UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA
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Psicologia Sperimentale, Linguistica e Neuroscienze Cognitive (XXI Ciclo)

INTEGRATING ATTENTION, ALERTNESS AND CONTROL IN THE BRAIN:

AN ELECTROPHYSIOLOGICAL APPROACH

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Doctoral Thesis:
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Anno accademico 2008/2009

A mio padre, sempre con me
A mia madre e mia sorella, miei sostegni

Integrating attention, alertness and control in the brain: an electrophysiological approach

Abstract

Converging evidences from neurophysiological, neuropsychological and functional neuroimaging literature suggested the involvement of a large-scale fronto-parietal network in the volitional and reflexive attentional control, which enables the biological systems to select relevant portions of the input stream for facilitating processing, in order to flexibly guide behavior on the basis of internal or external goals. This system acts in tight interplay with lateralized structures deputed to the achievement and maintenance of an adequate level of arousal, and with medial frontal structures responsible for the on-line modification of action and thought in response to an ever-changing external world. This project aims at clarifying the spatio-temporal dynamics of the recruitment of these three tightly related systems (alertness, orienting and executive control) and at a better explanation of integrative effects previously reported, by means of a series of high-density electrophysiological recording experiments combined with source localization methods. Experiment 1 combined a spatial cueing paradigm with a flanker task, showing early occipital and parietal activations in response to valid cues, and a lateralized pattern of sources for the responses of the phasic alertness system to both spatially valid and spatially neutral cues; additionally, we reported behavioral, electrophysiological and functional indexes of a modulation exerted by the orienting system upon the executive control one. Experiment 2 compared lateralized shifts of attention elicited by centrally and peripherally presented spatially valid and neutral cues, in a combined cueing and go/no-go task. The results again suggested an early involvement of the selective attention system in response to the task-relevant cues, as expressed in occipito-temporal enhanced responses to the valid cues as compared to the neutral ones; additionally, lateralized superior parietal and frontal activations were recorded, concurrently with attentional shifts. Again, a modulation of the conflict monitoring/response inhibition system was observed in case of validly cued stimuli, as indexed by anticipations of the fronto-central *NoGoN2* in response to non-targets preceded by valid warning signals. Experiment 3 tested the hypothesis of bidirectional modulations between the attention and control systems, by means of an integrated stop-signal/flanker task. The results showed that the selective response inhibition, required in case of incompatible flankers in the primary stimuli, interfered with the attentional switch towards the relevant stop-signals, as reflected in dimmed auditory responses to the stop-tones. All in all, the present results point toward a complex interplay among the three systems, and suggest that any interpretation of the scientific results obtained in paradigms addressing the attentional networks should account also for alertness and executive control effects, which are indirectly manipulated when capitalizing on cueing/switching paradigms.

Key-words: Attentional networks, alertness, executive control, ERP, source reconstruction, exogenous and endogenous attention, interference, inhibition.

Riassunto

Evidenze neurofisiologiche, neuropsicologiche e di neuroimmagine funzionale convergono nell'indicare il coinvolgimento di un'ampia rete fronto-parietale nel controllo endogeno ed esogeno dell'attenzione, la quale permette agli organismi di selezionare porzioni rilevanti del flusso di informazione in entrata per un processamento facilitato, al fine di guidare il comportamento in modo flessibile sulla base di scopi interni od esterni. Questo sistema agisce in stretta collaborazione con strutture lateralizzate deputate al raggiungimento e al mantenimento di un adeguato livello di attivazione, e con strutture frontali mediali responsabili della modificazione flessibile di pensiero e comportamento in risposta ad un ambiente esterno in continuo mutamento. Il presente progetto ha lo scopo di raggiungere una migliore comprensione delle dinamiche spazio-temporali del reclutamento di questi tre sistemi strettamente correlati (allerta, orientamento, controllo esecutivo), e di spiegare meglio alcuni effetti integrativi tra i sistemi, tramite una serie di esperimenti di registrazione elettrofisiologica ad alta densità, combinati con algoritmi per il computo delle soluzioni inverse. In Esperimento 1 un compito di cueing spaziale combinato con la presenza di distrattori ha rivelato attivazioni precoci in cortecce occipitali e parietali in risposta agli indizi validi, e un pattern di attivazione lateralizzato corrispondente alle risposte agli indizi (sia validi che neutri) da parte del sistema di allerta fasica; addizionalmente, sono stati riportati indici comportamentali, elettrofisiologici e funzionali di un effetto modulatorio del sistema di orientamento su quello di controllo. In Esperimento 2 sono stati comparati spostamenti laterali dell'attenzione in risposta a indizi spazialmente validi e neutri presentati in posizione centrale o periferica, in combinazione con un compito *go/no-go*. Nuovamente, i risultati suggeriscono un coinvolgimento precoce del sistema di attenzione selettiva in risposta agli indizi rilevanti, espresso in risposte occipito-temporali magnificate per gli indizi validi rispetto ai neutri; addizionalmente, attivazioni lateralizzate parietali superiori e frontali sono state registrate in concomitanza con spostamenti attentivi. Di nuovo, modulazioni del sistema di inibizione motoria e di monitoraggio del conflitto sono state osservate in caso di stimoli correttamente segnalati, riflesse in anticipazioni della componente fronto-centrale *NoGoN2* in risposta a stimoli non-target preceduti da indizi validi. L'Esperimento 3 ha avuto lo scopo di testare l'ipotesi dell'esistenza di modulazioni bidirezionali tra i sistemi di attenzione e di controllo, tramite l'utilizzazione di un compito integrato (*stop-signal/flanker task*). I risultati hanno mostrato che l'inibizione motoria selettiva, richiesta in caso distrattori incompatibili siano presenti negli stimoli primari, interferisce con lo spostamento dell'attenzione verso i segnali di stop, riflettendosi in una diminuzione delle risposte uditive ad essi. Complessivamente, i risultati indicano un complesso intergioco fra i tre sistemi, e suggeriscono che qualsiasi interpretazione di risultati scientifici ottenuti con paradigmi disegnati per lo studio del controllo attentivo dovrebbe anche spiegare gli effetti di allerta e di controllo esecutivo indirettamente elicitati in paradigmi di cueing/switching.

Parole chiave: Circuiti attenzionali, allerta, controllo esecutivo, ERP, ricostruzione della sorgente, attenzione esogena ed endogena, interferenza, inibizione.

Introduction

Coordinated and adapted behavior depends on the deployment of *selective attention* mechanisms: in the context of a cluttered external environment, in which stimuli are competing for cognitive resources, the ability to pay heed to a subset of them is crucial, for it allows organisms with cognitive systems characterized by limited resources to analyze the relevant portions of the information stream in great detail. At the same time, the attentional control system enables the organism to actively suppress the irrelevant information, and directly biases the allocation of cognitive resources upon goal-directed activities. Over the past two decades, converging neurophysiological, neuropsychological and functional neuroimaging evidences have suggested that developing expectations in respect to the external world modulates brain activity at sensory cortical levels (Desimone & Duncan, 1995; Luck *et al.*, , 1997; Kastner & Ungerleider, 2000); moreover, the sources of control for this system are distributed across anterior and posterior networks of brain regions (Posner & Petersen, 1990; Corbetta & Shulman, 2002).

In the present work, a detailed review concerning the scientific production which addressed the functional and neural bases of the attentional control systems will be presented (Chapter 1), with a particular consideration for the works based on an intriguing and highly influential account: the attentional networks theory (Posner and Petersen, 1990, Chapter 2). Since this theoretical position builds on a multi-componential model of the attentional system, strongly interrelated with the executive functions, a review of the research on the monitoring and control systems will also be provided.

The analysis of the theoretical and empirical state of the art in neurofunctional research addressing attention and control systems stimulated several research questions; therefore, this reasoning and the general and specific aims of the present work will be delineated in Chapter 3, while the scientific results of the doctoral project will be presented and discussed in the experimental sections (Chapters 4, 5 and 6).

The results of the three electrophysiological experiments composing this work will be integrated in a broader perspective in the context of the general discussion section (Chapter 7), followed by the complete list of references utilized in the ideation, implementation and finalization of the present scientific project.

Chapter 1.
Models and theories of attention and control in the brain

In this chapter, the scientific research on visuo-spatial attention and executive control will be reviewed, with particular emphasis over data obtained under the cognitive neuroscience perspective, which set its foundations upon converging evidences deriving from cognitive and experimental psychology, and from neuropsychological, clinical, and neurofunctional approaches.

1.1 Attention

The term "*attention*" refers to a complex theoretical construct, whose meaning ranges from the ability to maintain an adequate level of wakefulness to the mental capacity to select portions of the inner or outer stimulus stream (memories, thoughts, responses, objects, locations, sounds) in order to favor them in respect to other parts of the same stream. Because of the complexity of the theoretical construct, a brief taxonomy of the attentional system will be provided, in order to precisely specify the different levels of description and explanation (functional, structural, neural) of the complex and interrelated phenomena which will be the objects of this scientific work.

1.1.1 Taxonomy of attention

Sustained and selective attention. The attentional function can be described as including interdependent *sustained* and *selective* components. The *sustained attention* network works in tight cooperation with the *vigilance* system, named also *arousal* or *alertness*. A complete account of the alertness/vigilance construct will be discussed in detail in the first paragraph of Chapter 2, within the theoretical framework of the attention networks theory (Posner & Petersen, 1990). Here, we anticipate that the sustained attention system is based on right hemisphere and sub-cortical circuits mediated by the neurotransmitter noradrenaline (NA), and it supports the ability to achieve and maintain an adequate level of wakefulness in order to perform goal-related activities (Sturm *et al*., 1989 & 1999; Posner, 2008).

