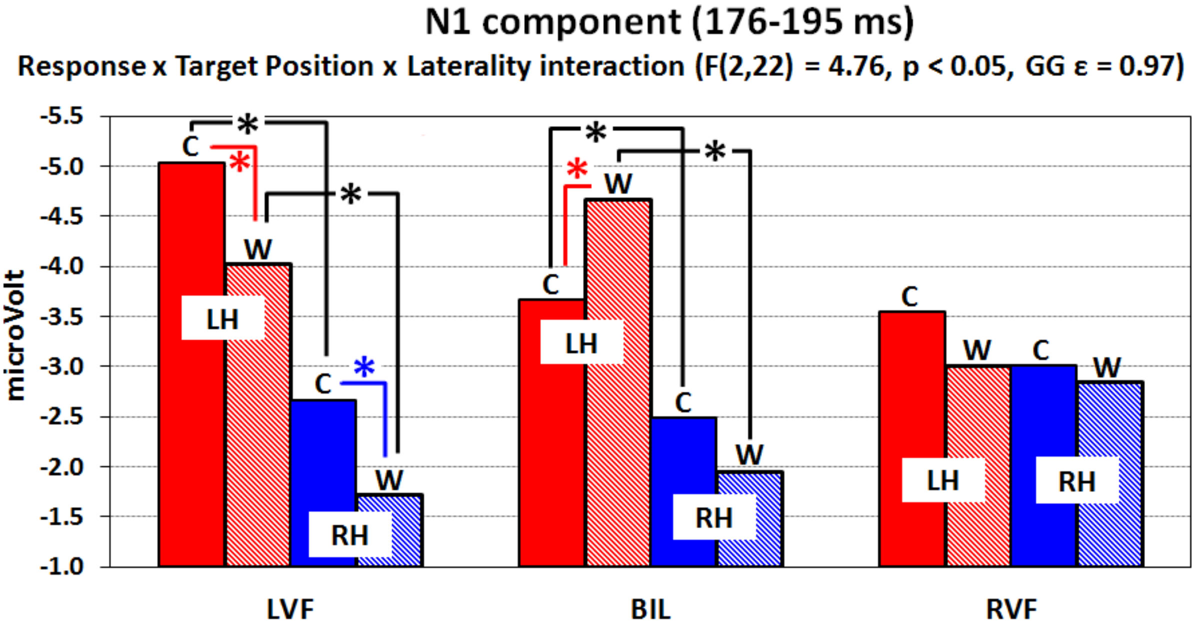


Fig. 2.6. N1 component elicited on posterior sites in the sub-sample (correct vs. wrong responses). Response by Target Position by Laterality interaction. LH = Left Hemisphere; RH = Right Hemisphere; LVF = Left Visual Field targets; BIL = Bilateral targets; RVF = Right Visual Field targets; C = trials corresponding to Correct behavioural responses; W = trials corresponding to Wrong behavioural responses.
* significant post-hoc comparisons.

N2 component

The ANOVA carried out in the time interval corresponding to the late N2 component (281-301 ms after target onset) showed a significant Target Position by Laterality interaction ($F_{(2,22)}$= 5.10, $p < 0.01$, GG $\varepsilon = 0.78$). Again, LVF and Bilateral targets elicited greater amplitude in the Left vs. Right hemisphere (all *ps* < 0.001), whereas RVF had a bilateral pattern of activation. With respect to within-hemisphere differences, greater right negativity was measured for RVF compared with both LVF and Bilateral targets ($p < 0.01$). In addition, the ANOVA revealed a significant Response by Target Position interaction ($F_{(2,22)}$= 3.38, p =0.05, GG $\varepsilon = 0.72$): both LVF and RVF targets elicited higher negativity in Correct compared with Error responses (all *ps* < 0.05; Fig. 2.7).

Moreover, we found greater amplitude for RVF than Bilateral targets in the Correct responses only ($p < 0.05$). No differences were found between type of Responses for Bilateral stimuli.

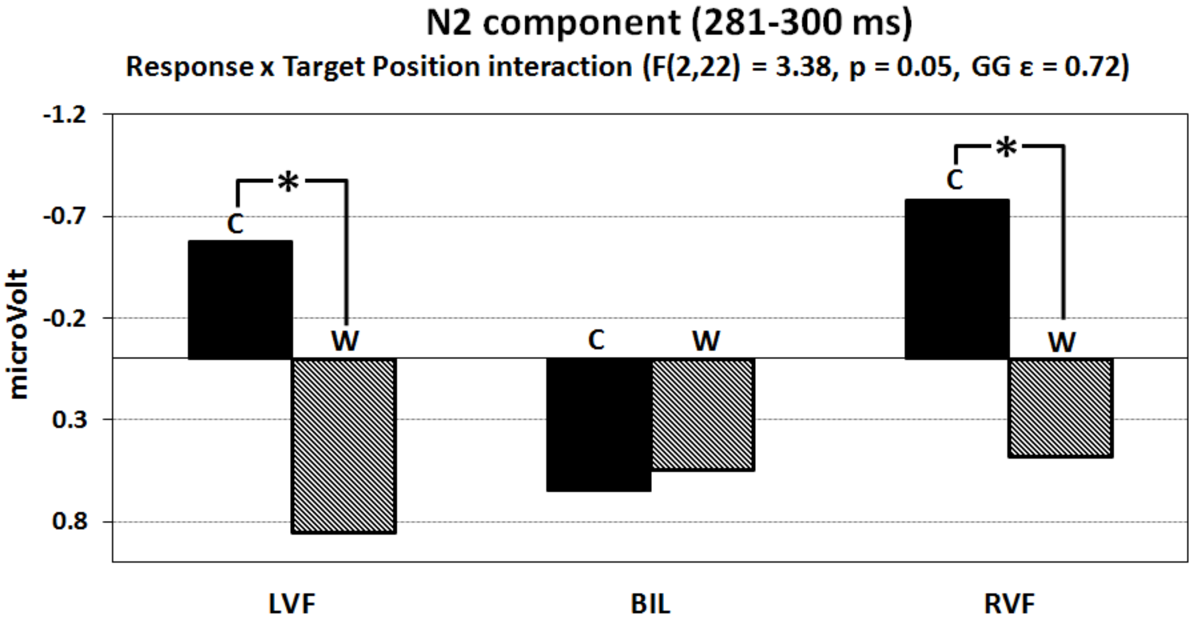


Fig. 2.7. N2 component elicited on posterior sites in the sub-sample (correct vs. error responses). Response by Target Position interaction. LVF = Left Visual Field targets; BIL = Bilateral targets; RVF = Right Visual Field targets; C = trials corresponding to Correct behavioural responses; W = trials corresponding to Wrong behavioural responses.
* significant post-hoc comparisons.

4. Discussion

The present study investigated the neurophysiological correlates associated with the correct and the erroneous processing of lateralized targets appearing within a multitasking context. The methods were based on a paradigm previously validated by Bonato, Spironelli et al. (2015). At the behavioural level, multitasking approach was proven extremely sensitive in detecting severe patterns of contralateral omissions in chronic patients who suffered from a left as well as from a right unilateral stroke. The changes with respect to the previous ERP study aimed to make the perception of the target particularly difficult, and successfully resulted in a substantial number of spatial omissions. In a nutshell, the aim was to recreate – by experimental manipulations – the difficulties in spatial processing experienced by patients during multitasking. To this end, the duration of the target was calibrated according to average performance of the whole group, and added a visual mask. This simple experimental manipulation allowed to analyse not only the automatic ERP components associated with correct target detection (i.e., P1, N1 and N2 components) in a sample of young healthy adults, but also to contrast the electrophysiological patterns of activation elicited by correct and error trials in a sub-sample of participants that showed a significant number of errors on their behavioural performance.

Participants' behavioural data confirmed the effectiveness of multitasking in increasing task demands, with slower RTS to targets in both Dual tasks in comparison to the Single task condition, and lower accuracy in the Visual Dual compared with both Single and Auditory Dual tasks.

Considering the electrophysiological data, the main analyses carried out on correct trials only in the whole group and comparing the three tasks highlighted several correlates of multitasking during spatial processing. As a first, important result, the load effect appeared from the first component (P1) and reached the maximum in the next ERP component, the N1. As in our previous study (Bonato, Spironelli et al., 2015), the Visual Dual task showed a strong load effect in comparison with both the Single and the Auditory Dual task. It is important to point out that not only the lateralized dot(s), but also the other two types of stimuli (i.e., the central shape and the sound) were always presented in all conditions, even when they were task-irrelevant. By only manipulating task instructions and keeping constant the sensory information available to the participants, we therefore obtained a pure measure of the top-down attentional load induced by multitasking. The cross-modal load condition (i.e., Auditory Dual task) included in our paradigm is then useful to disentangle specific visual multitasking effects from a general effect of divided attention on unspecific task demands.

With respect to the previous study (Bonato, Spironelli et al., 2015), in which the load effect was significant in the P1 component interval, in the present work, a load main effect emerged in the N1 component temporal window (not significant in our past work). This shift from P1 to N1 component might be the consequence of the small, but critical, changes adopted in the experimental paradigm that resulted in a drastically more difficult target detection, as documented by a much larger number of omissions, especially in the Visual Dual task. In our previous study, indeed, the accuracy showed a ceiling effect in all tasks and stimulus position, regardless of load effect: in particular, considering the Visual Dual task (i.e., the most complicate multitasking due to the intra-modal competition for attention resources) accuracy greater than 98.1% was found using the standard paradigm (Bonato, Spironelli et al., 2015) and 57% in the current version of the task. Notwithstanding this P1/N1 difference, however, the most important finding was the steady load effect on the Visual Dual task, i.e., the condition in which all task-relevant information required an intra-modal processing, with respect to both the cross-modal analysis (Auditory Dual task) and the simple target detection (Single task).

A second, important result was the steady, different pattern of activation that characterized left vs. right visual field targets (i.e., a posterior lateralization for LVF and a bilateral activation for RVF stimuli). This finding clearly mirrors a genuine neural response to stimuli appearing across different positions, and suggests that the mask we added to our standard paradigm had no effect on automatic ERP analysis of lateralized targets. In line with our previous study with a different sample of participants (Bonato, Spironelli et al., 2015), in the P1 component, only LVF stimuli elicited greater contralateral activation, whereas in all other conditions no differences between hemispheres emerged. In addition, this pattern of activation was not only present in all the ERP components analysed for the whole group, but also in the sub-sample selected for the analysis of correct vs. error responses.

Compared with previous research in which bilateral targets were administered but not analysed (for technical details, see Bonato, Spironelli et al., 2015), in the present study the bilateral key-press response was introduced, allowing to inclusion of bilateral targets in statistical analyses. Thus, the third important finding was the electrophysiological pattern of activation elicited by these stimuli: significantly lateralized, similar – yet less extreme – to the activation triggered by LVF targets. This result might allow to better understand the biased competitive attentional mechanisms present in brain damaged patients suffering from USN. Several neglect patients, after some months from the stroke continue to omit contralesional targets only when an ipsilesional, competing one is concurrently presented (extinction) which is sometimes conceptualized as mild USN (Kaplan et al., 1995). Since bilateral stimuli elicited, in the present study, a pattern of activation similar to that highlighted by LVF targets in the ERP components analysed (i.e., N1 and N2), it is not surprising that a damage of the right hemisphere affects not only LVF, but also bilateral stimulus processing. In addition, taking into account that the pattern of lateralization was less prominent than for LVF targets, we speculate that the condition of bilateral stimuli might become comparatively more complex when the inter-hemispheric attentional imbalance decreases with recovery. A possible explanation is that in the case of bilateral stimuli the activation did not reach the threshold criterion adopted for unilateral stimuli; this subthreshold activation leads to reporting the right stimulus only. Future studies on right-hemisphere damaged patients with different severity of unilateral spatial neglect/extinction will allow us to determine what really happens in the cortical pathway of lateralized and bilateral stimulus processing.

The present research was also aimed at clearly detecting how and when the visual information processing leads to different behavioural (i.e., correct vs. error) responses.

Participants showed significantly lower accuracy in the Visual Dual Task only; accordingly, a sub-sample with a sufficient number of correct responses and errors was selected. Results on the twelve selected participants revealed a clear electrophysiological signature of the error responses at the level of the N1 component, i.e., when stimulus information reaches visuo-associative areas, at least for LVF and bilateral targets. Both these stimulus positions, associated with correct and error responses, elicited the same left-lateralized pattern of activation: however, correct responses to LVF targets were associated with significantly greater N1 amplitude in both left and right posterior regions of interest than LVF target errors. In contrast, correct responses to bilateral targets showed significantly smaller N1 amplitude in left hemisphere than error responses to the same stimuli. It seems as if an under-threshold (LVF) and an over-threshold (bilateral) activation led to erroneous information processing. With respect to RVF target, that always elicited bilateral activation, the difference between correct and error responses was evident on the later ERP component, i.e., the N2. This “delay” in RVF stimulus processing was also found in our previous study, in condition of maximum load effect, i.e., during the Visual Dual task (Bonato, Spironelli et al., 2015). This pattern of results suggests that the mechanism underlying the processing of visual information – within a multitasking context – is based on a threshold criterion: when the critical N1 component amplitude is reached, subsequent processing along the whole pathway leads to a correct behavioural response; in contrast, when the N1 amplitude (LVF targets) or the N2 component amplitude (RVF targets) are under-threshold, as well as when the N1 amplitude reaches a significant over-threshold value (bilateral targets), the subsequent processing leads to a behavioural error. In other words, the electrophysiological signature of stimulus position is already altered about 176-195 ms after target onset, well before the behavioural response (which is completed at least 500 ms later, and around 700 ms for Visual Dual task).