On the other hand, the selective aspect of attention refers to the cognitive faculty that allows organisms to respond selectively to individual objects in a cluttered visual or auditory environment, or to select portions of the visual space in order to facilitate the processing of stimuli that might fall at the preferred location. Selection is necessary because of computational limitations in the brain's capacity to process relevant information in order to control behavior. Theories implicating early or late attentional filters (Broadbent, 1958; Duncan, 1980) long debated about the nature and the time course of the selection mechanisms, and, in the visual domain, gave rise to several metaphors of the attentional movements. Historically, these metaphors have been highly influential and will be briefly reviewed here. The visual attentional focus have been compared to the beam of a *spotlight* (Broadbent, 1958 & 1982), to a *zoom lens* (Eriksen & St-James, 1986) or to a *gradient* (Downing & Pinker, 1985; Mangun & Hillyard, 1988; De Yoe & Brefczynski-Lewis, 2004): with small differences, in all of these models the spatial domain plays a crucial role for visual attention, as attention necessarily selects contiguous regions of the visual field, with sharper (*spotlight*) or less defined (*gradient*) borders. An alternative account to the *spotlight* metaphor predicts that attention might sometimes be assigned to noncontiguous regions of the visual field, but conversely can be directed to perceptual groups as defined by Gestalt principles of organization (Duncan, 1984). However, since in many cases the predictions of these different cognitive models are rather similar, these influential metaphors will not be contrasted here.

One particular aspect of selective attention is the mechanism of *divided attention*, by which biological systems are able to attend more than one location or stimulation source at once (e.g., attending stimuli coming from the visual *and* auditory streams contemporarily). Since the construct of divided attention implicates the ability to control the interference between the multiple input sources, and to analyze in parallel several types of stimuli, for brevity these aspects of the attentional function will be discussed more in detail in the section concerning the control of interference and performance monitoring.

Covert and overt aspects of attention. In most of the natural situations, we explore the visual scene by means of saccadic eye movements that rapidly (in 50–70 ms) bring the fovea, the retinal region of highest acuity, onto locations or stimuli of interest. The relevant stimuli are then processed during interspersed periods of fixation that last up to 250 ms: this set of processes is defined as *overt visual orienting*. When, conversely, behaviorally relevant stimuli are attended in the absence of exploratory saccadic eye movements, the set of processes underlying the dissociation of the locus of visuo-spatial attention from eye movements is defined as *covert visual orienting*. The debate regarding the covert and overt attentional mechanisms has concerned the investigation of the functional relationship between attentional and saccadic movements, and the cerebral bases for these systems. Shepherd and colleagues (Shepherd *et al*., 1986) proposed three possible functional architectures for the relationship between eye movements and attentional shifts. At one extreme stands the independence hypothesis, following which attentional shifts and saccadic generation involve entirely different mechanisms (i.e., separate locations could be simultaneously computed in spatial maps by attentional and oculomotor systems). At the other extreme (identity hypothesis), attentional and ocular movement generation involve identical mechanisms (i.e., any location is encoded by the attentional mechanism in a set of motor coordinates that specify direction and amplitude of possible planned saccades). An intermediate position (interdependence hypothesis) claims that attention and eye movement processes share resources or computations at some stage; when both systems select the same location, their performance is optimal; when different locations are selected by each system, their performance is partially impaired. From this theoretical position stemmed several research lines which led to somehow contrasting results: to summarize, following an influential review about the mechanisms for directing attention and the eyes in the visual space (Corbetta, 1998), attention and eye movements systems seem to be tightly related, according to the results of several psychological experiments carried out in combination with neuroimaging techniques. At the neural level, the meta-analysis on PET and fMRI studies on covert and overt mechanisms of attention discussed in the review suggested that a robust set of neural signals in the posterior parietal and frontal cortices reflects spatial attentional processes during covert orienting. These signals can be reasonably linked to some of the psychological processes described when subjects reflexively or voluntarily allocate attention to a visual location; furthermore, the patterns of cortical activation for attention and eye movements largely (but not entirely) overlapped in the meta-analysis, suggesting that attentional processes are tightly linked to oculomotor processes, yet without complete identity among their anatomical mediators. This pattern of strong overlap, accompanied by partial segregation of regions for attention and eye movements, points towards a moderate interdependent hypothesis, claiming a pattern of tightly linked cerebral networks for the two functions.

Automatic and voluntary selective attention. In the visuo-spatial domain, overt and covert attentional shifts can be endogenously or exogenously driven. *Reflexive*, *bottom-up* or *exogenous* shifts are quickly and effortlessly elicited by abrupt, salient stimuli appearing in the periphery of the visual field, even when these stimuli are not goal-related and completely non-informative in respect to the organism scopes. Attentional cueing tasks as the Posner’s cueing paradigm (Posner, 1980; Posner & Cohen, 1984) made use of this type of warning signals, which are able to capture attention regardless of their informative value. When participants are asked to respond as quickly as possible to visual stimuli presented peripherally in respect to a central fixation point, their behavioral index of performance (Reaction Time, RT) is modulated by the context in which the relevant targets are presented. In particular, interesting phenomena happen in case brief peripheral stimuli (flashes of light, flickering of boxes or other stimuli) are interspersed with the presentation of the task-relevant targets, even though the cues are completely non-predictive in respect to the target position (i.e., the coupling between cue position and target position is completely randomized). Crucially, the manual responses to targets show temporal benefits (i.e., shorter RTs) in case of identity of the position of target and preceding warning signal, and show costs (i.e., longer RTs) in case of targets preceded by cues presented at the opposite location. However, this ability of peripheral cues to elicit *automatic* attentional movements, causing more efficient (or faster) processing of signals that appear at the cued location, has a fast time course and does not persist for long: the attentional benefits arise and peak within the first 300 ms after cue presentation, but when cue and following target are separated by longer intervals (500 ms or more) the benefits for valid cueing dissipate, and responses are typically slower and/or less accurate for targets presented at the cued location. This phenomenon, unique for reflexive attention, is referred to as Inhibition of Return (IOR, Posner & Cohen, 1984; Posner *et al*., 1985); its widely agreed interpretation (Posner & Cohen, 1984) states that inhibition would improve spatial selectivity by favoring the exploration of new positions at the expenses of those already sampled, and which proved to be not relevant. In other words, the attentional system, after an orienting response towards an event at a particular location, would then inhibit a second orienting response to the same location for a certain period of time (up to 1.5 seconds, following Maylor and Hockey, 1985). Note, however, that the temporary inhibition of the cued location can be overcome through *voluntary* orienting, and, therefore, the phenomenon does not occur with central, informative cues. More recent neuroimaging and electrophysiological studies indicated that the IOR phenomenon is underpinned by cerebral mechanisms which take place in areas deputed to the control of attention, as well as, at early latencies, in sensory areas (Mayer *et al*., 2004; McDonald *et al*., 1999; Hopfinger & Mangun, 1998 & 2001; Hopfinger, 2004).

In contrast to exogenous shifts, the *endogenous* control of attention can be directed on a trial-by-trial basis with the use of symbolic cues presented at fixation: warning signals belonging to this category need to be cognitively interpreted in order to elicit movements of the attentional focus towards relevant locations. Centrally presented arrowheads (Posner, 1980; Hopf & Mangun, 2000; Corbetta *et al*., 2000), letters (Wilson, Woldorff & Mangun, 2005; Giesbrecht *et al*., 2006; Grent'-t-Jong and Woldorff, 2007) and many other types of symbolic cues (Coull & Nobre, 1998; Nobre, Sebestyen & Miniussi, 2000; Hahn *et al*., 2006; McDonald & Green, 2008; Brignani *et al*., 2009) can be used in order to elicit *top-down* or *voluntary* shifts of visuo-spatial attention, on the basis of their informative value: in fact, in contrast to peripheral uninformative cues, which automatically capture the focus of attention by means of their physical saliency, an endogenous cue must be highly predictive in respect to the following target presentation location, in order to engage the voluntary control of attention system. In other words, only when the informative value of the warning signals is higher than chance level (typical informational values are situated around 80% of validity) the voluntary control of attention system can be engaged and elicits attentional shifts compatible with the cued direction; consequently, the information processing of targets falling at the cued location will be facilitated, as reflected in faster and more accurate behavioral responses as compared to uncued or invalidly cued targets. The *endogenous* control of attention can also be directed in a sustained mode (e.g., Eason, Harter & White, 1969; Zani & Proverbio, 1997 & 2009; Natale, Marzi & Macaluso, 2009): as an example, the participants can be asked to attend one hemifield only for a full experimental block, ignoring the other parts of the visual space, in order to rapidly detect and respond to stimuli presented at the attended location. The effects of this type of endogenous control of attention on behavioral measures (RTs) and on the modulation exerted upon sensory areas are quite similar to the effects of symbolic trial-by-trial spatial cueing, therefore this differentiation will not be discussed any further.

Although providing flexibility, the top-down voluntary control of attention requires effort and cognitive resources, and its engagement is relatively slow as compared to the reflexive attention system; on the other hand, the time course of the voluntary modulation of attention is more stable and long-lasting than the exogenous mechanisms of attention, and, as previously anticipated, it doesn’t suffer of inhibitory effects at long cue-target intervals (i.e., the behavioral responses to stimuli falling at the cued location are faster and more accurate even when the targets are separated from the cues by intervals longer than 500 ms). Experiments in the cognitive neuroscience domain have supported the idea that the various aspects of the attentional function (overt and covert, sustained or selective, voluntary or automatic) are based upon separate and functionally discernible mechanisms, underpinned by partially segregated circuits in the brain. It is therefore plausible that cerebral lesions damaging portions of this network of systems might elicit selective deficits in one or more of the attentional subdivisions: evidences deriving from the neuropsychological domain, sustaining the idea of anatomo-functional dissociations within the attentional function, will be provided in the next paragraph.

1.1.2 The neuropsychology of spatial attention

Brain damages in several cerebral districts can disrupt spatial selective attention, by interfering with the ability to attend the opposite (contralesional) side of space, particularly in case of right-sided brain lesions. The resultant syndrome, defined *contralesional hemispatial neglect* is a disabling consequence of brain stroke: it doesn’t correspond to a visual, auditory, or movement disorder, but instead it seems to reflect a disability in looking, detecting, listening or exploring the external space (Mesulam, 1999; Vallar, 2001), often accompanied by alertness deficits (Robertson *et al*., 1995 & 1998). Patients with unilateral neglect behave as if sensory events within the contralesional hemispace have lost their saliency, especially when competing events are concurrently presented in the ipsilesional hemispace. Such patients may fail to dress, groom or shave properly the left side of their bodies; they might not copy the left half of drawings, read the left half of pages, sentences or even words; additionally, the reaching movements towards stimuli in the contralesional hemispace can be inhibited, together with exploratory vectors towards the left hemispace. This constellation of symptoms suggests an attentional and representational dysfunction, characterized by a strong asymmetry: left neglect deriving from right lesions is common, while right neglect is rare (Vallar & Perani, 1986 & 1987; Mesulam, 1999); furthermore, experimental inactivation of the right hemisphere through sodium amytal injections caused visual neglect an tactile extinction, while left hemisphere inactivations did not elicit them (Spiers *et al*., 1990). Several models have been proposed to explain the asymmetry of spatial attentional processes (Heilman & Van den Abell, 1980; Mesulam, 1981; Kinsbourne, 1987): according to an influential combination of these different models (Mesulam, 1999 and Mesulam *et al*., 2004), each hemisphere has a greater tendency to shift attention towards the contralateral hemispace; at the same time, the left hemisphere tendency to contraversive shifts is more pronounced, and its activity coordinates attentional distribution only within the right hemispace; on the other hand, the right hemisphere attributes saliency to events in both hemispaces and controls a more balanced attentional vector, besides being intrinsically more engaged in spatial attention tasks (see also electrophysiological evidences in Proverbio *et al*., 1994 in a split brain patient). The predictions of this model are in line with the observed attentional impairments in neglect patients: the severe deficits arising after right hemisphere lesions are therefore due to the key role of this hemisphere in spatial attentional tasks, coupled to the little capacity of the left hemisphere in coordinating the distribution of spatial attention within the left side and in endowing left-sided events with salience, triggering leftward attentional shifts. As a result, following right hemisphere lesions left-sided events would lose representational saliency, and the focus of attention would then keep being pushed rightwards, eliciting diverse deficits grouped under the hemispatial neglect syndrome definition.

Neural localization of brain lesions underpinning hemispatial neglect. This syndrome is related to severe damage to the cortical right-hemisphere epicenters of a ventral parieto-frontal stream of sensory processing (Vallar, 2001): neglect-causing lesions are mostly located at the conjunction between the posterior parietal and superior-temporal lobes (temporo-parietal junction, TPJ), but the syndrome can be drawn also by right frontal lesions damaging the conjunction between the precentral and the superior frontal sulci (Frontal Eye Field, FEF, Paus *et al*., 1996), subcortical or limbic lesions (Watson & Heilman, 1979; Heilman *et al*., 1983). More specifically, in the theoretical framework of the spatial orienting as being divided into operations of disengagement, shift and re-engagement of attentional focus (Posner & Petersen, 1990; see Chapter 2 for a more detailed account of the attentional networks theory), lesions located in different cerebral districts are associated with independent attentional deficits. In details, patients with right TPJ lesions, tested in an exogenous cueing paradigm, demonstrated to be able to elicit cued shifts of the attentional focus towards the left hemispace, unless the left-sided targets were preceded by invalid right-hemifield cues (Posner *et al*., 1984): this pattern of results was interpreted by the authors as a disengagement and re-orienting deficiency. Subsequently, Posner and collaborators (Rafal & Posner, 1987) tested in similar spatial attention tasks patients with lesions in different brain areas, as the subcortical structures of the thalamus and the superior colliculus. The different behavioral patterns associated with the diverse brain damages has been taken as an indication for a dissociable role of these subcortical areas in spatial attention: the thalamus was selectively involved in the operation of engaging attention, while the shifting was independently subserved by the superior colliculus. More recently, Deouell and Knight (2004) reviewed the electrophysiological literature involving patients with lateral prefrontal lesions: the results showed selective deficits in several attentional subsets, such as impaired inhibition of irrelevant stimuli, poor facilitation of the attended stimuli, together with impoverished novelty detection; this pattern of results is also in line with the reflexive attention deficits reported in prefrontal patients by Snyder & Chatterjee (2006). In addition, one study addressed the role of left parietal damage in attentional mechanisms (Han & Jiang, 2004): the results showed lesion-dependent degraded modulation upon the ipsilateral extrastriate cortex, in line with superior parietal involvement in spatial attention mechanisms.

The facts that a host of different lesions might cause the hemispatial neglect syndrome, and that brain damages located in different cortical or subcortical regions might elicit diverse patterns of deficient behavior, suggested the existence of a complex supra-modal system involved in the control of attention. This network, based on an architecture of several frontal and parietal areas, is distributed in both hemispheres: in the next paragraph a more detailed review of functional imaging studies delineating the cerebral networks for spatial attention will be provided.

1.1.3 The contributions of functional imaging studies to the investigation of visuo-spatial attention

Source signals and site signals. Covert or overt visuo-spatial attentional shifts are elicited in order to enhance stimulus processing in the brain. This facilitation in feature analysis may plausibly happen in the modality-specific areas deputed to the primary and secondary sensory processing, whereas the control of the onset and modulation of this biasing is suggested to take place in supra-modal areas. Therefore, conceptually, attentional modulations can be divided into those that are domain-specific, and those which are modality-independent; consequently, different types of signals recorded in the brain correspond to the control of the attentional mechanism (modality-independent or *source* signals) and to the interactions of the top-down control with the sensory systems (modality-dependent, or *site* signals). For example, a source signal recorded in high-order functions brain regions or in sensory areas responsible for stimulus analysis can be associated with a shift of attention to a location. Once a stimulus is presented, or even in advance to stimulus presentation, activity in the sensory areas may be enhanced by attention, and this modulation of visual processing marks the interface between attentional control and visual processing. Thus, whereas *source* signals provide information on the organization of attention systems, *site* signals provide information on how sensory (or motor, or cognitive) systems are affected by attention.

1.1.3.1 Source signals.

Capitalizing on the insights deriving from studies on the neurophysiology of selective attention in trained animals (e.g., Maunsell *et al*., 1991; Luck *et al*., 1997), several neuroimaging studies have investigated the human brain systems for the control of attention (source signals), and the areas which show enhanced signals for stimulus processing in case attentional mechanisms were previously engaged (site signals). Since the earliest positron emission tomography (PET) studies performed in the nineties (Corbetta *et al*., 1993; Nobre *et al*., 1997), there has been wide agreement about the cerebral networks for visuo-spatial attention, addressed with various modified cueing paradigms. More recently, functional magnetic resonance imaging (fMRI) studies and the development of the event-related fMRI technique allowed a more resolute (in both spatial and temporal domains) investigation of the brain systems that support the control of voluntary covert attentional orienting. Sabine Kastner and coworkers (1998) designed an innovative cueing paradigm for the study of selective attention: a condition in which participants received visual cues and used them for attending a specific location of the visual field, in order to detect certain visual patterns, was compared with a baseline condition, in which the same visual patterns were delivered, but were not cued nor task-related. In an event-related fMRI study combined with this behavioral paradigm (Kastner *et al*., 1999), a distributed fronto-parietal network of brain areas was found to be activated in response to attention-directing cues: the foci were concentrated within and around the intra-parietal sulcus (IPs), with activation spreading towards the superior parietal lobule (SPL), bilaterally; frontal activations comprised the FEFs and the supplementary eye fields (SEFs), situated more anteriorly in respect to the FEFs; additionally, the inferior parietal lobule (IPL) and the middle frontal gyrus (MFG) were found to be activated. Moreover, by means of time series of the fMRI signals, the authors demonstrated that the frontal and parietal areas showed increase in the signals during the expectation period (10 seconds), not followed by any further increase in activity evoked by the onset of visual stimulation. Almost contemporarily, a very similar pattern of brain activations (intra-parietal sulcus, SPL, precentral sulcus and FEFs, plus middle and superior frontal gyri) was recorded by an independent research group, with an entirely different cueing task. In this fMRI study (Gitelman *et al*., 1999) participants were asked to selectively respond to target shapes and to withhold responses to non-target stimuli, in an endogenous cueing paradigm. Activations recorded in this experimental task, characterized by cued shifts of attention, were compared to activations in the baseline condition, which was constituted by a simple reaction time task in response to foveally presented stimuli (specifically, the targets in the control task corresponded to the stimuli that acted as central cues in the experimental task, in order to control for visual stimulation). Besides the aforementioned pattern of activations, triggered by the attentional shift task, supplementary foci were recorded in the dorsal aspect of the anterior cingulate cortex (ACC), in the posterior temporal lobes and in the insula, bilaterally, and in subcortical structures as the thalamus and basal ganglia; all in all, this pattern of widespread activations pointed towards a large-scale distributed network for covert spatial attention (Gitelman *et al*., 1999). The same task, utilized in an experimental comparison between endogenous and exogenous cueing modalities, has been used for further validating the construct of distributed fronto-parietal attentional networks (Kim *et al*., 1999): a very similar pattern of cerebral activated areas were recorded during both types of tasks, with differential hemispheric asymmetries in parietal cortex for the two orienting modalities (in particular, a more rightward asymmetry of posterior parietal activation for exogenous cueing). The parietal component of the network has been further investigated in an influential event-related study by Corbetta and coworkers (2000), with the use of an endogenous cueing paradigm in which a percentage of noise trials was added to the classical valid and invalid distribution of cued targets. The noise trials were characterized by the presentation of the attention-directing cue, not followed by any target, thus enabling the modeling of cerebral responses to cues without the possible confound of target-related activations. Besides the expected SPL and IPs activations in response to cued trials, by means of the elongated waiting period introduced by the use of noise trials, the time course of the enhanced parietal activations could be recorded. The only areas showing sustained activity during the delay period were the anterior and ventral portions of the intra-parietal sulcus, with a left-hemisphere bias. Crucially, these activations decreased in magnitude in response to targets, while foci in the temporo-parietal junction (TPJ) of the right hemisphere were selectively responsive to target presentation, predominantly in case of invalidly cued targets (i.e., when a quick re-orienting of attention towards the uncued location was required in order to perform the task). This pattern of results (further replicated in an independent study by Thiel and coworkers, 2004, and by a double-cue study by Natale and coworkers, 2009), with the right TPJ principally involved in reorienting of attention, together with ventral portions of the frontal lobes, fits with the proposed explanations of the extinction and reorienting deficits in hemispatial neglect patients as caused by right TPJ lesions extending to the IPL (Morrow & Ratcliff, 1988; Vallar, 2001); additionally, patients with lesions involving the frontal lobes showed re-orienting deficits in a spatial cueing task (Snyder & Chatterjee, 2006), providing data in line with the frontal components for the reorienting networks. Conversely, the involvement of the FEF, superior parietal lobules and IPs cortices in cued orienting has been confirmed in a host of other PET and event-related fMRI studies, providing converging evidences in favor of the fronto-parietal model for attentional control (Vandenberghe *et al*., 2000 & 2001; Hopfinger, Buonocore & Mangun, 2000; Corbetta, Kincade & Shulman, 2002; Mayer *et al*., 2004; Giesbrecht & Mangun, 2004; Wilson, Woldorff & Mangun, 2005; Woldorff *et al*., 2004; Natale *et al*., 2009).