In summary, the present ERP study investigated the multitasking processes involved when spatial processing is performed concurrently with the processing of additional, visual or auditory, stimuli. A task that induced a consistent amount of errors in healthy participants was devised, therefore allowing for a more direct comparison with the omissions shown by brain damaged patients. ERP components mirrored both the effect of multitasking and the presence of asymmetrical brain networks for the processing of lateralized stimuli. The results suggest that ERPs are particularly informative in unveiling the temporal dynamics of complex cognitive processes like those involved in multitasking.

Chapter III

Electrophysiology of resting state networks as a neuropsychological marker

1. Introduction

“Our brain is a network. A very efficient network to be precise.” (van den Heuvel & Hulshoff Pol, 2010).

Over the last decades, the organization of the human brain has been the focus of intense debate among neuroscientists. Ever since the knowledge about brain networking has been diffused in the neuroscience community, a new picture of the brain has emerged, which is based on the concept that spatially independent but functionally connected areas continuously share information with each other (van den Heuvel & Hulshoff Pol, 2010). Consequently, the fundamental question in neuroscientific research has been to understand how large groups of neurons cooperate in the brain and which mechanisms underlie this complex assembling.

At the end of the ’80s, Functional Connectivity (FC) was defined as the temporal dependence of neuronal activity patterns involving spatially distinct brain regions (Aertsen, Gerstein, Habib, & Palm, 1989; Friston, Frith, Liddle, & Frackowiak, 1993). From this moment, neuroimaging studies provided key contributions to the characterization of brain networks in primates and humans. In particular, several studies (Biswal, Yetkin, Haughton, & Hyde, 1995; Greicius, Krasnow, Reiss, & Menon, 2003; Lowe, Dzemidzic, Lurito, Mathews, & Phillips, 2000) started to examine the FC between brain areas during resting state condition. Resting state experiments measure spontaneous fluctuations in brain activity asking participants to relax and not to think of something in particular, for a fixed interval of time. Pioneering studies of Biswal and colleagues (Biswal, Van Kylen, & Hyde, 1997; Biswal et al., 1995) for the first time showed that the brain is not silent during rest, as demonstrated by the correlations between fMRI BOLD time-series in the left and right hemispheric regions of the primary motor network. Later studies (Buckner, Andrews-Hanna, & Schacter, 2008; Buckner & Vincent, 2007; Greicius, Supekar, Menon, & Dougherty, 2009) further investigated intrinsic activity patterns and their correlations between brain regions, confirming and promoting the idea that our brain is never lazy.

While exploring the neuronal organization at rest, several neuroimaging studies provided evidence of functionally linked sub-networks (Beckmann et al., 2005; Damoiseaux et al., 2006; Fox et al., 2005; Fox & Raichle, 2007). Commonly, the term *resting-state networks* (RSNs) is used to describe brain regions that are anatomically independent, but functionally linked. The most interesting characteristic of these networks is that they show high levels of ongoing FC during resting state condition, which might guarantee a better flexibility of brain dynamics by increasing efficiency and speed of network mobilization (Deco, Jirsa, & McIntosh, 2013), or which might partially reflect the full repertoire of functional dynamics emerging during task execution (Smith et al., 2009).

Over last years, RSNs have been explored and described by several research groups (Buckner & Vincent, 2007; Buxbaum et al., 2004; Fox et al., 2005; Fox & Raichle, 2007; Greicius et al., 2003; Raichle et al., 2001; Raichle & Snyder, 2007). Though the number and the spatial organization of RSNs may vary depending on the methodology used to detect them, the most prominent RSNs invariably emerge across methods and studies (Lee et al., 2012). Figure 3.1 depicts fourteen RSNs obtained by Mantini et al. (2013) in a resting state fMRI (rs-fMRI) study on twenty-four healthy subjects. While some RSNs are clearly related to basic sensory and motor processes, others include regions of the associative cortex known to be activated during complex cognitive/behavioural tasks.

Special interest has been devoted to the Default Mode Network (DMN), which includes bilateral inferior parietal lobule (angular gyrus), posterior cingulate/precuneus, bilateral superior frontal gyrus and medial frontal gyrus (Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007). DMN is characterized by increased level of neural activity across its constituent regions during rest, which tends to disappear when a cognitive task is performed (Bullmore & Sporns, 2009; Gusnard & Raichle, 2001; Raichle & Snyder, 2007). Nevertheless, DMN has been described as a network involved in several cognitive processes, such as the mind-wandering (Mason et al., 2007), the integration of cognitive and emotional information (Greicius et al., 2003) and the monitoring of the surrounding environment (Gusnard & Raichle, 2001). It is not surprising that DMN has also a key role in cognitive dysfunctions as observed in psychiatric and neurological disorders (Greicius et al., 2003; Rombouts et al., 2009; Wang et al., 2015; Zhou et al., 2007).

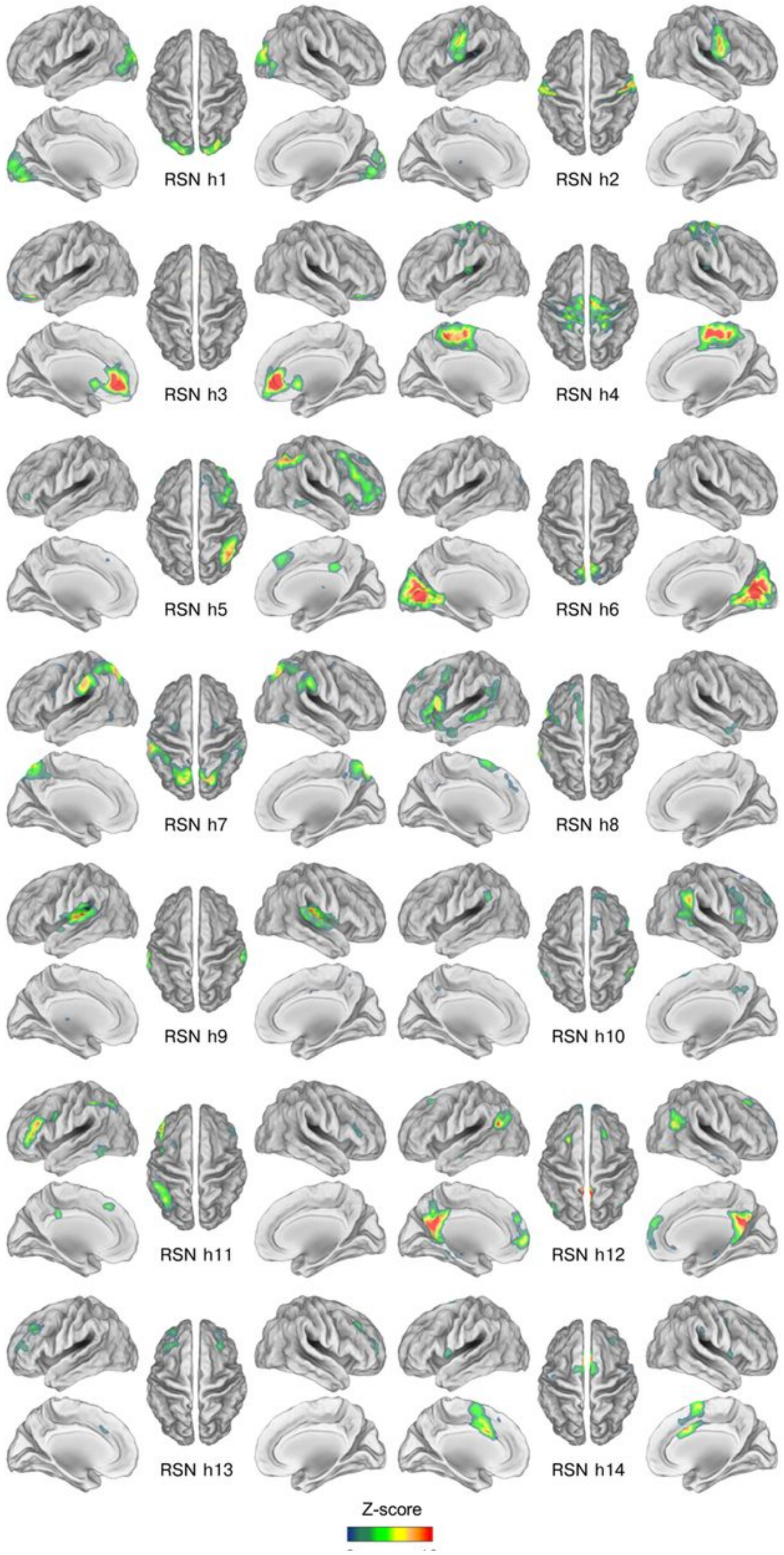


Fig. 3.1. Fourteen fMRI-RSNs maps. The figure from Mantini et al., (2013) shows fourteen maps obtained from twenty-four healthy subjects at rest. RSN h 1: Parafoveal visual; RSN h 2: Ventral somatomotor; RSN h 3: Medial prefrontal; RSN h 4: Dorsal somatomotor; RSN h 5: Right fronto-parietal; RSN h 6: Pheripheral visual; RSN h 7: Dorsal attention; RSN h 8: Language; RSN h 9: Early auditory; RSN h 10: Ventral attention; RSN h 11: Left fronto-parietal; RSN h 12: Default mode; RSN h 13: Lateral prefrontal; RSN h 14: Cingulo-insular.

Anatomical and functional characteristics of the Dorsal Attention Network (DAN) and the Ventral Attention Network (VAN) have been also systematically explored. DAN includes bilaterally the intraparietal sulcus, cortex at the intersection of precentral and superior frontal sulcus near/at the human frontal eye field, ventral precentral, and middle frontal gyrus. It is involved in executive control (Kim, 2010; Mantini et al., 2007) and selective attention processes, especially in visual and spatial domains (Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). In contrast, VAN consists of ventral frontal and parietal cortices, the insular cortex and the caudate regions, and mediates the salience processing (Kim, 2010).

Finally, there is increasing evidence supporting the hypothesis that the Cingulate Opercular Network (CON) is involved in maintenance of task control (Dosenbach et al., 2006, 2007) and tonic alertness (Sadaghiani & D'Esposito, 2015). This network includes anterior insula/operculum, dorsal anterior cingulate cortex, and thalamus.

Functional magnetic resonance imaging (fMRI) is classically used to measure FC within and between brain networks, however the study of the neural organization has also benefited from the contribution of other techniques, such as the electroencephalography. Interestingly, several simultaneous EEG-fMRI studies have shown significant correlations between BOLD signal fluctuations in specific human brain networks and alpha (Goldman, Stern, Engel, & Choen, 2002; Laufs et al., 2006) and beta (Laufs et al., 2003) power in the EEG. However, biophysical evidence demonstrated that neurons can oscillate at different frequency rhythms (Buzsaki & Draguhn, 2004; Llinas, 1988) and various studies have revealed the coexistence of multiple rhythms in the same region or their interaction among different brain areas (Steriade, 2001; Varela et al., 2001). A key contribution has been provided by the study of Mantini and collaborators (Mantini et al., 2007), which investigated the correspondence between neuronal oscillatory processes in different EEG frequency bands and fMRI fluctuations. The analysis were focused on six resting states networks: Default Mode Network; Dorsal Attention Network; Visual Network; Auditory Network; Sensory-motor Network; Self-referential Network. The results, displayed in Fig. 3.2, revealed that each network was characterized by a specific combination of EEG frequency rhythms and, in particular, showed an association between DMN and alpha and beta bands. In contrast, the ventro-medial prefrontal cortex (Self-referential Network) was correlated to gamma power.