Hemispheric specialization for the control of spatial attention. Recently, the debate has moved from the shaping of the attentional orienting network, towards the potential hemispheric lateralization of visuo-spatial attentional processes: although wide agreement has been reached regarding the modules composing the cerebral network for attention, the lateralization of some components (in particular the superior parietal cortex and intraparietal sulcus) is not entirely understood and thus object of debate. In a recent study by Shulman and colleagues (2009), based on a cued rapid-serial-visual-presentation (RSVP) paradigm, besides the expected right-sided TPJ activations observed in response to re-orienting cues, strong contralateral activations were contemporarily recorded in the dorsal network for spatial attention, including both the FEFs and IPs. An independent event-related fMRI study (Hahn *et al*., 2006) collapsed together cues indicating on a trial-by-trial basis one out of the four quadrants of the visual field, and contrasted this highly informative situation with cues pointing towards two, three or all of the four quadrants at the same time (i.e., the authors linearly manipulated the spatial predictive value of cues): the recorded blood oxigenation level-dependent (BOLD) signals recorded in the left parietal cortex (IPs, SPL and IPL) inversely correlated with the predictive value of the cues, suggesting that the more precise was the cue in indicating the to be attended location, the more the attentional system supported by the parietal cortex was engaged. A discussion concerning the major involvement of the left parietal cortex in spatial attention processes was beyond the goal of the study, but the observed left-biased pattern was nevertheless in line with previous works by independent groups (e.g., Nobre *et al*., 1997; Corbetta *et al*., 2000). Additionally, a functional neuroimaging study (Wilson *et al*., 2005), addressing the object-centered versus viewer-centered dimensions of visuo-spatial attention, using symbolic centrally presented spatial cues (letters), found bilateral activations of the IPs, with a left-hemisphere bias (although this left involvement was stronger in an object-centered condition in respect to a viewer-centered condition). Again, stronger event-related fMRI activations in the left IPs have been associated with endogenous shifts of attention, as compared with exogenous visuo-spatial attentional mechanisms by Mayer and coworkers (2004), in line with neuropsychological and neuroimaging studies (Friedrich *et al*., 1998; Rushworth, Paus & Sipila, 2001; Yantis *et al*., 2002). In contrast with this body of evidences reporting a left-hemisphere preference for spatial attention mechanisms, a more bilateral pattern of activations in the intraparietal sulci (Coull and Nobre, 1998) and superior parietal gyri were recorded by (1) Kastner and coworkers (1999), in the "attend" condition of the spatial and feature attention task described above, (2) Gitelman and colleagues (1999) in the context of the aforementioned endogenous cueing task, (3) Vandenberghe *et al*. (2001) in a spatial attention paradigm, in which the subjects were required to covertly or overtly shadow the movements of the relevant targets, and (4) Brefzynski & De Yoe (1999; De Yoe & Brefczynski-Lewis, 2004) in a verbal cueing task. Yet conversely, Kim *et al*. (1999) observed a completely overlapping set of areas for endogenously and exogenously triggered shifts of attention, including posterior parietal activations, but reported larger extensions for the activated areas over the right hemisphere, even more prominent for the exogenous cueing task (somehow in line with a left hemisphere advantage for endogenous cueing reported by Mayer and colleagues, 2004).

If the lateralization of the superior parietal and intraparietal sulci activations are highly inconsistent across studies, most probably because of wide methodological differences among experimental paradigms, baseline or control conditions, experimental comparisons and functional analyses, the lateralized contributions of the inferior parietal lobule and of the temporo-parietal junction are consistently found for bottom-up or re-orienting within the right hemisphere (Corbetta *et al*., 2000 & 2002, Thiel *et al*., 2004 and Natale *et al*., 2009, in invalid trials; Mayer *et al*., 2004, in case of inhibition of return; Hahn *et al*., 2006, in case of bottom-up target activations related to non-informative spatial cues; Shulman *et al*., 2009 in response to shifts of attention, especially in low shift-probability conditions), in line also with a body of neuropsychological evidences reported above. Furthermore, the right IPL activations showed sensitivity to cue validity levels, with stronger engagement when highly informative cues were followed by rare invalidly cued targets (Vossel, Thiel and Fink, 2007): this evidence is compelling in indicating the involvement of the right inferior parietal lobe in re-orienting mechanisms.

Besides the parietal dissociation between a widely agreed right ventral activation for stimulus-driven orienting, as opposed to a less consistent bilateral or left superior parietal involvement in voluntary orienting mechanisms, a dissociation has been recorded between fronto-ventral activations, often found in the right hemisphere (Corbetta *et al*., 2002; Hahn *et al*., 2006; Shulman *et al*., 2009), and superior frontal sulcus, precentral, superior and middle frontal gyri activations, reported mostly bilaterally or contralaterally (Kastner *et al*., 1999; Gitelman *et al*., 1999; Corbetta *et al*., 2002; Snyder & Chatterjee, 2006 with data from frontal patients; Hopfinger *et al*., 2000, with a left-hemisphere bias).

Interim conclusions for functional activations in the control of attention. In order to incorporate the complex pattern of activations collected by several and very diverse studies in a more integrated perspective, a model for the attentional control function was proposed in a highly influential review paper by Corbetta and Shulman (2002), already briefly anticipated in a more experimental work by Corbetta, Kincade, Ollinger and Shulman (2002). The model suggested the existence of two separate networks underpinning the brain architecture for the control of attention: one set of areas acts selectively in case of voluntary orienting (dorsal frontoparietal network for goal-directed attention) and a different anatomical system is involved in the processes of bottom-up orienting (ventral frontoparietal network for stimulus-driven attention). The dorsal frontoparietal network is engaged during shifts of attention in endogenous cueing paradigms, and shows sustained responses to the cues in areas as the parietal cortex along the intraparietal sulcus, extending dorsomedially into the superior parietal lobule, and in the frontal cortex, in the human homologous of the monkey FEFs (i.e., at the conjunction between the superior frontal sulcus and the precentral sulcus, spreading in the precentral, superior and middle frontal gyri, following numerous suggestions in literature, as Paus, 1996). As previously discussed, relatively to the literature reviewed above, the putative system for top-down control of visuo-spatial attention is mostly bilateral, but a subset of areas (ventral IPS and FEF) responds strongly when attention is directed towards the contralateral visual field, with a left hemisphere bias for the right hemifield and a more balanced involvement of the right cortices in response to attentional shifts towards both hemifields. Whereas the top-down control of attention is crucial in goal-related situations, the ability to detect salient unexpected stimuli in a bottom-up modality can be highly adaptive for biological systems. The putative system supporting this ability has been tested with peripheral cueing paradigms or with the analyses of brain responses to unexpected or invalidly cued relevant stimuli. Corbetta and Shulman (2002) suggested that the circuit-breaking process, engaged in order to reorient attention towards these unexpected sensory events, takes place outside the IPs/FEF (dorsal) network: the locus of this operation is a more ventral cortical network that includes the temporo-parietal junction cortex and the ventral frontal cortex. Moreover, this network is thought to be strongly lateralized to the right hemisphere, in line with functional and neuropsychological evidences provided earlier in this text. Noteworthy, the involvement of the ventral fronto-parietal network in bottom-up or stimulus-driven ‘circuit-breaking’ strongly resembles, the *disengagement* function in the model or spatial orienting proposed by Posner and Petersen (1990). This function is precisely the subcomponent of the attentional system which has been suggested, by the same group, to be impaired in neglect patients characterized by right TPJ lesions (Posner *et al*., 1984). In Corbetta and Shulman's model, however, both the dorsal and ventral systems are proposed to be impaired in neglect patients, since the tight cooperation and functional interdependence of these components of the system are strong: perturbed activations in the ventral network are reflected in functional disactivations of the IPs and FEF, since their triggering in dependence from unexpected events relies upon the functionality of the bottom-up ventral system. Crucially, a pattern of spatial selectivity has been proved only for the dorsal component of the attentional system, while the right TPJ and IFG respond to the abrupt onset of stimuli in both hemifields with the same intensity: therefore, the spatial left-sided bias characteristic for the neglect syndrome depends only secondarily from lesions located at the right TPJ, and more directly from the disturbed activations of the ipsilesional component of the dorsal network. The functional and anatomical dissociation and tight cooperation between dorsal and ventral networks for the control of attention have been further substantiated by data presented in a review proposed by Pessoa, Kastner and Ungerleider (2003), and by a most recent event-related fMRI and resting-state functional connectivity magnetic resonance imaging (rs-fc-MRI) study (Shulman *et al*., 2009), which addressed with the combination of the two techniques the functional specifications of the ventral fronto-lateral networks for re-orienting and expectation. All in all, the evidences provided so far delineated a comprehensive anatomical and functional model concerning the neural system for the top-down and bottom-up control of visuo-spatial attention, involving multiple dorsal and ventral fronto-parietal network.

Following a key prediction of the models hypothesizing a dissociation between source and site signals in the study of attention, the attentional control system, embedded in the aforementioned frontal and parietal networks, should be involved in the generation of attentional signals that in turn can bias sensory processing in favor of attended items. From this prediction, it directly descends that the control networks need to interface the sensory systems which physically carry out the perceptual analyses upon the incoming stimulus stream. In the next section, functional imaging evidences for the existence and loci of these interfaces in the brain will be provided.