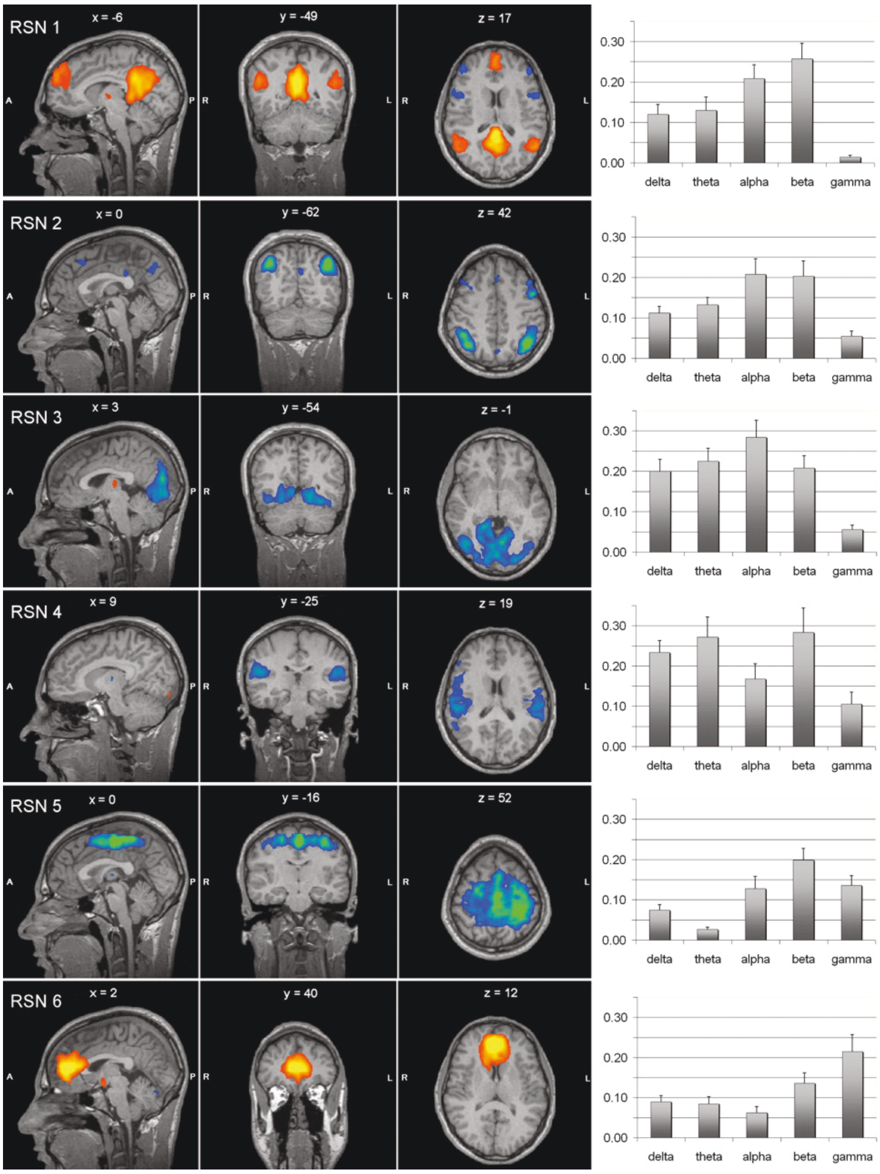


Fig. 3.2. Association between EEG frequency spectrum and Resting State Networks (RSNs). RSN1:Default Mode Network; RSN2:Dorsal Attention Network; RSN3: Visual Network; RSN4: Auditory Network; RSN5: Sensory-motor Network; RSN6: Self-referential Network. (Mantini et al., 2007).

Recently, Liu and collaborators (2017) provided the first empirical evidence that large-scale brain networks can be detected even by only relying on the EEG signal. The same fourteen brain networks previously studied by means of fMRI measures (Mantini et al., 2013) were also reproduced from resting state high-density EEG recordings (256 channels).

The modern conception of the brain as a collection of organized neuronal networks is having important implications also for neuropsychological research. Indeed, it should be noted that specialization and integration are two distinct, but at the same time complementary, mechanisms underlying the structural and functional organization of brain networks (Friston, 2002). This implies that, although we know a fair amount of detailed information about the function of a specific brain region, the information that it processes might be strongly related to the long-range interactions that this area establishes with other regions (Varela et al., 2001). A deeper understanding of how brain areas cooperate has thus important consequences to better elucidate the link between functional connectivity and human behaviour, with the potential to also clarify how network organization can be altered or disrupted in neurological and neuropsychiatric diseases (Baldassarre et al., 2014; Bullmore & Sporns, 2009; Greicius, 2008). For example, it is well known that localized damages to different regions of the brain can cause specific behavioural impairments. However, it has long been known that even the function of brain areas that are far from the lesion site can be modified after a stroke insult (Beis et al., 2004; Carrera & Tononi, 2014; Carter et al., 2010; Hillis et al., 2002; Perani et al., 1987). Interestingly, these physiological transformations show a strong relation with the behavioural deficits caused by a stroke (Baldassarre et al., 2014; He et al., 2007; Hillis et al., 2002; Park et al., 2011; Wang et al., 2010) thereby supporting the view that neuropsychological disorders should be interpreted by also considering the large-scale organization of the brain.

In this respect, a series of recent studies (Carter, Shulman, & Corbetta, 2013; Varsou, Macleod, & Schwarzbauer, 2013) investigated the effects of stroke on the brain networks aggregation using measures of FC at rest. In particular, unilateral spatial neglect has been associated with dysfunctions of the DAN (Carter et al., 2010; He et al., 2007). Baldassare and colleagues (Baldassarre et al., 2014) found abnormal activation patterns, consisting in a decrease in the magnitude of interhemispheric FC, both within DAN, motor and auditory networks. Other evidence showed a strong correlation between resting FC abnormalities in the motor network and motor deficits (Carter et al., 2010, 2012; Chen & Schlaug, 2013; Park et al., 2011; Wang et al., 2010; Yin et al., 2012). Moreover, a recent study explored the functional connectivity profiles for attention and motor impairments following right hemisphere damage (Baldassarre et al., 2016). A double dissociation between abnormal functional connectivity patterns and motor and attention deficits emerged. More specifically, motor deficits were more strongly correlated with abnormal interhemispheric functional connectivity within the motor network than within the DAN in acute phase. In contrast, attention deficits were more strongly correlated with patterns of abnormal interhemispheric functional connectivity within the DAN than within motor networks. In summary, all these studies support the idea that physiological dysfunctions of specific brain networks underlie specific behavioural deficits. This is revolutionizing the way of thinking about deficits post-stroke, inasmuch they do not only depend on lesion site. It has been convincingly shown that deficits in several behavioural domains can be predicted by disruptions of resting state network connectivity (Baldassarre et al., 2016; Siegel et al., 2016). More specifically, decreasing interhemispheric integration and intrahemispheric segregation represents a general marker of the physiological network dysfunction following a stroke.

The debate on the link between human brain organization at rest and behavioural manifestations after brain damage is still open, and the greater challenge is to uncover neural markers that are able to predict the cognitive performance. Indeed, the study of RSNs has provided important insights concerning the functioning and the organization of the human brain when cognitive tasks are not required. However, it is now becoming evident that properties of RSNs can also be used to predict cognitive/behavioural outcomes, thus motivating a deeper investigation of the relation between spontaneous brain activity and task-related performance. From a clinical point of view, the possibility to compare and integrate neurofunctional and neuropsychological data could also be very informative in order to optimize the prognosis of functional recovery from stroke.

In order to contribute to this research topic, in this chapter we present an in-depth correlation analysis between RSNs and behavioural indices in brain damaged patients. An important aspect to consider is to define which are the best behavioural measures to include in this investigation. The classical batteries for cognitive evaluation consist of several tests that are commonly used to assess the presence of deficits in multiple domains (i.e., attention, memory, language, general cognitive functioning). On the other hand, it has been demonstrated that a multitasking approach is more sensitive than paper-and-pencil tests in uncovering spatial deficits both in left and right hemisphere damaged patients (Blini et al., 2016; Bonato et al., 2010; Bonato, Priftis, et al., 2012), as further documented in Chapter 1 of the present thesis. For this reason, two correlation analyses were performed, including classical neuropsychological measures and Load indices obtained administering our multitasking paradigm.

Notably, until now this type of analysis has been performed using fMRI measures (e.g., Baldassarre et al., 2014, 2016; Siegel et al., 2016). Here we build on the state-of-the-art approach of Liu et al. (2017) in order to extract RSNs from the electrophysiological signal. Resting state (10 minutes) was recorded using EEG (64 channels) in a group of chronic left and right hemisphere damaged patients. FC analysis was performed by using a 12-layer head model, low-resolution brain electromagnetic tomography source localization (eLORETA) and independent component analysis (ICA). As in the study of Liu et al. (2017), our analysis identified 14 brain networks overlapping with those previously showed in fMRI studies (Mantini et al., 2013).

EEG-RSNs time-courses were then correlated with several behavioural indices. The first analysis included 32 patients and five neuropsychological indices: total score for Behavioural Inattention Test (BIT); total score for Function Independence Measure (FIM); cognitive index of FIM; motor index of FIM; Attentional matrices. The second analysis concerned the correlation between EEG-RSNs time-courses and Load indices in a group of 19 patients who were administered our multitasking paradigm. Patients were asked to detect peripheral stimuli with and without a secondary concurrent task (Visual Dual Task vs. Auditory Dual Task; see Chapter 1 for details). The correlation analysis was initially carried out within each brain network considering a wide frequency interval (1-80 Hz). However, FC analysis was also performed on power in specific frequency ranges: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-80 Hz).

In summary, the present study examined the link between intrinsic brain activity and behaviour to investigate whether the integration of specific areas within a brain network can explain the presence of neuropsychological deficits. The novelty of our study stems from the use a sophisticated methodological approach to investigate human brain networks by means of electroencephalography, validating the recent method of Liu et al. (2017) in a clinical setting and with a much more limited number of electrodes.

2. Materials and methods

Participants

Thirty-two chronic stroke patients took part in the study. All participants (mean age: (mean age= 60.06 years; DS= 11.06; mean education level= 11.66 years, SD=4.11), of which 9 left hemisphere damaged (LHD) patients and 23 right hemisphere damaged (RHD) patients, were admitted to the San Camillo Hospital to receive neurocognitive rehabilitation. All patients were in the subacute to chronic phase (minimum time from onset: 52 days, see Tab. 3.1). Inclusion criteria for the study were: presence of unilateral hemispheric damage (first episode), absence of history of neurodegenerative disorders and of substance abuse. The study was approved by the regional Ethics Committee (Comitato Etico per la Sperimentazione Clinica della Provincia di Venezia e IRCCS San Camillo; protocol n. 2014.09). All participants gave their written informed consent to take part in the experiment, in accordance to the principles of the Declaration of Helsinki. According to a standard questionnaire (Oldfield, 1971), participants were right-handed and presented normal or corrected-to-normal vision. Detailed information is provided in Tab. 3.1.

Patient	Sex/Age/ Education (ys)	Lesion side	Lesion site	Etiology	Handedness	Double Simultaneous Stimulation	Lesional Volume (cc)	Time from stroke (days)
1	M/46/8	LH	C	H	R	-	32	133
2	F/49/13	LH	Ta	H	R	-	8	339
3	M/60/13	LH	Ta;C	H	R	-	7	2665
4	M/56/13	RH	C; T	I	R	-	n.a.	93
5	F/68/5	RH	C	H	R	-	11	133
6	F/79/5	RH	C	I	R	+	19	82
7	F/43/8	RH	C	H	R	+	46	173
8	M/47/13	LH	BG	H	R	-	55	52
9	M/41/13	LH	T	I	R	-	32	380
10	M/59/13	RH	F;T	H	R	-	77	2506
11	F/63/13	RH	Ta	H	R	+	134	694
12	M/72/13	RH	C	H	R	-	7	93
13	M/58/16	RH	O;P	I	R	+	170	259
14	M/67/13	RH	MCA	I	R	-	n.a	160
15	M/69/13	RH	MCA	I	R	+	194	84
16	F/65/17	RH	F;P	H	R	+	n.a.	697
17	M/51/13	RH	T;C	I	R	-	n.a.	77
18	M/49/8	RH	BG	H	R	-	35	111
19	M/42/18	LH	T;I	I	R	-	52	749
20	M/69/8	LH	Ta;C	I	R	-	7	88
21	M/79/5	RH	O	I	R	-	2	352
22	M/57/8	RH	F;P	I	R	+	153	101
23	F/72/5	RH	F;P	H	R	-	131	170
24	M/73/5	RH	BG	I	R	-	44	130
25	M/45/13	LH	T;P	H	R	-	73	317
26	M/68/18	LH	P;O	I	R	+	155	71
27	M/62/13	RH	T	I	R	-	98	156
28	M/58/17	RH	T; I	I	R	+	312	71
29	F/56/18	RH	MCA	H	R	+	185	187
30	M/56/8	RH	F;P	I	R	-	n.a.	106
31	M/75/13	RH	P	I	R	-	62	104
32	M/68/13	RH	P	I	R	-	130	1294

Tab. 3.1. Demographical and neurological data. M/F: male, female; Lesion site: F= frontal; O=occipital; P=parietal; T=temporal; BG=basal ganglia; C=capsula; I=insula; MCA= middle cerebral artery; Pu=putamen; Ta=thalamus. I/H: ischemic, hemorrhagic; R: Right-handed. +/-: presence, absence of contralesional omissions. n.a.: data not available.

Neuropsychological Assessment

In order to assess the cognitive performance in multiple domains, all patients underwent an in-depth neuropsychological assessment (see Tab. 3.2).

The Functional Independence Measure (FIM) (Linacre, Heinemann, Wright, Granger, & Hamilton, 1994) was administered to quantify the severity of disability of all patients. The battery consists of 18 items and provides two clinical indices: a motor index (13 items) and a cognitive index (5 items). Each index was scored separately, and contributed to a global score. Higher scores indicate higher level of independence. In order to assess visuo-spatial abilities the Behavioural Inattention Test (BIT, (Wilson et al., 1987) was administered. The evaluation included the conventional part of the BIT, consisting of: lines, letters, and stars cancellation, line bisection, figure copy and spontaneous drawing. Though each subtest provides an individual score, in the present study we considered only the overall BIT. According to the overall BIT scores, 8 RHD patients showed signs of neglect. Attentional matrices (Spinnler & Tognoni, 1987) were also administered to assess selective attention deficits. This task is a digit cancellation test consisting of three different matrices. Patients had 45 seconds to bar the digit(s) printed at the top of each matrix (1 target in the first matrix, 2 targets in the second matrix and 3 targets in the last matrix). Raven's test evaluated general cognitive abilities free of verbal interference and consists of 36 coloured matrices. Patients were asked to identify the missing item in a series of figural patterns, without time constraints. The items are grouped in sets and they are presented in ascending difficulty order. A global score that expresses the overall number of correct responses was computed. For all patients the presence of contralesional omissions/extinction was assessed using the Double Simultaneous Stimulation test (Làdavas, 1990). Contralateral or bilateral omissions emerged in 10 RHD patients. Neuropsychological data are displayed in Tab. 3.2.

Patient	**BIT Cut-off: <130**	**FIM (max 126)**	**FIM motor index (max 91)**	**FIM cognitive index (max 35)**	**Attentional matrices Cut-off: <30**	**RAVEN Cut-off: 18.96**
1	142	39	17	22	43/39	31/32.8
2	146	84	58	26	43/37.75	34/31.8
3	138	86	55	31	52/52	31/29.8
4	142	95	63	31	34/27.75*	32/30.3
5	143	80	53	27	47/40.5	35/38.9
6	98*	40	21	19	19/27	10/15.2*

7	140	47	26	21	34/27.75*	40/36
8	136	29	18	11	45/37.5	29/26.3
9	145	107	79	28	38/27.75	35/31.8
10	144	116	81	35	50/43.5	29/21.5
11	140	89	57	32	52/50.75	27/26.4
12	138	84	58	26	46/43.75	33/33.2
13	124*	56	29	27	31/22*	28/25.2
14	118*	55	26	29	29/25.25*	21/20.4
15	142	97	66	31	52/49.75	33/33.1
16	102*	73	40	33	22/14.25*	27/24.7
17	145	118	91	27	53/41.25	32/28.1
18	143	104	75	29	49/43	30/30.3
19	142	112	80	32	48/33.25	36/36
20	144	119	89	30	42/41.25	33/35.6
21	137	69	43	26	35/39.75	16/22
22	66*	88	58	30	22/17.5*	27/27.8
23	71*	80	51	29	16/20.05*	17/21.5
24	125*	111	84	27	34/37.75	26/31.2
25	145	98	75	23	34/26.5*	34/31.3
26	138	103	72	31	27/20.75*	20/18.4*
27	145	109	83	26	36/31	31/29.8
28	107*	53	23	30	37/28*	29/26.2
29	144	84	49	35	57/49	33/29.6
30	141	74	42	32	38/33.5	28/28.8
31	139	56	28	28	25/24.25*	24/24.8
32	141	65	30	35	42/42.25	31/31.1

Tab. 3.2. Neuropsychological assessment. BIT (Behavioural Inattention Test, (Wilson et al., 1987): global scores. FIM (Functional Independence Measure, (Linacre et al., 1994): global scores and raw scores at two subscales: motor index and cognitive index. Attentional matrices (Splinner e Tognoni, 1987): raw scores/age and education corrected scores. Raven's progressive matrices (Carlesimo et al., 1996): raw scores/age and education corrected scores Across all tasks, age and education corrected scores *: performance below cut-off.

Scores obtained from BIT, FIM, cognitive index of FIM, motor index of FIM and Attentional matrices were included in the first correlation analysis within 14 EEG-RNSs in a group of 32 patients.

19 out of 32 patients, with no signs of neglect or visual field deficits at the neuropsychological testing, performed also a computerized multitasking paradigm consisting

in three experimental conditions: Single Task, Visual Dual Task and Auditory Dual Task (for details see Chapter 1). In the Single Task patients had to monitor the position of peripheral stimuli that could be appear on the left or on the right side of fixation, or bilaterally. In some trials, no stimulus was presented on the screen (Catch trials). In Dual Tasks conditions (Visual vs. Auditory), a second concurrent task was performed in addition to the simple spatial monitoring. For the second analysis carried out in this study, six indices were computed. Specifically, two Load cost indices were computed subtracting the global accuracy (in percentage) in Visual and Auditory Dual Task from accuracy in Single Task. Therefore, two scores were obtained corresponding to Visual cost and Auditory cost indices, respectively (see Fig. 3.3 for a graphical representation). Positive values indicate the presence of cost in accuracy induced by increased attentional load.

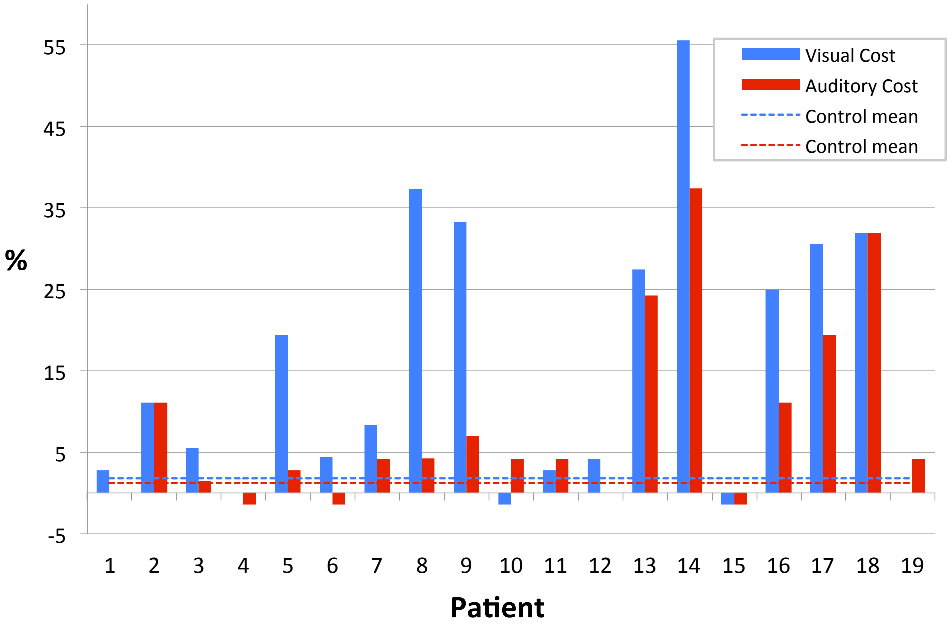


Fig. 3.3. Visual and Auditory Cost Indices for 19 stroke patients. Dashed lines represent the mean cost indices for a group of 13 healthy controls (same participants tested in Chapter 1) for visual (blue line; mean = 1.6) and auditory (red line; mean = 1.4) conditions.

Moreover, the presence of spatial biases during targets detection was assessed by means of Asymmetry Indices that showed how errors were spatially distributed among the three different task conditions (for details, see the Asymmetry Indices section in Chapter 1). AIs reveal which response (Left vs. Right) prevailed among errors, subtracting the proportion of "left" responses from the proportion of "right" responses both for unilateral and bilateral trials. Positive values represent a rightward bias, while negative values index a leftward bias. In the present study, AIs for Catch trials were not considered because patients were highly accurate in reporting the absence of stimuli in all task conditions. For bilateral and unilateral AIs the cost indices were computed by subtracting AIs in Single Task from AIs in Visual and Auditory Dual Tasks. Therefore, four indices were obtained: AI-Visual Cost for unilateral targets; AI-Visual Cost for bilateral targets; AI-Auditory Cost for unilateral targets; AI-Auditory Cost for bilateral targets. As previously reported in the second study of Chapter 1, LHD patients always showed leftward bias (negative scores), while RHD patients showed a rightward bias (positive scores). In order to measure the relative difference in bias size under multitasking compared to Single Task, all cost indices were computed considering absolute values of AIs. Thus, these indices do not reveal the direction of the bias, but rather express how much the bias changes between single and dual task conditions. Positive scores index an increase in AI induced by multitasking. All Load cost indices for AIs are showed in Fig. 3.4.

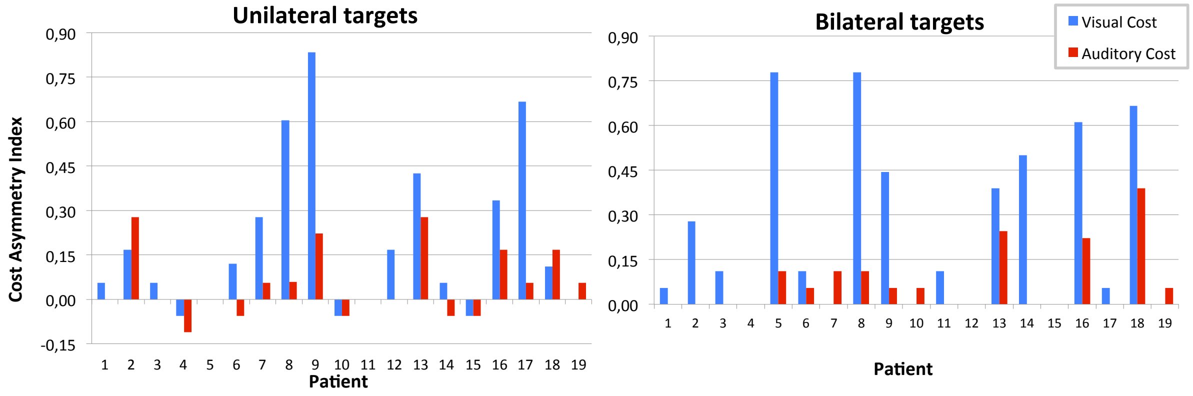


Fig. 3.4. Asymmetry Indices - Visual and Auditory Cost for 19 stroke patients. Left panel shows asymmetry costs for unilateral targets, right panel shows asymmetry costs for bilateral targets.

Brain lesion segmentation

MRI scans were available for 9 LHD and 18 RHD patients. An automated lesions segmentation was performed using LINDA software (Pustina et al., 2016) and the resulting lesion mask was visually inspected at least by two researchers under the supervision of a neurologist. Whenever necessary, lesion masks were manually corrected using ITK-snap software. Individual scans were reoriented and then normalized to an age-appropriate template brain using FSL. MRIcron was used to obtain the overlay of the lesions (Fig. 3.5) for the whole group and the maximum overlap (7 patients) occurred in the white matter adjacent to the putamen (MNI: X= -27, Y= -12, Z=116) for LHD. For RHD group the maximal overlap (17 patients) occurred in the putamen (MNI: X=30, Y= -15 to -16, Z=78).

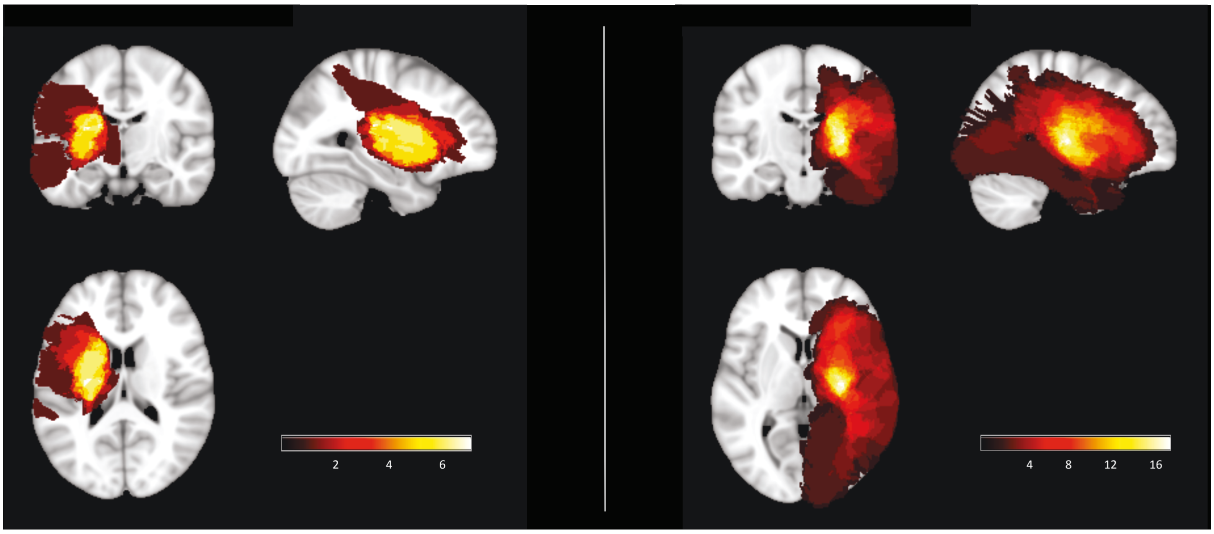


Fig. 3.5. Lesion overlays. The lesion mapping, normalized to a template of aged healthy individuals, is shown as an overlay on a standard template using MRIcron (Rorden & Brett, 2000). The different colors code for the number of overlapping lesions from dark red (minimal/no overlap) to white (maximal overlap).