1.1.3.2 Site signals

Several neuroimaging studies reported enhanced activations in sensory areas (*site* signals) in response to targets falling at the cued locations (Corbetta *et al*., 1993; Nobre *et al*., 1997; Vandenberghe *et al*., 1997; Brefczynski & De Yoe, 1999; Vandenberghe *et al*., 2001; Natale *et al*., 2006 & 2009; Sylvester *et al*., 2009), further validated by studies using combined neuroimaging and electrophysiological measures (Heinze *et al*., 1994; Woldorff *et al*., 1995; Mangun *et al*., 1997). The earliest attempts to disentangle enhancements of the sensory activations in response to cued targets from attention-related enhancements (biasing) in the baseline activity of the sensory cortices in the pre-target interval in humans, go back up to the influential fMRI studies from Sabine Kastner and coworkers (1999) and from Joseph Hopfinger and colleagues (2000). Kastner and colleagues' cueing study was described earlier, in the context of the evidences provided for the existence of a system for the top-down control of spatial attention. In addition to the aforementioned results, with the use of the event-related fMRI technique in combination with a behavioral paradigm including the use of cue-only (noise) trials intermingled with cue-target trials, the authors were able to record increases of activity in the visual cortices in absence of visual stimulation, caused by covertly directing attention to a particular location and expecting the occurrence of visual stimuli at that location. The attentional effects on the baseline activity were recorded in V2, V4, temporo-occipital areas and, in a subset of participants, also in V1. Additionally, spatially specific activations were observed in the left ventral portion of the lingual gyrus and the left medial part of the fusiform gyrus (the targets were presented in the upper right visual quadrant). The attentional effects upon the baseline activity in striate and extrastriate cortices appeared to be qualitatively similar to the results obtained in single-cell recording studies in monkeys during attentional tasks (e.g., Luck *et al*., 1997), and were interpreted as clear indexes for the biasing activity exerted from the parieto-frontal network for the control of attention upon the sensory areas in order to facilitate detection of the upcoming stimuli, in line with the "biased competition" model (Desimone & Duncan, 1995). Shortly after this study, the work by Hopfinger and colleagues (2000) was published, further confirming the enhancement of contralateral extrastriate cortex activations in response to attentional tasks prior to target presentation: crucially, in accordance with models of spatial attention suggesting a gain-control mechanism that enhances the excitability of extrastriate neurons coding attended regions of the visual space, the cue-related activations closely overlapped with the extrastriate regions which showed attentional modulations in response to targets. The results of these two outstanding studies influenced the course of scientific research on the attentional systems, and were replicated in several neuroimaging experiments (Woldorff *et al*., 2004; Wilson, Woldorff and Mangun, 2005; Hahn *et al*., 2006; Sylvester *et al*., 2009; in addition, Capotosto *et al*., 2009 with a combined repetitive transcranial magnetic stimulation and EEG study). In an interesting fMRI study by Barry Giesbrecht and coworkers (2006), the hypothesis of the existence of biasing signals, originating in the frontoparietal network for attention and acting upon sensory areas, so to cause an advantage of the attended features or locations in the competition for neural resources, was further developed including measures of behavioral performance. The study investigated the magnitude and time course of pre-stimulus activity in regions of visual cortex in response to attention-directed cues, and addressed the question whether pre-stimulus modulations that occurred during cued spatial attention predicted subsequent behavioral discrimination performance of targets that were presented in the cued location. Indeed, the results indicated retinotopic organized pre-target biasing in extrastriate visual areas (lingual gyrus for the spatial task), and, crucially, strong linear correlations between the magnitude of the pre-target baseline activity increase and task-specific behavioral performance. All in all, this corpus of scientific evidences strongly supports the idea that the control of attention in dorsal and ventral fronto-parietal networks interacts with sensory mechanisms, directly facilitating the processing of relevant features or locations. The neuroimaging evidences are straightforward; however, the functional imaging techniques (even the more resolute event-related fMRI) cannot provide data with fine temporal resolution, which is a crucial feature when addressing the functional integration of fast-performing mechanisms as the attentional and sensory systems. For this reason, the review of the contributions of high temporal resolution ERP studies addressing visuo-spatial attention mechanisms is provided in the next paragraph.

1.1.4 The contributions of electrophysiological studies to the study of visuo-spatial attention

1.1.4.1 ERP responses to targets in visuo-spatial attentional paradigms

The electrophysiology of the effects of visual selective attention to spatial locations is extremely rich. Spatial attentional mechanisms have been proved to influence in parallel behavioral performance and the amplitude of several event-related potentials (ERP) components, for instance the series of visually evoked deflections (P1, N1, P2, N2) known as visual evoked potentials. Starting from the earliest studies of sustained spatial attention conducted by Eason, Harter and White (1969), reporting enhanced negative potentials around 120 ms after target appearance in response to targets presented at the attended location, several studies implicating spatial modulations of attention found contrasting results: Van Voorhis & Hillyard (1977), with a paradigm similar to Eason and colleagues', replicated the N1 modulation but also a less clear P1 modulation centered at the right-sided occipital electrode (O2); Hillyard & Münte (1984) confirmed spatial attentional modulations of the P1 contralaterally to the attended hemifield, further replicated (in addition to contralateral N1 modulations) in a series of works by Mangun & Hillyard (1987 & 1988). These latter studies provided electrophysiological evidences for the *gradient* model of spatial visual attention (Downing & Pinker, 1985), and for the idea of a gating system in the sensory cortices acting as early as 130 ms after stimulus onset (Eimer, 1994). A different research group, however, in contrast with the most commonly recorded contralateral pattern, observed effects of spatial attention on the occipital ipsilateral P1 (Rugg *et al*., 1987, but see also Skrandies & Lehman, 1982 and Skrandies, 2000). In line with the work by Mangun & Hillyard (1988), more recent combinations of the electrophysiological technique with functional neuroimaging (Heinze *et al*., 1994; Mangun *et al*., 1997) provided further evidences that the gating process takes place in the extrastriate cortex contralateral to the attended location, in accordance with the body of evidences offered by the functional neuroimaging literature. The effects produced by trial-by-trial endogenous cueing are similar, if not identical, to those observed in tasks in which attention is sustained on a single visual field location throughout a block of trials while comparable stimuli are flashed to that location and other unattended locations in the visual field; it remains rather unclear, however, the precise temporal locus at which top-down attentional influences affect the visual operations (Mangun, 2003). Some studies reported that attention to features can influence processing in V1 (Zani & Proverbio, 1995, 2006 & 2009), but for the spatial attention domain the electrophysiological contributions sustaining this position are inconsistent, with the majority of studies finding a lack of effects earlier than in the P1 window (e.g., Zani & Proverbio, 1997, 1999 & 2005). Indeed, the functional evidences for the putative locus of spatial selectivity in V1 (Kastner *et al*., 1999; Tootell *et al*., 1998) do not specify the time-course for this activation: as a consequence, still in debate is the true nature of the V1 modulation (early sensory activation or feedback reafferent modulation by top-down influence, as suggested by Martinez *et al*., 1999). In the domain of reflexive attention, Fu and coworkers (Fu *et al*., 2001 & 2005) reported null modulations of the earliest visual evoked component (C1), thus supporting attentional modulations at later stages than the primary visual cortices. However, most recent studies in animals (McAlonan, Cavanaugh & Wurtz, 2008) and humans (Kelly et al., 2008) showed signs of early attentive modulation in visual cortex or even in subcortical structures for spatial attention processes, opening up new scenarios for the investigation of these effects. In the same attentional modulation domain, Joseph Hopfinger & George Mangun (1998) elegantly demonstrated with an exogenous cueing paradigm in which the stimulus-onset-asynchrony (SOA) was manipulated, differential effects on the occipital components of the visual evoked potentials. Uninformative peripheral cues were able to modulate behavior in line with previous literature (Posner & Cohen, 1984): at short SOAs, validly cued targets elicited faster motor responses; at long delays, the pattern was different, and targets presented at cued locations elicited responses which were not faster than the uncued trials. Crucially, when the SOA was short, targets at the cued location elicited enhanced visual components (P1), as compared to targets presented at uncued locations, with correspondent scalp distribution. The pattern of results resembled the configuration obtained for endogenous attention, further confirming the notion that attentional control interfaces sensory processes at early stages. At longer SOAs, however, the pattern of enhanced P1s for cued targets was not present, and, reversely, cued targets elicited significantly smaller P1s as compared to uncued targets, mirroring behavioral effects of inhibition of return (IOR, Posner & Cohen, 1984). The inconsistency between behavioral and electrophysiological results (the ERPs showed an IOR-like pattern, while RTs for cued and uncued targets at long SOAs were not significantly different) was further confirmed in a follow-up study (Hopfinger & Mangun, 2001), requiring speeded responses to the reflexively cued targets: the behavioral IOR pattern was significant at long SOAs, but the electrophysiological modulation observed in Hopfinger & Mangun (1998) was not replicated. Nonetheless, the highly consistent findings for the short SOAs (P1 enhancements and behavioral facilitations) indicated that when attention is reflexively captured by a sensory event, cortical visual processing is modulated at the same stage of visual processing as in case of endogenously driven shifts of attention. Whereas the provided ERP evidences concerned studies that addressed the processes of attention-related sensory facilitation of target processing, the pre-target modulations of sensory areas driven by the areas that control spatial attention (as indicated by the body of functional neuroimaging data provided in the previous paragraphs), has been poorly addressed in the electrophysiological literature. The sparse body of ERP literature concerning the cue-target interval will be presented in the next section.