Data Collection

All electrophysiological data were collected at the San Camillo Hospital (Lido-Venice, Italy) in a dedicated lab. Resting state EEG was recorded for 10 minutes for each patient. Data were acquired using an elastic cap (Acticap, BrainProducts) consisting of 64 channels according to the International 10-20 system (Oostenveld & Praamstra, 2001). The sampling rate was set at 500 Hz and the impedance was kept below 5 kΩ. During the EEG recording, patients were asked to keep their eyes open and to fixate the centre of a computer monitor in order to reduce eye movements.

Method for EEG RSNs Detection

We employed the method of Liu and collaborators (Liu et al., 2017) for EEG networks detection. The pipeline of analysis, displayed in Fig. 3.6, consists of 4 steps: 1) Data preprocessing; 2) Volume conduction model creation; 3) Brain activity reconstruction; 4) Connectivity analysis.

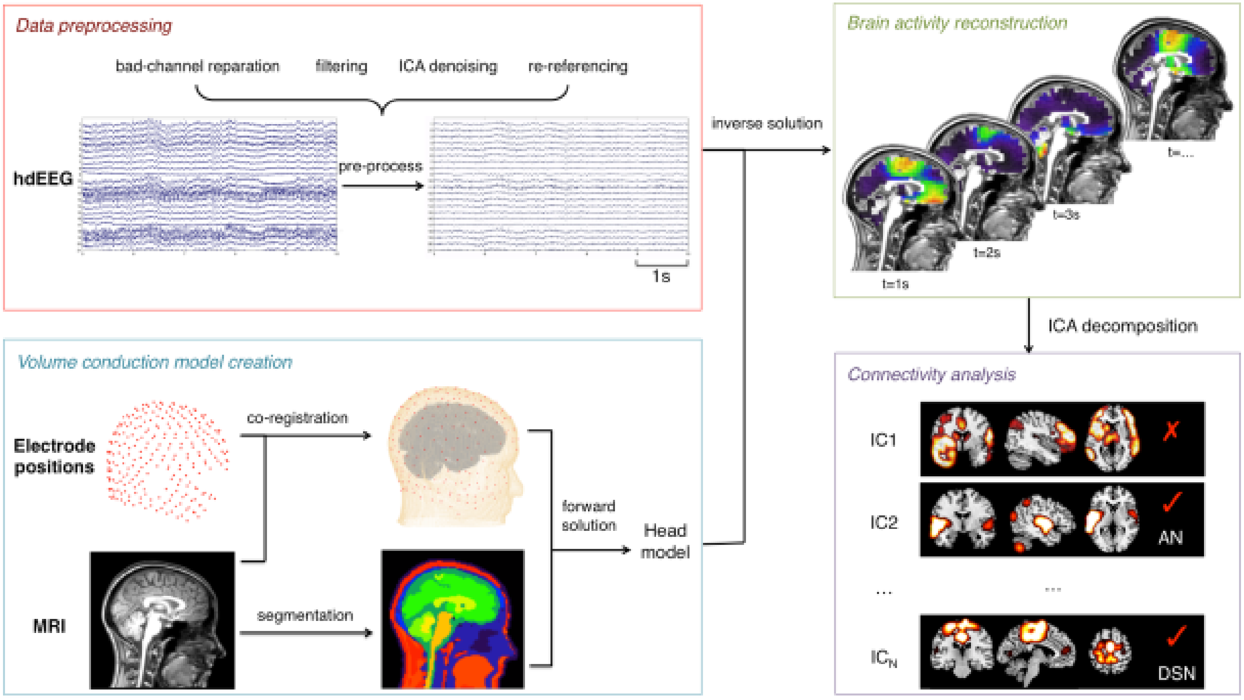


Fig. 3.6. Pipeline for obtaining RSNs from hdEEG recordings. The main analysis steps include: 1) Data preprocessing, involving bad-channel detection, filtering, ICA-denoising, and re-referencing; 2) Volume conduction model creation, involving electrodes co-registration, MRI segmentation and forward modeling solution; 3) Brain activity reconstruction, to estimate the distribution of active brain sources that most likely generates the potentials measured over the hdEEG sensors; 4) Connectivity analysis, extracting ICs from the power time series of voxels and selecting the components associated with large-scale brain network activity. Figure from Liu et al., (2017).

Data preprocessing

Data preprocessing pipeline includes state-of-art techniques in order to identify and reduce noise and artifacts that are usually mixed in the data. The first step was the detection of “bad channels” using an automated procedure that takes into account: 1) the minimum Pearson correlation of the signal in a wide frequency band (1-80 Hz) against all signals from all other channels; 2) the noise variance. Bad channels were interpolated by means of FieldTrip toolbox (http://www.fieldtriptoolbox.org) that considers information from the neighbouring channels. Second step was the removal of muscular and ocular artifacts using a band-pass filter in the frequency range 1-80 Hz (Mantini, Franciotti, Romani, & Pizzella, 2008). Later, independent components (ICs) were extracted using the FastICA algorithm (http://research.ics.aalto.fi/ica/fastica) and the artifactual ICs were automatically identified. After artifact rejection, EEG signal was re-referenced using an average reference approach.

Volume conduction model creation

The following procedure was used to obtain a volume conductor model using a standard MR image and to estimate correct electrodes positions with respect to it. Through three steps, EEG channels were coregistered to MNI space. First of all, predefined Montreal Neurological Institute (MNI) coordinates were projected to individual space in order to estimate the positions of three landmarks (nasion, right and left preauricolar) in the MRI image. After that, the three landmarks in electrode space were matched to the corresponding landmarks in MNI space. Electrode positions were aligned to the surface of the head extracted from the MR image by means of the Interactive Closest Point (ICP) registration algorithm (Besl & McKay, 1992). For the generation of the head model 12 tissue classes were used: skin, eye muscle, fat, spongy bone, compact bone, cortical/subcortical grey matter, cerebellar grey matter, cortical/subcortical white matter, cerebellar white matter, cerebrospinal fluid and brain stem).

Brain activity reconstruction

Brain activity reconstruction in source space was performed considering the preprocessed EEG data and the volume conduction model. The method used was the exact low-resolution brain electromagnetic tomography (eLORETA) (Pascual-Marqui et al., 2011). Because of the signal transmission delays between distant brain areas (Deco, Jirsa, & McIntosh, 2011), all power time series was downsampled to 1 Hz according to MEG connectivity studies (Brookes et al., 2011). This is a convenient procedure because it allows an accurate detection of coherent fluctuations of band-limited power.

Connectivity analysis

Brain network detection was obtained by means of temporal ICA on the reconstructed power time course (Calhoun, Adali, Pearlson, & Pekar, 2001). For this step, FastICA algorithm was run 10 times. ICA generates a series of ICs consisting in spatial maps and an associated time-course. A template-matching procedure was used for the selection of the EEG RSNs. The templates were warped in the MR space and a Pearson correlation was computed to estimate the similarity between EEG-ICs and the template RSN maps. As last step, for each template map the best EEG-ICs match was extracted.

All these procedures allowed to reconstruct the power of oscillatory activity for all participants. Successively, band-limited powers were reconstructed in the whole brain source space, transformed in MNI space using SPM software and concatenated across subjects.

Therefore, temporal ICA was used for the functional connectivity analysis. This last analysis calculated the power in a wide frequency band (1-80 Hz), but also separately for delta band (1-4 Hz), theta band (4-8 Hz), alpha band (8-13 Hz), beta band (13-30 Hz) and gamma band (30-80 Hz). For the EEG-RSNs detection an fMRI-RSNs template was used (Mantini et al., 2013) consisting of 14 networks: default mode network (DMN), dorsal attention network (DAN), ventral attention network (VAN), right fronto-parietal network (rFPN), left fronto-parietal net- work (lFPN), language network (LN), cingulo-opercular network (CON), auditory network (AN), ventral somato-motor network (VSN), dorsal somatomotor network (DSN), visual foveal network (VFN), visual peripheral net- work (VPN), medial prefrontal network (MPN), and lateral prefrontal network (LPN).

Statistical analysis

Two separated analyses were carried out using the SPM software. The first one included 5 neuropsychological scores (BIT; FIM; motor index of FIM; cognitive index of FIM and Attentional matrices (raw scores)) in the group of 32 patients. In the second analysis 6 Load indices were considered (Visual cost; Auditory cost; AI Visual cost for unilateral targets; AI Visual cost for bilateral targets; AI Auditory cost for unilateral targets; AI Auditory cost for bilateral targets) for the group of 19 patients who performed the computerized multitasking paradigm. For each group analysis, linear regressions were performed considering as predictors each EEG-RSN time-course, and as dependent variables the neuropsychological and Load indices. The first analysis was performed on the wide frequency band (1-80 Hz), producing a correlation map expressed in terms of T-scores. Local clusters were then identified by only considering regions showing a significant correlation ($p \leq 0.05$, FDR corrected for multiple comparisons) and containing at least 50 adjacent voxels. For each cluster identified within a particular network for the band 1-80 Hz, linear regressions were repeated by separately considering the contribution of each of the 5 EEG frequency bands.

3. Results

The Results section is organized as follow. First, EEG-RSN maps obtained using temporal ICA in the wide frequency band (1-80 Hz) are presented in order to show the correspondence with the fMRI-RSNs template. Then, the results of the first analysis are presented, showing for each EEG-RSN significant clusters of voxels identified and their correlation with the neuropsychological indices. Finally, the results of the second analysis concerning Load indices are presented. T-scores and probability levels are reported for each significant result.

EEG-RSN maps detection

Temporal ICA was applied to reconstruct RSN maps in the full frequency band corresponding to 1-80 Hz interval. While spatial ICA is commonly preferred in fMRI studies, temporal ICA is a convenient approach in case of EEG/MEG connectivity analysis (Brookes et al., 2011). Figure 3.7 shows the detection of 14 RSNs in the group of 32 chronic stroke patients and reveals a successfully match with the EEG-RSN maps obtained using temporal ICA by Liu et al., (2017) (Fig. 3.8).

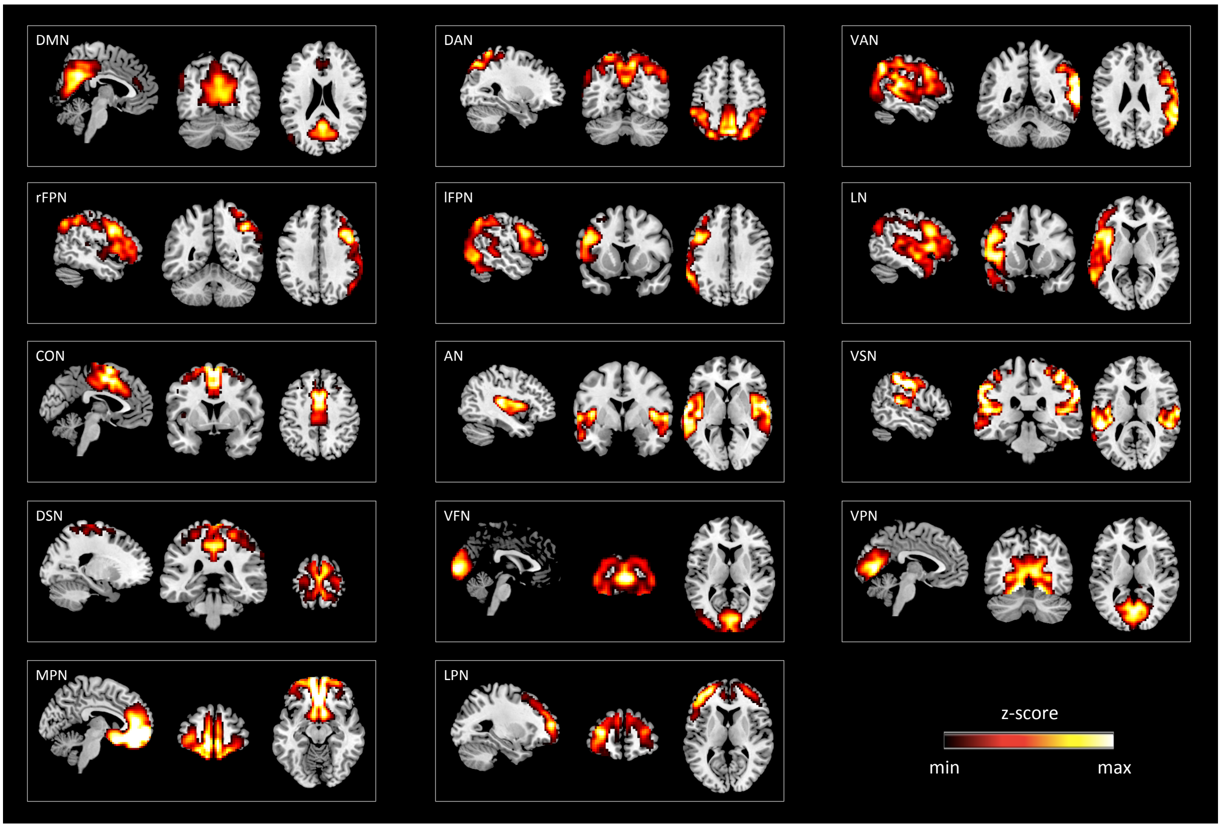


Fig. 3.7. Large-scale networks reconstructed using temporal ICA from wide-band EEG signals (64 channels). EEG-RSNs were selected and labelled on the basis of the spatial overlap with fMRI-RSN: DMN, DAN, VAN, rFPN, lFPN, LN, CON, AN, VSN, DSN, VFN, VPN, MPN and LPN. Group-level RSN maps (N= 32) were thresholded at z >2 for visualisation purposes.