1.1.4.2 ERP responses to cues

The first attempt to address processes taking place in the period following attention-directing cues and preceding target appearance was a study by Harter and coworkers (Harter *et al*., 1989). In a trial-by trial cueing paradigm administered to a large group of children (6-9 years of age), centrally presented cues (arrows) anticipated by 600 ms the presentation of target stimuli in either hemifield. The participants were instructed to direct their attention towards the cued hemispace, and to respond whenever a target occurred at that location. The ERPs in response to leftward cues were arbitrarily subtracted from the cerebral responses to rightward cues, obtaining difference wave ERPs (dERPs). The earliest component which showed modulation dependent by cue (i.e., attention) direction was recorded at posterior sites, contralaterally to attentional shift, with an onset around 200 ms. This component was defined by the authors *early directing attention negativity* (EDAN), and it was interpreted as a reflection of the cognitive interpretation processes of the symbolic cue, which in turn guided top-down attentional shifts. The second modulation was recorded between 500 and 700 ms after cue onset at posterior electrodes, again over the hemisphere contralateral to cue direction: this positive contralateral drift, which lasted up to target presentation, was defined *late directing attention positivity* (LDAP). As the name might suggest, also the LDAP was interpreted as an electrophysiological correlate of attentional shifts, reflecting the modulation of the cortical excitability in regions which are preparing to receive relevant visual information (i.e., the upcoming targets). An additional dERP modulation, called *anterior directing attention negativity* (ADAN, Hopf & Mangun, 2000) was recorded at late latencies over frontal sites, but was not modulated by the direction of attention, and, therefore, it was most probably linked to motor preparation processes. In order to be able compare with Harter's work, the subsequent studies addressing the electrophysiological responses in the cue-target interval maintained a similar structure for the behavioral paradigms and for the ERP analyses, with statistical comparisons between responses to cues pointing towards the left and right hemifields, with additional manipulations of the shape or of the informative value of the cues. Yamaguchi and colleagues (1994) compared an endogenous cueing paradigm (central arrow cues with 80% validity) and an exogenous cueing paradigm (peripheral appearance of boxes, with 80% validity), in a within-subjects design with healthy adult participants. They also introduced a SOA manipulation, which did not harvest attentional-related differences and was therefore not discussed. The results indicated, for the top-down cueing modality, a more negative ERP deflection starting at about 240 ms after cue onset at contralateral electrodes in respect to the cue direction, replicating the EDAN effect described by Harter *et al*. (1989). Subsequently, regardless of cue direction, a right posterior-temporal negativity was found starting around 500 ms after cue onset and lasting until target presentation (800 ms). In this study, no endogenous driven LDAP effect was recorded. In the exogenous part of the experiment, the earliest effects were contralateral enhancements of the N1 component in response to cues (plausibly reflecting a combination of differences in the physical attributes of the lateralized stimuli and attention-directing processes). Unfortunately, the complexity of the design and the intermixing of factors made it difficult to interpret the results. Martin Eimer (1993), using a spatial orienting task with central predictive arrow cues, measured anticipation/preparation potentials preceding the targets, as the Contingent Negative Variation (CNV) and lateralized readiness potentials (LRPs). These potentials were large in response to cues, and even larger in a condition in which the cues carried relevant predictive information about the target response to be delivered. Unfortunately, the complete waveforms elicited by the cues were not reported and analyzed, which made the results rather difficult to compare to other studies. More recently, two studies were published by Hopf & Mangun (2000) and by Nobre, Sebestyen & Miniussi (2000). The two studies had different aims: whereas Nobre and coworkers were interested in recording ERP signals in response to the same physical stimuli (centrally presented colored diamonds) in different conditions (i.e., when they cued covert peripheral shifts of attention to either the left or the right visual fields), Hopf and Mangun sought to further investigate the electrocortical processes involved in visual-spatial attention shifts by providing detailed topographical analyses of the ERPs in the cue-target interval, in order to provide electrophysiological evidences sustaining the fronto-parietal network model (Gitelman *et al*., 1999; Corbetta & Shulman, 2002) in the context of an endogenous cueing paradigm. In the study by Nobre and coworkers

(2000), the earliest ERP differences elicited by the foveal cues according to the direction of the predicted target location were recorded starting around 160 ms after cue presentation, and consisted of enhanced negative potentials over the posterior scalp contralateral to the cued location. The differences persisted until the occurrence of the target stimuli, in shape of enhanced positivities in the hemisphere ipsilateral to attention direction (i.e., being the comparison arbitrary, corresponding to contralateral negativities, in line with Yamaguchi *et al*., 1994). In the study by Hopf and Mangun (2000), the earliest attention shift-related modulations of ERP components were observed in a later time-window (i.e., between 200 and 400 ms after the centrally presented cues). This occipital effect resembled for polarity and scalp distribution the EDAN recorded by Harter *et al*. (1989) and by Yamaguchi *et al*. (1994). Crucially, the EDAN maximum was indeed recorded over occipito-parietal sites, in line with the hypothesized early attentional role of the parietal cortices in attentional shifts, as reflected in the EDAN ERP response. A left-sided bias for the EDAN scalp distribution, discussed in the text as surprising, was in fact consistent with a body of neuroimaging evidences, described earlier in this chapter (e.g., Nobre *et al*., 1997; Corbetta *et al*., 2000; Wilson *et al*., 2005; Mayer *et al*., 2004). An additional contribution to the ERP literature addressing the cue-target interval (Van Velzen & Eimer, 2003) tackled a different research question: by means of a dissociation between cue position and attention direction, they aimed at resolving the issue whether the EDAN reported in several previous studies (Harter *et al*., 1989; Hopf & Mangun, 2000; Nobre *et al*., 2000) was a true reflection of the cerebral processing directing attention, or if it was principally related to the physical attributes of the attention-directing cues (for example, their position or salience). The study reported EDANs which were steadily contralateral to cue *position*, regardless of the cued *direction* of attention; conversely, the LDAP and ADAN components were consistently observed at electrode sites contralateral to cue *direction*, regardless of its *position.* These results led to the conclusion that the LDAP and ADAN are the electrocortical reflections of mechanisms of attentional control, indicating a later stage for attentional shifts, as compared to the EDAN time-range (or, alternatively, a stage of more sustained attentional maintenance of the cued location). To our knowledge, few additional studies carried out using the ERP technique concerned the cue-target interval. One study by Grent-‘t-Jong & Woldorff (Grent-‘t-Jong & Woldorff, 2007) was conceived in combination with an event-related fMRI study conducted using the same behavioral task (Woldorff *et al*., 2004): remarkably, the authors were able to construct a paradigm with experimental parameters which made it suitable for both ERP and fMRI employment (i.e., cue-target intervals comprised between 900 and 1900 ms). The results, obtained with the use of several different analysis techniques, led the authors to the conclusion that the pre-target attentional activations are composed by at least two intervals: a long window, lasting 400 ms after cue onset, should involve the cognitive interpretation of the meaning of the cue, carried out by lateral frontal and parietal cortices; after this interval, the attentional modulations take place, with an involvement of more medial frontal and parietal areas. The onset of the attentional activation was recorded at frontal sites, followed, at later latencies (around 700 ms after cue onset) by parietal foci; these medial parietal foci are then thought to trigger the enhancement of contralateral negativities in response to targets, which starts several milliseconds before target appearance as a *biasing related negativity* (BRN) over contralateral extrastriate cortices. Recently, a series of papers presented by Jessica Green and John Mcdonald (Green *et al*., 2005; McDonald & Green, 2008; Green *et al*., 2008) was aimed at better understanding the classical ADAN, EDAN and LDAP/BRN components and their anatomical foundations. The discussion has been centered about the plausible supramodality of the ADAN component, and the possible cerebral bases of the LDAP, i.e., parietal activity related to the deployment and maintenance of attention at the cued location, rather than biasing activity in lateral occipital cortices. The conclusions of the authors sustained that the ADAN is generated in the frontal cortex, but does not truly reflect supramodal attentional control mechanisms, because it was not possible to steadily record it with cues delivered in different modalities; conversely, the LDAP was consistently recorded over contralateral occipital sites, even when the analyses included a comparison between lateralized (and upwards) shifts of attention and neutral cues not eliciting any attentional movement. In addition, source reconstruction performed upon the observed components, revealed unexpected results, which led to twofold conclusions: first, the contralateral LDAP was generated by sources that were ipsilateral to the direction of the attentional shift; second, distributed source activities in the inferior parietal lobe and in the superior frontal gyrus were obtained starting during the same temporal window. These results suggested that the LDAP might not reflect facilitation of the attended location, but the active suppression of the unattended one; second, the parietal and frontal cortices were suggested to be activated for attentional control at approximately the same time in the spatial cueing task specific for these studies.

All in all, the review of the ERP literature concerning the cue-target interval showed rather contrasting results about the timing and lateralization of components considered the true reflection of attentional shifts; moreover, several predictions about the classical lateralized ERP components detected during shifts of spatial attention in different modalities were not always clarified by the experimental datasets obtained with different paradigms. This pattern leaves open some key questions about the real lateralization of the recorded components and about their anatomical bases, which have been addressed by this experimental work.

1.2 Executive functions

The cognitive abilities needed for flexibly guiding and adapting behavior on-line following internally-guided intentions are grouped under the definition of *executive functions*. These skills include the capacity to select actions in order to achieve current goals, rather than merely responding to urgent pressures deriving from the external environment (e.g., Baddeley, 1986; Norman & Shallice, 1986): thus, cognitive control is mainly exerted when we need to ignore interfering stimuli or to face novel or complex tasks, especially when they include requirements for planning of new strategies, organized or sequential behavior, and the ability to overcome or inhibit prepotent responses.

1.2.1 Taxonomy of the executive functions

The executive functions have been studied in the framework of cognitive psychology and modeled by several theoretical approaches, as the *central executive* component of Baddeley's working memory system (1986), or the *Supervisory Attentional System* (SAS) embedded in the attentional control model by Norman & Shallice (1986). More recently, the taxonomy of the executive functions has been discussed in the light of contrasting accounts supporting the existence of a unitary system, without subcomponents or subdivisions, against evidences for a non-unitary nature of the *frontal lobe functions*, as they are also often called. The strongest demonstrations for subdivisions internal to the executive functions system derive from neuropsychological data (i.e., performance dissociations in diverse tasks tapping at the executive functions are evident among patients affected by different lesions), and from interindividual differences studies. One influential model of the frontal lobe functions (Miyake *et al*., 2000; Friedman & Miyake, 2004) included under the same definition of executive functions the *shifting* between tasks or mental sets, the ability to *update and monitor* working memory representations and the *inhibition* of responses, in turn subdivided in *inhibition of prepotent responses*, *resistance to distractor interference*, and *resistance to proactive interference*. A different, but equally influential theoretical account (Botvinick *et al*., 2001 & 2004) proposed that the executive functions are involved in *response override*, in *response choice in case of undetermined responding* (which comprises a *planning* component) and in the processes of *error detection and correction*. These three functions are unified under the definition of *cognitive control*, which is responsible for the on-line adjustment of perceptual selection, for processes of response biasing and for the maintenance of contextual information. In the model by Botvinick and coworkers (2001 & 2004), the medial frontal cortex, and in particular the anterior cingulate cortex in its dorsal component, constantly monitors for response (and in some cases, stimulus) conflict in information processing; once the conflict monitoring system detects the need for intervention of cognitive control mechanisms, a triggering signal is produced by the medial frontal cortex, and the intervention of more dorsolateral or ventrolateral frontal cortices, which are able to implement strategic processes, is recruited. Again, following a yet different prominent account, the *selection for action* hypothesis (Posner & Petersen, 1990, Bush, Luu & Posner, 2000), the function defined *executive control* is a unitary system, sustained by the anterior cingulate cortex in its more dorsal component, which carries out both conflict detection and resolution.