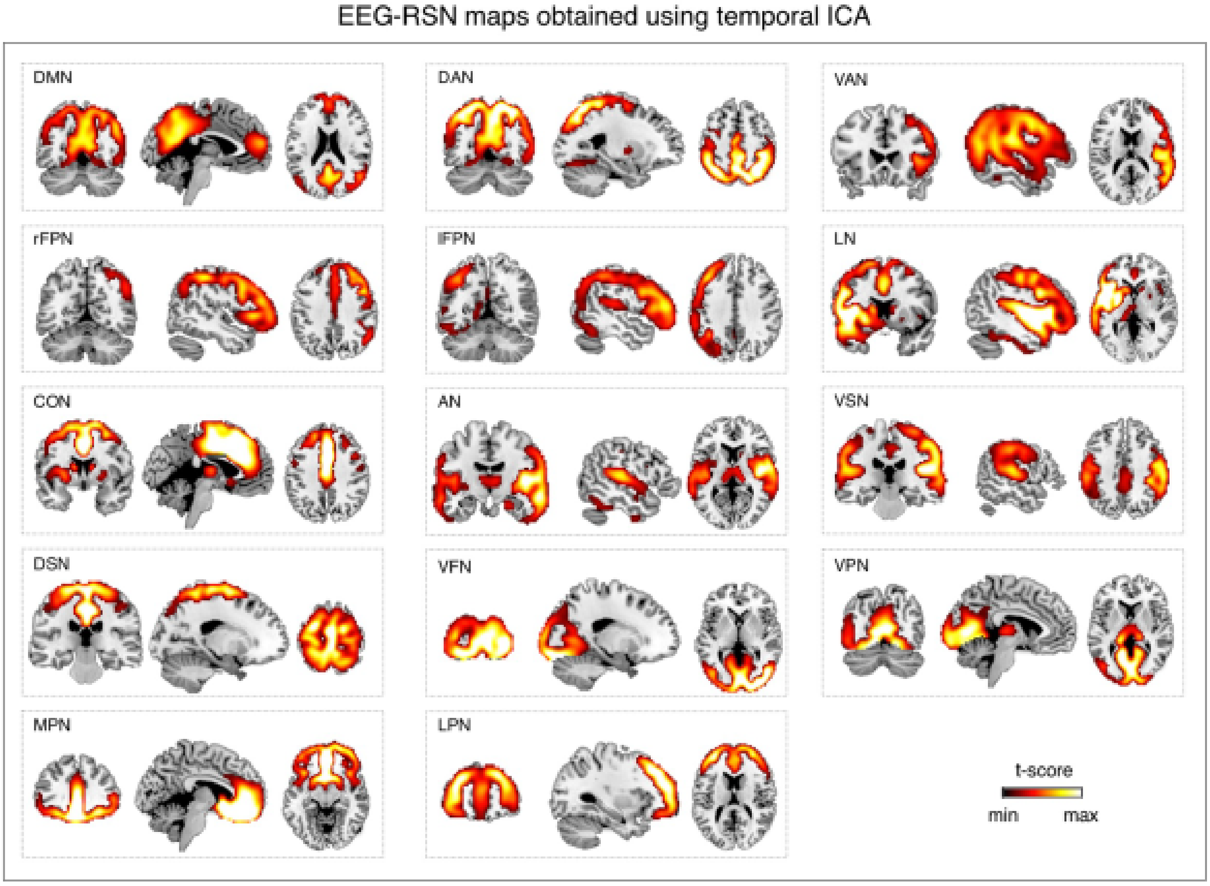


Fig. 3.8. Large-scale networks reconstructed using temporal ICA from wide-band EEG signals (256 channels). Figure from Liu et al. (2017). EEG-RSNs were selected and labelled on the basis of the spatial overlap with fMRI-RSN: DMN, DAN, VAN, rFPN, lFPN, LN, CON, AN, VSN, DSN, VFN, VPN, MPN and LPN. Group-level RSN maps (N= 19) were thresholded at P < 0.01 TFCE-corrected.

Correlation between EEG-RSNs and neuropsychological indices

BIT

The analysis carried out on the global BIT score showed a significant negative correlation with two clusters of voxels (MNI coordinates: X= -49; Y=5; Z=31; and X=-44; Y=-44; Z=44; respectively) that are part of the lFPN (t = -2.48, p = 0.009 FDR-corrected and t = -2.43, p = 0.010 FDR-corrected, respectively), when the wide EEG band (1-80 Hz) was considered. The first cluster corresponds to the precentral gyrus of the Left Hemisphere (LH) and the second cluster is located in the inferior parietal gyrus (LH). Moreover, when each EEG frequency band was considered, this negative correlation was also found in beta and gamma for the first cluster (t = -1.71, p = 0.048 FDR-corrected and t = -2.95, p = 0.003 FDR-corrected, respectively) and for the second cluster (t = -2.38, p = 0.011 FDR-corrected and t = -3.30, p = 0.001 FDR-corrected, respectively). The significant T-score indicates that the higher is the integration of these clusters within lFPN, the lower is the BIT score.

Cognitive index of the FIM

For the full band analysis, a significant negative correlation emerged between the cognitive index of FIM and a cluster of voxels located in DAN (t = -2.25 FDR, p = 0.015 FDR-corrected). The node identified corresponded to the inferior temporal gyrus (MNI coordinate: X=54; Y=-60; Z=-12) of the Right Hemisphere (RH). Considering individual EEG rhythms, a negative correlation was also found within beta frequency range (t = -2.25, p = 0.015 FDR-corrected). These results suggest that, both for full and beta band, when the cluster in well integrated within DAN the cognitive score of FIM is lower.

No significant correlations emerged for the other EEG-RSNs.

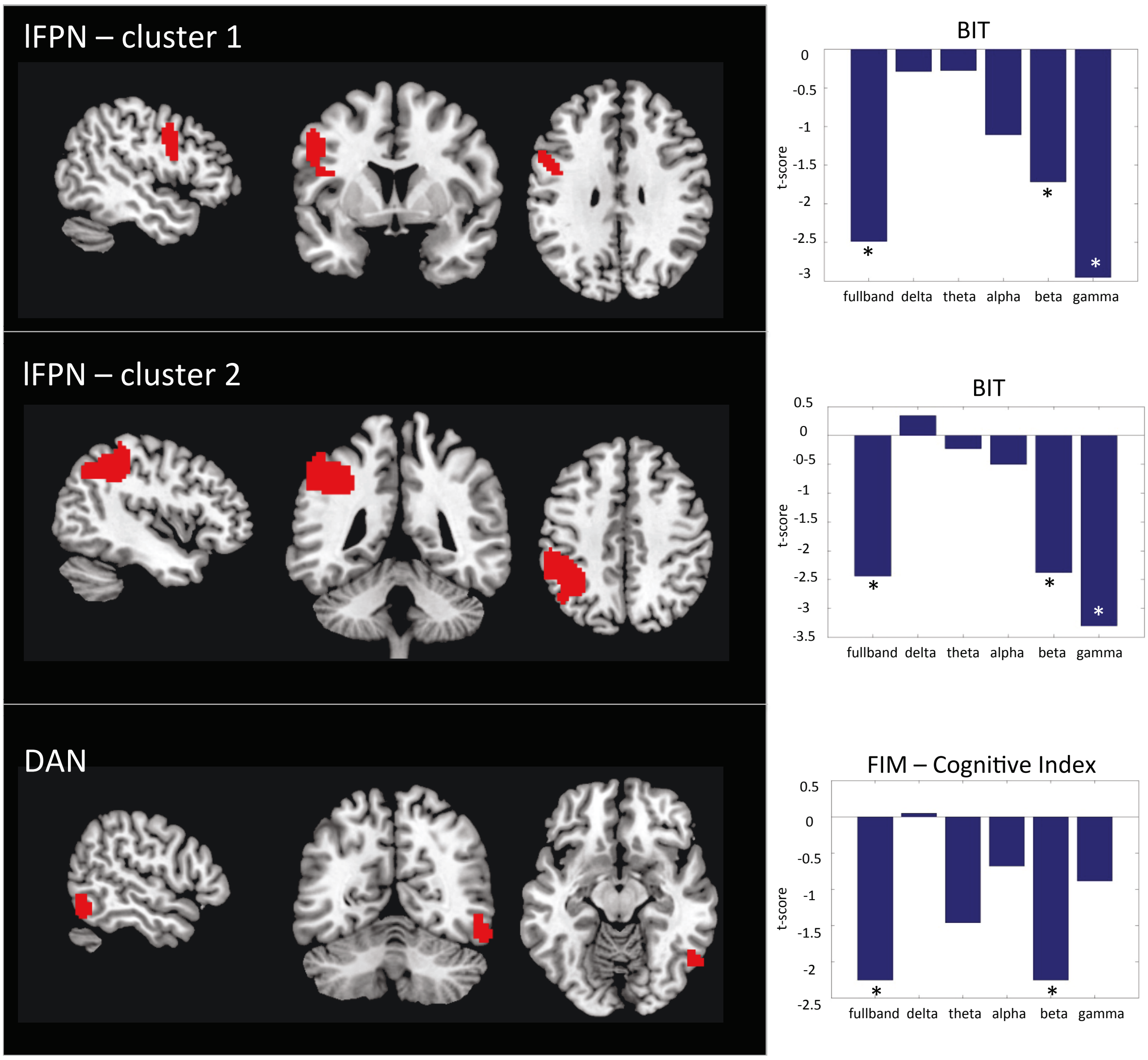


Fig. 3.9. ***Correlation between EEG-RSNs and neuropsychological indices.*** The figure shows significant clusters of voxels within lFPN and DAN and their correlations with neuropsychological indices.

Correlation between EEG-RSNs and Load indices

Visual Cost index

The analysis carried out on the cost induced by an increased visual load revealed a significant positive correlation within two regions of the CON (t = 2.46, p = 0.012 FDR-corrected and t = 2.52, p = 0.010 FDR-corrected). These two areas are located in the rolandic operculum (LH) (MNI coordinates: X=-55; Y=8; Z=5;) and anterior cingulate (RH) (MNI coordinates: X=2; Y=26; Z=21;), respectively. The results suggest that in a frequency interval from 1 to 80 Hz, the higher is the integration of these two nodes within the CON, the higher is also the cost elicited by visual dual tasking.

Within the full EEG band, a positive correlation also emerged between the Visual cost index and a cluster of voxels in the middle temporal gyrus (LH) (MNI coordinates: X=-48; Y=-67; Z=15;) that is part of the DMN (t = 2.47, p = 0.011 FDR-corrected). Moreover, this effect emerged also within the theta frequency band (4-8 Hz) (t = 2,25, p = 0.018 FDR-corrected). The significant T-scores reveal that the higher is the integration of this specific node within the DMN, the higher is the cost caused by a visual dual task and also show the significant contribution of theta rhythm.

Auditory Cost index

Considering the Auditory cost index a positive correlation emerged in a region within the CON (t = 2.71, p = 0.007 FDR-corrected). More specifically the region of interest identified corresponds to the rolandic operculum (LH) (MNI coordinates: X=-48; Y=8; Z=2;). This effect was found in the full EEG frequency range (1-80 Hz), while no significant contribution of the individual bands emerged. More specifically, this analysis revealed that when this region shows a strong integration within the CON, the cost induced by auditory load is higher.

AI-Visual Cost for bilateral targets

This analysis examined the relation between EEG-RSNs and the cost in spatial bias induced by a concurrent visual task during the detection of bilateral stimuli. The results showed the presence of a positive correlation for a cluster within the DMN in the wide frequency range (1-80 Hz) (t = 2.265, p = 0.008 FDR-corrected). As depicted in Fig. 3.10, the region in which this effect emerged is the middle temporal gyrus (LH) (MNI coordinates: X=-

48; Y=-65; Z=14;). When exploring the contribution of the different EEG bands, a positive correlation was found for the theta rhythm (t = 1.94, p = 0.033 FDR-corrected). In detail, greater integration of this specific cluster of voxels is associated with a significant increase of the spatial bias for bilateral targets during multitasking.

AI-Auditory Cost for unilateral targets

The analysis carried out on the Auditory cost for AI during unilateral targets monitoring showed a positive correlation with a cluster belonging to the DMN (t = 2.36, p =0.014 FDR-corrected) considering the wide frequency band (1-80 Hz). The cluster was located in the middle temporal gyrus (LH) (MNI coordinates: X=-46; Y=-65; Z=12;). A significant positive correlation emerged also for the delta and theta frequency bands (t = 2.05, p = 0.027 FDR-corrected and t = 2.16, p = 0.022 FDR-corrected, respectively). In particular, this result suggests that higher integration of this cluster within DMN is related to increasing spatial bias for the detection of unilateral stimuli under multitasking.

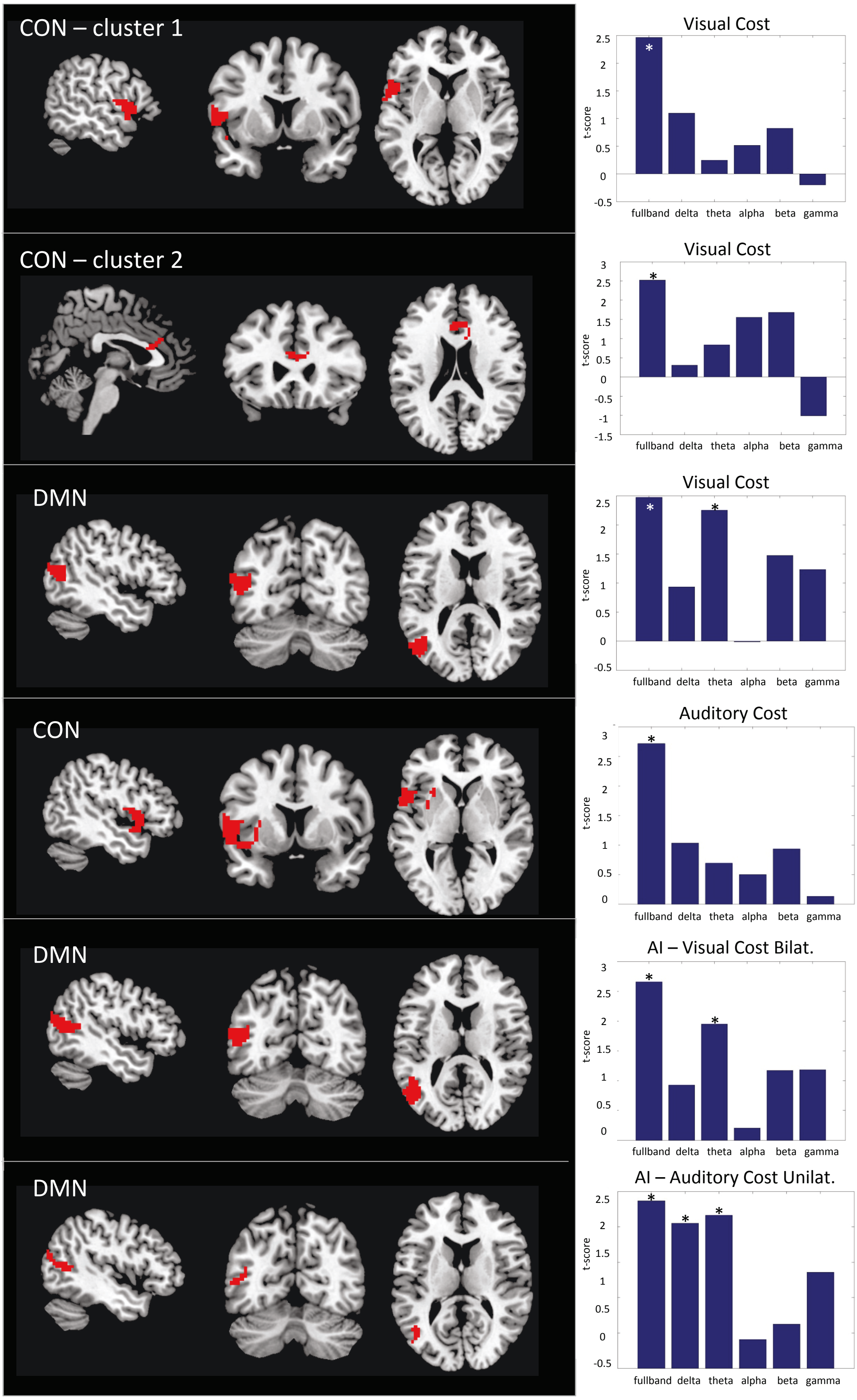


Fig. 3.10. ***Correlation between EEG-RSNs and Load indices***. The figure shows significant clusters of voxels within CON and DMN and their correlations with Load indices.

Summary of results

In the previous section, the clusters identified from each analysis have been presented in order to show the correlation between the network organization and the behavioural performance. Though 14 EEG-RSNs were considered, the results systematically pointed to only four of these networks: DAN; DMN; CON; lFPN. An examination of the anatomical coordinates of these clusters revealed that within a specific network the same regions contributed to the correlation with different behavioural scores. More specifically, regarding the Load indices, it is interesting to note that the cluster within CON correspond to the rolandic operculum in the left hemisphere both for Visual and Auditory cost. Other consistent result concerns the cluster of voxels emerged from the analysis within DMN. In this particular case, the middle temporal gyrus was found for the correlation with Visual cost, but also with AI-Visual cost for bilateral targets and AI-Auditory cost for unilateral targets. The clusters overlay within CON and DMN is displayed in Fig. 3.11.

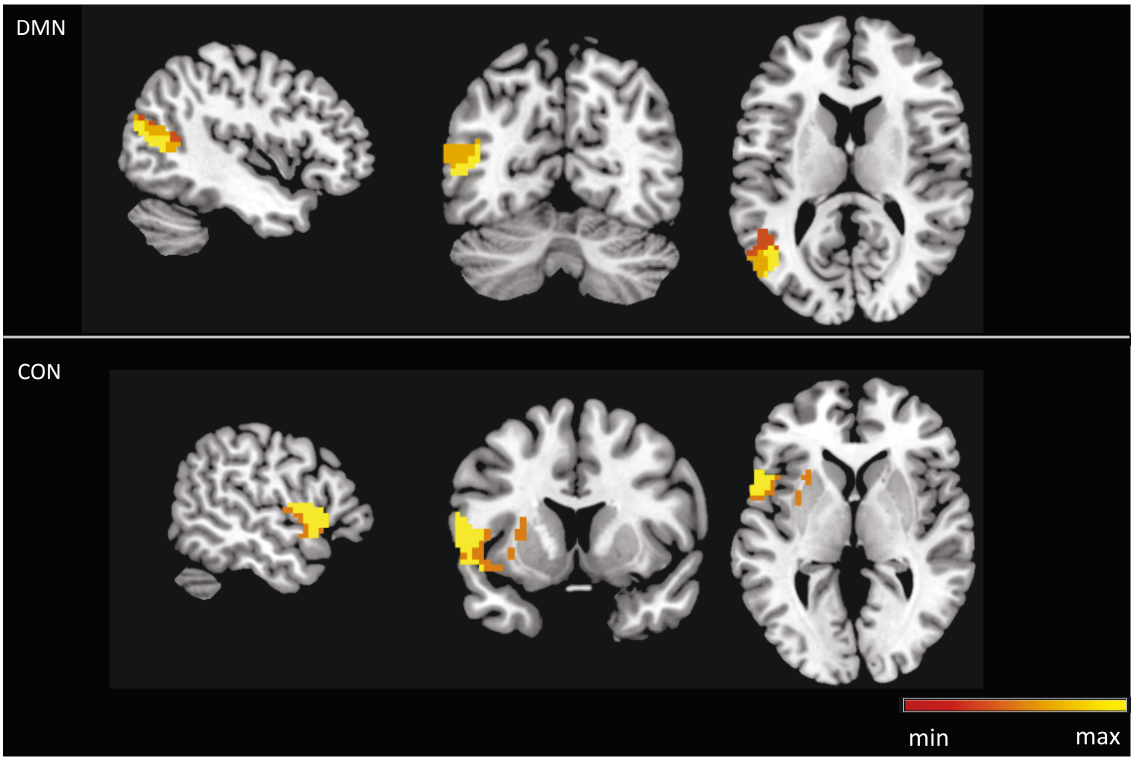


Fig. 3.11. Clusters overlay. Top panel shows clusters overlay within DMN for the correlation with Visual cost index, AI-Visual cost for bilateral targets and AI-Auditory cost for unilateral targets. Bottom panel shows clusters overlay within CON for the correlation with Visual and Auditory cost indices.

4. Discussion

Several recent studies (Baldassarre et al., 2014, 2016; Siegel et al., 2016) support the hypothesis that the disruption of RSNs connectivity can predict the presence of cognitive deficits following cerebral stroke. The present study examined the correlation between RSNs extracted from electrophysiological data and cognitive performance assessed by means of classical neuropsychological tests and a computerized multitasking paradigm in a group of chronic stroke patients. A sophisticated, recently developed approach was employed in order to extract functional brain networks from EEG data. Our investigation therefore served two main purposes: the validation of the reconstruction of RSNs from EEG signal in a neurological population, and the study of the potential link between intrinsic brain activity and behaviour considering a wide frequency band, but also exploring the contribution of different EEG rhythms.

While fMRI techniques are usually employed to detect brain networks at rest, the recent work of Liu et al. (2017) revealed that RSNs can be effectively reconstructed also using high-density electroencephalography. This approach included state-of-the-art analysis techniques that allow: an accurate pre-processing of the EEG signal, a construction of a head model by considering electrode positions and structural MR images, a precise source localization, and finally functional connectivity analysis based on ICA. Liu and colleagues (2017) demonstrated that EEG-RSNs can be detected by means of both spatial and temporal ICAs, showing a good correspondence with previously published fMRI-RSNs. In our study, we applied this technique to assess whether the same EEG-RSNs can also emerge from a 64 channels EEG using the temporal ICA method. Notably, although the number of channels was noticeably lower, the same 14 EEG-RSN maps were obtained. In particular, these maps correspond to the following RSNs: DMN, DAN, VAN, rFPN, lFPN, LN, CON, AN, VSN, DSN, VFN, VPN, MPN and LPN. Thus, although information extracted from a high-density system is certainly more accurate, our results suggest that this methodology allows network reconstruction also using a much more limited number of electrodes. Furthermore, it is worth noting that the present spatial maps were reconstructed from a population of patients with left and right hemispheric damage, while previous studies on EEG-RSNs included only healthy participants. Overall, this suggests that the coarse-grained spatial and temporal resting state profiles are preserved following a localized, unilateral brain damage. Nevertheless, the presence of more subtle RSNs alterations in our patients remains to be established and will be the focus of future research efforts.

Once the spatial maps were obtained and the time-courses for each EEG-RSNs were extracted, our main analysis aimed at exploring their correlation with neuropsychological and Load indices. These two analyses included 32 and 19 patients respectively, because only patients without visual field deficits performed the multitasking paradigm. The main purpose of this analysis was to explore whether the spontaneous organization of brain networks could be predictive of cognitive performance, thereby providing a new assessment tool based on sensitive neural markers that could complement classical paper-and-pencil measures or computerized multitasking paradigms. One strength of such markers is that they can be measured in a very short scanning session without requiring active subject engagement, which is particularly relevant in clinical settings where patients often manifest behavioural deficits that hinder neuropsychological assessment.

A first, interesting result was that correlations were found only between a subset of EEG-RSNs and specific behavioural indices. In particular, cognitive impairment was mostly associated with neural markers within Default Mode Network, Dorsal Attention Network, Cingulate Opercular Network and left Fronto Parietal Network, in line with the hypothesis that there is a core system of brain networks involved in attentional processes (Baldassarre et al., 2016; Corbetta & Shulman, 2002; Fox et al., 2006; Gusnard & Raichle, 2001; Heilbronner & Hayden, 2016).

Regarding the Load indices, it is interesting to note that all the significant correlations emerged within clusters of voxels that are part of CON and DMN. In particular, within CON two clusters of voxels that are part of the rolandic operculum (LH) and the anterior cingulate (RH) positively correlated with the Visual Cost. Note that all the indices considered in this analysis express the cost induced by dual task. Interestingly, also the cluster identified for the Auditory Cost corresponds to the rolandic operculum (LH), suggesting that regardless of the sensory modality involved in the secondary task (visual vs. auditory), the integration of this region within CON modulates multitasking performance. Moreover, all the significant correlations emerging between CON and Load indices were found only within the full frequency band.