All of the aforementioned models have been widely used by experimental psychology, neuropsychology and cognitive neuroscience in order to build up and validate useful tools which are implied in measures of the executive system functionality in healthy populations and in patient studies. Thus, the executive control system is often experimentally tested using tasks involving conflict at the response level, although the role of the frontal lobes in situations involving conflict only at the sensory level are also under questioning (see Van Veen & Carter, 2002). Examples of such tasks are the classical color-word Stroop interference task, which involves conflict between a word name and its ink color (Stroop, 1935), the Eriksen task, in its classical version or variously modified (Eriksen & Eriksen, 1974), which makes use of congruent or incongruent distracters in order to elicit conflict in choice reaction times tasks; the Simon task (Simon & Berbaum, 1990), which capitalizes on a spatial kind of response incompatibility; additionally, many other tasks involving the need to override or to inhibit prepotent responses (as in the go/no-go task, or in the stop-signal task) and tasks characterized by undetermined responses (such as all the linguistic fluency or stem completion tasks) are useful tools for neuropsychological or experimental studies interested in the executive system. In addition, tasks involving planning, as the Tower of Hanoi (or its variant, the Tower of London task), and tasks requiring flexibility and resistance to perseveration, as the Wisconsin Card Sorting Test (WCST) are used in the clinical practice in order to test the functionality of the control system, but will not be discussed in this work because, for their complexity, are not widely utilized in controlled experimental settings.

1.2.2 Brief account of the neuropsychology of executive control

Historically, the research on the executive functions is a direct derivation of the neuropsychological studies involving patients with frontal lobe damage. It has been known for decades that patients with lesions located in the frontal lobes often demonstrate severe problems in the control and regulation of their behavior (i.e., in inhibition or in situations involving planning), and are seldom high functioning patients in everyday life, for they tend to show some impairments on a multitude of complex tasks. Neuroanatomically, the highly differentiated cortices of the frontal lobes can be distinguished on the basis of their position, function and connectivity. Medially, the anterior cingulate can be portioned in two subdivisions: a rostro-ventral section, more involved in the processing and integration of emotional information, and highly connected to limbic structures; a dorsal portion, more involved in cognitive processes, is highly connected with the lateral prefrontal cortex and the motor system (Bush *et al*., 2002; Matthews *et al*., 2004; di Pellegrino *et al*., 2007). Regarding the lateral surface of the frontal lobes, the rostral component (dorsolateral-prefrontal cortex, with the medial components of the supplementary motor area, SMA, and pre-SMA) is involved in control functions and in motor preparation (e.g., Miller & Cohen, 2001), while more posterior areas contain primary and secondary motor areas. At last, the more ventrolateral portions of the frontal lobes, together with the orbitofrontal cortices (mainly in the right hemisphere) are involved in motor inhibition and in re-orienting functions (Chambers *et al*., 2007; Forstmann *et al*., 2008; Shulman *et al*., 2009). From the functional partition of the cortices supporting the executive control network, it derives that lesions selectively damaging one or the other subcomponent of the frontal network cause deficits which are reflected in various and often dissociated behavioral impairments. For example, a patient who received bilateral anterior cingulotomy in order to contain depression and seizures was shown to suffer of selective deficits in the ability to sequence novel cognitive operations and in the ability to override an automatic response in favor to a controlled and unpracticed one (Ochsner *et al*., 2001), while patients with more selective rostral ACC lesions showed impaired behavioral adjustments in case of errors or sequences of high conflict situations (postconflict and posterror adjustments: di Pellegrino, Ciaramelli & Làdavas, 2007). Conversely, lateral frontal patients (and, in particular, right as compared to left ventrolateral patients) showed impaired behavioral inhibition (Aron *et al*., 2003), as measured in a stop-signal task. In line with the clinical data, experimental studies involving lateral prefrontal patients showed impairments in response inhibition (for a review, Deouell and Knight, 2004): the observed host of deficits was traditionally attributed to response-selection perturbations, but this explanation has been recently challenged by electrophysiological evidences demonstrating abnormal suppression of information processing at the level of unimodal sensory cortices in case of distracting information (Deouell and Knight, 2004). This lack in the modulation of irrelevant stimulation was also mirrored, in lateral prefrontal patients, by poor facilitation of the relevant inputs, which is normally exerted by the frontal cortices upon the ipsilateral posterior sensory systems: the combination of the two phenomena gave rise to the behavioral deficits reported for these patients, together with impairments in novelty or change detection. In addition, lesions involving the supplementary motor area (SMA) and the pre-SMA region have also been linked to motor initiation or inhibition impairment, but the lateralization of SMA lesions leading to inhibitory deficits is less clear (Chambers *et al*., 2009). All in all, the neuropsychological data concerning frontal patients, taken together with cytoarchitectonic and connectivity data, indicate high levels of specialization in the frontal lobes, which justifies the complex architecture of the executive functions which are subserved by the frontal cortices. The multicomponential nature of the executive control function, and its multiple definitions and models have caused the development of a large number of research lines investigating one (or more at once) of the subcomponents of the network: a full account of this literature is impossible in this work, for its complexity and the amount of branches. We will therefore concentrate on a brief revision of the literature concerning the cognitive neuroscience of the interference control function and the inhibitory systems, which are the most relevant sub-components of the executive functions in light of the scope of this scientific project.

1.2.3 The contributions of cognitive neuroscience to the study of the executive functions

1.2.3.1 Inhibitory circuits

As earlier mentioned in the paragraph concerning the taxonomy of the executive functions, the mechanism of response inhibition is one of the fundamental subcomponents of the control/monitoring system, and includes the ability to suppress actions that are no longer functional or relevant, or, in a more specific context, the ability to selectively choose one response over another one, equally primed but not appropriate. This latter aspect of response inhibition, which does not compare conditions in which the emission or suppression of a motor response is required (e.g., in the go/no-go task, or the stop-signal task), whereas a choice between a prepotent response and a non-prepotent, but correct, one is implicated (e.g., the Stroop task, the Simon task or the flanker task) will be discussed in the next paragraph, in interaction with processes of conflict monitoring and interference.

A long tradition of animal and human studies (e.g., Butters *et al*., 1973; Watanabe, 1986; Pfefferbaum *et al*., 1985; Kok, 1986) utilized the go/no-go paradigm in the investigation of behavioral inhibition, for its simple design and implementation. In this paradigm, a selection is required between either executing or inhibiting a motor response, triggered by one or more Go and Nogo visual (or auditory) stimuli. Since Go trials are, in the typical design, more frequent than Nogo trials, a prepotency towards response execution builds up, and a process of response inhibition is required in order to refrain from responding to Nogo trials. RTs to Go stimuli, as well as omission and commission errors, can therefore be examined. Several neuroimaging studies implying this task consistently indicated frontal circuits related to the no-go activity (Kawashima, 1996; Casey *et al*., 1997; Konishi *et al*., 1998 & 1999; Watanabe *et al*., 2002) and to motor impulsivity indexes (Asahi *et al*., 2004); quite recently, a combined event-related fMRI and ERP experiment (Swainson *et al*., 2003) recorded anterior cingulate activations related to conflicting situations, and interactions between motor response withholding and task switching in right prefrontal and ventrolateral cortices, accompanied by enhancements in a frontal ERP response. This frontal component, called *NogoN2*, is commonly elicited in go/no-go tasks, principally in response to Nogo stimuli, while is hampered or not present at all in response to Go stimuli. For this reason, the interpretation of this ERP deflection, together with the later and more posteriorly distributed *NoGoP3*, has been traditionally related to inhibitory processing (Jodo & Kayama, 1992; Kopp *et al*., 1996; Falkenstein *et al*., 1999). However, in light of the controversial results of more recent studies, the theoretical discussion about these electrocortical responses is still highly debated. In contrast with the early accounts, suggesting that the N2 reflects the inhibition of a prepotent motor response, a host of recent experiments suggested a more complex role of the frontocentral negativity in inhibition-related tasks. First, the N2 resulted sensitive to the proportion of Go versus Nogo responses (Nieuwenhuis *et al*., 2003, Bekker, Kenemans & Verbaten, 2005), regardless for the type of trial (Go vs Nogo): in case of infrequent Go responses (i.e., only 20% of the trials required the motor response, as compared to 80% of Nogo trials), the *NogoN2* was enhanced for the Go stimuli, in respect to the frequent Nogo trials. Moreover, in an experiment in which the required response to the Go stimuli was cognitive (counting task) instead of motoric (Bruin and Wijers, 2002), the *NogoN2* was nevertheless elicited in case of Nogo response, although no motor inhibition was involved in this type of task. Additionally, the aforementioned component has been shown to be sensitive to the amount of perceptual overlap between Go and Nogo stimuli (Nieuwenhuis, Yeoung & Cohen, 2004; Proverbio *et al.*, 2009): an indication that the amount of response competition (and not strictly the inhibitory process) was among the generators of the N2. However, the most compelling evidences for a role of the N2 different from simple response inhibition came from a study by Franc Donkers and Geert van Boxtel (2004), which recorded *NogoN2s* for infrequent stimuli in which the required response was the pressure of a response-key with maximal force (thus, no inhibition at all was involved in this case), as compared to Go stimuli which required responses with speeded key-presses with normal force. This effect, together with the observation that this *GoN2* showed highly similar distribution and responsivity to frequency manipulations as the traditional *NogoN2* (recorded in the same experiment in a within-subject design) was used to argument a possible role of this ERP component in conflict monitoring, rather than motor inhibition. Further studies using different materials for the go/no-go task or for choice reaction times tasks demonstrated N2 sensitivity in response to different levels of semantic categorization or stimulus ambiguity (Maguire *et al*., 2009; Szmalec *et al*., 2008), in line with the hypothesis of a relation of this component with conflict monitoring processes or with response activation, rather than inhibition (Bruin, Wijers & van Staveren, 2001; Smith, Johnstone & Barry, 2007; Szmalec *et al*., 2008). In the same direction, results from a study comparing children affected by Attention Deficit/Hyperactivity Disorder (ADHD) with healthy controls showed reduced N2s in the patients, accompanied by behavioral differences in the response speed to Go stimuli, but not in the rate of responses to Nogo stimuli (Johnstone *et al*., 2009). In line with data showing impaired decision making in AD/HD patients (DeVito *et al*., 2008), this pattern of results is compatible with an account of the N2 as a cerebral reflection of conflict monitoring or response activation deficits, as opposite to response inhibition deficits.