It has been recently shown that Cingulate Opercular Network is involved in multiple cognitive processes. In particular, it has been proposed that a set of regions including dorsal Anterior Cingulate Cortex (dACC), but also bilateral anterior insula and frontal operculum form a “core task-set system” (Dosenbach et al., 2006). More specifically, a series of contributions suggests that neurons of the dACC are specialized for the implementation of the task set, processing and organizing contextual information that is relevant for the task at hand (Dosenbach et al., 2006, 2007; Heilbronner & Hayden, 2016). dACC integrates strategies and task-relevant information to accurately represent the task space and to exert high-level control (Heilbronner & Hayden, 2016; Luk & Wallis, 2009) Moreover, it seems that in the dACC both spatial and non-spatial representations are computed by the same set of neurons (Hayden & Platt, 2010; Hosokawa, Kennerley, Sloan, & Wallis, 2013; Luk & Wallis, 2009; Procyk et al., 2016), suggesting that this region monitors a wide variety of information that is then used to generate and coordinate actions. It also has been suggested that by means of this monitoring process, dACC generates a signal that expresses the need of additional cognitive resources (Heilbronner & Hayden, 2016). The execution of concurrent tasks is generally characterized by a performance decline, which is usually explained in terms of interference between neural processes (Cohen, Konkle, Rhee, Nakayama, & Alvarez, 2014; Nijboer, Borst, van Rijn, & Taatgen, 2014; Rémy, Wenderoth, Lipkens, & Swinnen, 2010). Dux et al. (2009) associated dual task costs with the inability of networks to adapt to a multitask context, which is in line with the idea that dual task interference is related to brain network flexibility: Alavash et al. (2015) used graph analysis to correlate the modular organization of brain networks with dual task costs, and found that lower flexibility in modules involved in executive control or visuo-spatial processing was associated with higher visuo-spatial impairments under multitasking. In our case, the higher integration of clusters within Cingulate Opercula Network at rest predicted higher costs in visual and auditory dual tasks. Since the functional architecture during spontaneous brain activity might reflect task-dependent dynamics (Smith et al., 2009), these correlations suggest that an alteration in the reconfiguration capability of the network might be responsible for the increased cost caused by multitasking.

With respect to Default Mode Network, clusters located nearby the middle temporal gyrus positively correlated with Visual Cost, AIs-Visual Cost for bilateral targets and AIs-Auditory Cost for unilateral targets. Similarly to Cingulate Opercular Networks, also Default Mode Network is involved in several cognitive processes including cognitive control (Seeley et al., 2007), mental activity (Gusnard & Raichle, 2001; Mason et al., 2007) and also the regulation of the focus of attention (Bonnelle et al., 2011; Gilbert, Dumontheil, Simons, Frith, & Burgess, 2007; Hampson et al., 2006). However, the main feature of this network is that its activation is strongly reduced during attentionally demanding tasks (Buckner et al., 2008; Raichle et al., 2001). Notably, it has been shown that structural disconnection within the

DMN correlates with the level of sustained attention during task execution (Bonnelle et al., 2011). Also in this case, we observed a higher integration within DMN at rest related to an increase in costs during multitasking. This finding might be explained in terms of a difficulty in reconfiguring the DMN, whose activation is not properly suppressed during multitasking. EEG frequency analyses revealed a significant contribution of theta band in all clusters identified within DMN, and also of the delta band but only for the AI-Auditory Cost for unilateral targets.

Regarding the neuropsychological indices, two significant correlations were found. In particular, a negative correlation emerged between a cluster of voxel located in Dorsal Attention Network and cognitive index of FIM. The cluster corresponded to the inferior temporal gyrus within the right hemisphere. It has been shown that DAN is involved in establishing and maintaining preparatory patterns of activation for spatial attention (Roebroeck, Formisano, & Goebel, 2005). A recent study suggested that during visuo-spatial tasks, the connectivity at rest strongly decreases within visual cortex and, in contrast, it increases between visual cortex and dorsal attention regions (Spadone et al., 2015). Moreover, the authors observed that resting connectivity in the DAN remained relatively unchanged during attention tasks, suggesting that DAN plays a crucial role as prior for attention-related responses. Our results reveal that a higher integration within DAN predicts lower cognitive independence, not only considering a wide frequency range, but also within the beta band. These correlations suggest that an alteration in the dynamic reconfiguration ability of the network might explain the reduced levels of independence assessed by FIM.

The analysis carried out on the global score of BIT revealed a significant negative correlation within two clusters included in the left Fronto Parietal Network. It has been shown that fronto-parietal regions support cognitive control and decision-making processes (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). However, it has been also proposed that spatial neglect could reflect dysfunction of two fronto-parietal networks involved in the control of attention (He et al., 2007). In particular, Corbetta and colleagues (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005) suggested that a functional imbalance of evoked responses in left (hyperactive) and right (hypoactive) dorsal parietal cortex could be a key marker of spatial deficits after stroke. With respect of our results, we found that the greater integration of the precentral gyrus and of the inferior parietal gyrus within lFPN predicts lower scores at BIT. By checking the individual performance at BIT of our patients, we discovered that while the indices for LHD patients were always high, a subgroup of RHD patients showed low indices.

This implicates that the negative correlations are driven by the performance of the subgroup of RHD patients with lower scores. These results suggest that in this subgroup of patients an alteration in the dynamics within the lFPN might explain the presence of spatial deficits assessed by BIT.

Overall, despite more in-depth investigations are required to clarify the relation between intrinsic network organization and cognitive impairments following stroke, our findings suggest that the presence of specific alterations within particular networks might be responsible for patients' deficits, and that resting state activity can be predictive of cognitive abilities. In particular, we revealed that multitasking costs could be related to flexibility in reconfiguration in a set of regions included in Cingulate Opercular Network and Default Mode Network and that visuo-spatial abilities (BIT) and cognitive independence (FIM) could be mediated by functional dynamics within fronto-parietal and dorsal regions.

Conclusions

The present work aimed to explore how visuo-spatial abilities can be drastically affected after a brain stroke, considering occurrence and severity of the deficits in clinical populations, but also examining the electrophysiology of the underlying brain networks. The first important consideration is that we employed a multidisciplinary approach that combines the analysis of behavioural and electrophysiological data. The second aspect to consider is that all the empirical investigations had a common central topic: the cognitive demands of multitasking under visuo-spatial processing. Third, this work attempted to contextualize the study of cognitive disorders according to a "network-view" of the brain, which has important theoretical and practical consequences for neuropsychological research.

In Chapter 1, two studies have been presented concerning the assessment of visuo-spatial deficits in chronic stroke patients by means of a computerized multitasking tool, previous validated by our group within a patient population with right hemisphere stroke (Bonato et al., 2010; Bonato, Priftis, et al., 2012; Bonato et al., 2013). Our multitasking paradigm, which probes lateralized and non-lateralized mechanisms of attention, showed more sensitivity in detection of visuo-spatial impairments compared to standard neuropsychological batteries. In particular, the dual task condition, that combines a simple monitoring of peripheral targets with a concurrent visual or auditory task, unveils neglect and extinctions patterns that were not detected by means of paper-and-pencil tests (i.e., barrage or cancellation). Given that the effectiveness of this tool has been previously shown in patients with right hemisphere damages, we asked whether increased attentional load could uncover pathological spatial unawareness also in left stroke patients, despite the well-known finding that spatial deficits are infrequent in this clinical population (Stone et al., 1993). Interestingly, our results show that under increased attentional load lateralized biases can equally affect right and left hemisphere damaged patients, thereby confirming that the severity of neglect is strongly modulated by task demands (Azouvi et al., 2002; Bonato et al., 2010). These findings have important implications for clinical diagnosis, especially considering the undeniable discrepancy between assessment settings and ecological, daily contexts. Indeed, although the neuropsychological evaluation might not reveal the presence of visuo-spatial deficits, when patients leave the testing room they often manifest noticeable unawareness for the contralateral side of the space, overlooking obstacles and increasing the risk of falls. We suggest that susceptibility to multitasking could represent a reliable cognitive marker of the functional recovery of stroke patients, especially for its sensitivity in the assessment of visuo-spatial abilities during simultaneous monitoring of multi-sensory information. From a clinical perspective, we therefore suggest the use of our multitasking approach as an assessment tool that is complementary to classical batteries usually administered for neglect evaluation.

Intrinsic limitations in cognitive/brain resources demand the deployment of attentional mechanisms to filter and select the relevant information during task execution (Marois & Ivanoff, 2005). Attentional load is therefore a crucial aspect of cognition, and under specific circumstances it exacerbates the limitations imposed by processing bottlenecks. In our first study, the inclusion of a group of patients suffering from Mild Cognitive Impairment allowed us to also examine the occurrence of spatial deficits in a clinical condition characterized by a global reduction in cognitive performance. Overall, the finding that a pathological asymmetry was observed only in stroke patients suggests that visuo-spatial deficits are the consequence of unilateral brain damage, and not of an unspecific decrease of cognitive resources. In particular, we propose that task demands might be responsible for the increasing imbalance of interhemispheric inhibition, which consequently leads to a suppression of activity in the affected hemisphere. The typically symmetrical activity in the bilateral dorsal fronto-parietal network (Corbetta & Shulman, 2011) might thus become heavily asymmetrical under the joint influence of unilateral lesions and increased inhibition of the ipsilesional hemisphere induced by attentional load. The increase of attentional load induced by concurrent tasks therefore seems to strongly influence the allocation of spatial resources, especially after a stroke episode.

In order to elucidate the mechanisms underlying spatial unawareness in multitasking situations, we examined how and when visual information processing can lead to misses or correct detection of targets in a group of young healthy participants by means of EEG measures. Targets monitoring was made particularly difficult with the aim of reproducing the omission pattern classically showed by brain-damaged patients. The effect of Load emerged from the analysis of both behavioural performance and ERP dynamics, suggesting once more that attentional resources are limited. ERP analyses allowed us to identify the mechanisms underlying the processing of peripheral information during concurrent tasks execution. Our findings support the hypothesis that spatial monitoring is associated with a precise threshold criterion in cortical dynamics. Interestingly, this criterion seems to be different with regard to target position. When the N1 amplitude (left-side stimuli) or the N2 amplitude (right-side stimuli) are under-threshold, as well as when the N1 amplitude reaches a significant over-threshold value (bilateral targets), visual processing leads to misdetection of the target.

An interesting perspective for future studies is to examine whether the impact of multitasking on visuo-spatial processing depends on lesion site and size, testing a large sample of patients with heterogeneous unilateral damage. It has been proposed that the brain has both a modular and a hierarchical structural organization (Park & Friston, 2013). According to this view, within a brain network there might be several modules that include multiple sub-modules. A node of a module can be segregated, if it establishes local connections exclusively with nodes of the same sub-module, or it can act as a “hub”, if it serves as a connectivity bridge with nodes that are included in other sub-models. In the context of brain lesions, it would be interesting to explore whether damage to hub nodes would have a stronger impact on attentional load than damage to nodes involved in local integration.

Another aspect to clarify is whether the susceptibility to attentional load could be associated with specific alterations of large-scale networks. For example, it has been shown that fronto-parietal regions are massively involved in control functions. In particular, several studies suggested that the anterior prefrontal cortex is mostly activated during tasks that require the integration of several cognitive operations in order to achieve higher behavioural goals (Brade & D’Esposito, 2007; Ramnani & Owen, 2004). Instead, the lateral prefrontal regions mediate the selection and the maintenance of task set during ongoing actions (Koechlin & Hyafil, 2007). Others have proposed that fronto-parietal areas might even constitute a common attentional bottleneck (Tombu et al., 2011). In the present work, we have shown that susceptibility to attentional load correlates with the integration of specific nodes within Cingulate Opercular Network and Default Mode Network, suggesting that multitasking performance is also supported by the capability of specific networks to flexibly adapt to new and complex situations. The possibility to identify and localize alterations or disruptions within a specific network predictive of cognitive impairments could be very informative for clinicians in order to adopt *ad hoc* rehabilitation programs and to accelerate the functional recovery. In line with the hypothesis that the activation dynamics of particular areas facilitate the brain transition into multiple reachable states (Gu et al., 2015), the rehabilitation protocols could also include the stimulation of these critical circuits.

As previously proposed in the context of fMRI studies (Baldassarre et al., 2016; Siegel et al., 2016), our results support the idea that the presence of alterations in spontaneous network dynamics could be predictive of specific neuropsychological impairments. If our proposal is valid, such resting state studies would have a great impact on the clinical diagnosis. In this respect, our approach has the important advantage of allowing to study resting state networks from electrophysiological data, which is particularly convenient both in terms of time and costs. Indeed, our method only requires 10 minutes of EEG recording during rest condition: this is particularly effective in a clinical setting, where patient's collaboration is not always guaranteed. EEG, compared to fMRI, is very low cost, more comfortable for the patient and less contaminated by head and body movements; moreover, typical MRI exclusion criteria (e.g., metal plates, pace-makers, claustrophobia, etc.) do not apply to EEG.

It should be stressed that, although our investigations provided useful information concerning the correlation between EEG-RSNs and behavioural indices, the absence of a control group did not allow us to examine the presence of specific alterations in functional connectivity of our patients. As a next step, it would therefore be interesting to also systematically assess how brain damage affects the functional dynamics of EEG-RSNs, and how these results relate to those found using fMRI measures (Siegel et al., 2016). Moreover, our results with 64 channels should be more quantitatively compared with those obtained using high-density systems (128 o 256 channels), in order to show potential differences and advantages. Finally, our functional brain connectivity analysis assessed the modularity and the integration of clusters within each networks and within different frequency bands, but it did not examine patterns of cortical activation or deactivation. Investigation of the latter could provide additional information on the brain dynamics in relation to cognitive performance and should be further developed.

In conclusion, the ideas and the empirical results presented in this thesis show that clinical practice and experimental settings represent two essential and complementary components of the scientific study of cognitive functioning following brain damage.

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