Besides the go/no-go paradigm, the investigation of processes of inhibition of motor responses has employed a variety of tasks,: one of the traditional tools, the stop-signal paradigm, requires speeded responses to visually presented stimuli, which have to be withheld in case of a countermanding stimulus is auditorily or visually delivered shortly after the primary, imperative stimulus (Lappin & Eriksen, 1966; Logan & Cowan, 1984; Logan *et al*., 1984; Logan, 1994; Verbruggen & Logan, 2009 for a recent review). Therefore, the difficulty in the stop-signal paradigm derives from the need to retract a motor response which has already been triggered by the go signal; the timing and proportion of stop-signal trials, interspersed among the go trials, are further manipulated in order to model the speed and effectiveness of the inhibitory functions, often in combination with neuroscientific techniques as TMS, EEG and ERPs (De Jong *et al*., 1990; van Boxtel *et al*., 2001; Kok *et al*., 2004; Ramautar *et al*., 2004 & 2006; Bekker *et al*., 2005; Stahl & Gibbons, 2007; Chambers *et al*., 2007; Liddle *et al*., 2009; Tallet *et al*., 2009; van den Wildenberg *et al*., 2009). The most commonly used dependent variable of inhibitory performance in the stop-signal paradigm is the estimated finishing time of stop-signal processing, or stop-signal reaction time (SSRT). In contrast to the direct observation of processing speed in the primary task (the go-trials overt reaction time), the SSRT can be estimated only indirectly starting from the go RTs distribution and the proportion of correctly inhibited responses in stop-signal trials. Several techniques have been proposed for this estimation, but, under certain assumptions, all of the procedures lead to comparable results with similar levels of accuracy (see Verbruggen & Logan, 2009 for a comprehensive review). The numerous ERP studies conducted in combination with the stop-signal task have identified a pattern of electrocortical responses which are selectively elicited by go and stop trials, and which can differentiate between successful and failed motor inhibition in stop trials. As examples, enhanced frontto-central N1 and P3 components in the successful inhibition compared to unsuccessful inhibition conditions (e.g., Bekker *et al*., 2005; Overtoom *et al*., 2009) have been recorded in healthy controls and medicated patients, and interpreted as reflections of the inhibition of responses to the imperative stimuli, elicited by the stop signals. Furthermore, in line with the results obtained with the go/no-go task, the N2/P3 complex recorded in response to the stop-signals is resulted sensitive to the frequency of the stop-trials (Ramautar *et al*., 2004) but not to the stop-signaling modality (e.g., auditory versus visual, Ramautar *et al*., 2006). Taken together, these results might suggest that the frontal N2 elicited by Nogo stimuli and by stop-signals reflects the operation or outcome of an inhibitory process in frontal cortex (Konishi *et al*., 1999; Rubia *et al*., 2001; Garavan *et al*., 1999 & 2002; Rubia, Smith, Brammer, & Talyor, 2003); however, the fact that the fontal N2 recorded in several studies was more pronounced for unsuccessful stop-signal trials as compared to successful stop-signal trials argued against a simple inhibition explanation: if inhibition-related frontal activations were the source of the frontal N2, it would be plausible to observe higher amplitudes in situations in which the inhibition was successful; on the other hand, if the frontal N2 were elicited in situations of response competition in which a conflict monitoring signal is activated in the fontal cortex (Botvinick, *et al*., 2001 & 2004, Van Veen *et al*., 2001; Van Veen & Carter, 2002; Carter & Van Veen, 2007), then it should be expected to observe enhanced activations in case of low-probability stop-signal trials and in case of failed inhibitions as compared to successful ones (Nieuwenhuis *et al*., 2003; Bruin and Wijers, 2002; Ramautar, Kok & Ridderinkhof, 2006). Furthermore, the negative valence elicited by the unsuccessful stops might be one of the concurrent causes of enhanced negativities in this condition, in parallel with post-response enhanced negativities in case of error detection (Error-Related-Negativity, Gehring *et al*., 1993, or Error Negativity, Falkenstein *et al*., 1991).

One fMRI study (Rubia *et al*., 2001) explicitly addressed the common neural mechanisms underlying the inhibitory function in the go/no-go and stop-signal paradigms, under the hypothesis that the parts of the frontal lobes specifically involved in inhibitory control may be, to some extent, depend on the kind of action which needs to be inhibited (a primed response in case of the stop task, or a selective response in case of the go/no-go task), in line with the functional and neuropsychological evidences of high specialization of the frontal lobes cortices. The results of the study showed partially segregated frontal and parietal circuits for the two tasks, but also a common neurofunctional activation network which comprised bilateral middle and inferior frontal gyri, anterior cingulate, pre-SMA, and inferior parietal cortex. From the differential activations the authors derived the conclusions that the right inferior frontal cortices may be specifically related to motor response inhibition (further confirmed by the more recent study by Aron and coworkers, 2007), while dorsolateral, medial prefrontal and parietal cortices are possibly the mediators for more general executive control functions such as conflict monitoring and response selection, necessary for adaptive task performance. In conclusion, in a recent review of neuropsychological, psychiatric, genetic, functional and psychopharmacological evidences, Chambers, Garavan and Bellgrove (2009) suggested that the right IFG and SMA/pre-SMA are the crucial areas for response inhibition, although the single reviewed studies proposed alternate opinions about the key role of either of the structures. The authors concluded that, given the rich connectivity among these structures, the combination of more than one neuroscientific techniques (e.g., r-TMS and fMRI) is desirable in future research to further delineate the precise role of each area in the neurocognitive network of response inhibition.

1.2.3.2 Interference control

A very recent study (Forstmann *et al.*, 2008) tackled the neural networks subserving the interference control systems implying structural and functional neuroimaging techniques (fMRI and Diffusion Tensor Imaging, DTI) in combination with a spatial conflict task (Simon task). This task capitalizes on the incompatibility of the responses elicited by the position of the stimulus on the screen (e.g., in the left hemifield), which is task-irrelevant, and intrinsic characteristics of the same stimulus (e.g., its color) which are mapped onto a motor response (e.g., the right hand). The response primed by the position of the stimulus and the response required by the stimulus identity can be compatible or incompatible; to further emphasize the incongruency dimension, the targets can be cued (validly or invalidly) about their congruency level: invalidly cued stimuli are assumed to be associated with stronger inhibition, while valid incongruency cues can elicit a ‘control set’ in which the incompatibility costs are hampered. Since the response activation function is known to build up faster than the response inhibition function, by means of an analysis technique which plots the interference effect as a function of response speed (*delta plots*, De Jong *et al.*, 1994; Ridderinkhof, 2002; Ridderinkhof *et al.*, 2005) the individual differences in the speed of the inhibitory function could be inserted as covariates in the analyses of the blood oxygenation level-dependent (BOLD) fMRI activations. The results indicated a tight association between the fMRI responses in the right inferior frontal cortex (rIFC) and inhibitory efficiency, expressed as the speed of the inhibitory function in the RT distribution. Moreover, proficient inhibitors showed increased structural connectivity in the white matter of the rIFC, and the structural connectivity values, in turn, correlated positively with the BOLD activation in rIFC. The implication of the rIFC in motor inhibition and response selection has been previously supported by fMRI data (Hazeltine *et al.*, 2000 & 2003) recorded during a modified version of the flanker task (Eriksen & Eriksen, 1974): the right inferior frontal gyrus (IFG) activation was accompanied by foci of increased signal in the right middle frontal gyrus, right parietal and anterior cyngulate cortices; crucially, this network showed selectivity for the resolution of response competition, for it was similarly activated in case of incongruency in rather different experimental materials (colored circles vs letters used as targets and distracters). In line with these results, dorsal anterior cingulate cortex (dACC) activations have been reported in association with conflict resolution in a cued global-local conflict paradigm (Weissman *et al.*, 2005) and dACC has been shown to generate the P300 component in response to incongruent trials as compared to congruent ones in a classical color-word Stroop conflict task (Badzakova-Trajkov *et al.*, 2009); moreover, medial frontal activity has been reported in papers using flanker paradigms, in case of response conflict (Ullsperger & von Cramon, 2001; Van Veen *et al*., 2001, Fan *et al*., 2005). In a paper using several conflict tasks as an arrow version of the flanker task, a color-word Stroop task, a modified Simon task, and an hybrid Stroop/flankers task (Fan *et al*., 2003) the only common activation among all the tasks consisted in the ACC cortex, although the behavioral measures for conflict in the different tasks were not related (as expressed by weak or null correlations among behavioral incongruency costs). This result sustains theories suggesting that the role of the cingulate cortex in conflict situation is to monitor for inconsistencies in the stimulation/response matching, and perhaps to recruit more dorsolateral areas involved in the cognitive control and conflict resolution (Botvinick *et al*., 2001 & 2004): in line with this position, the foci in more medial dorsal and dorsolateral areas (SMA, pre-SMA) in all of the conflicting situations used in the series of experiments comprised task-specific regions, compatible with local conflict resolution monitored by cingulate areas (see also Ullsperger & Von Cramon, 2001). Additional implications of the right dorsolateral prefrontal cortex in conflict resolution and/or response selection have also been suggested by experiments conducted by means of a completely different technique: the rTMS. These studies used the Stroop task (Vanderhasselt *et al*., 2007) and arrow versions of the flanker task (Chambers *et al*., 2007) in order to elicit and measure conflict, and both reported that repeated stimulation upon the right dorsolateral prefrontal area modulated the behavior of the participants: the motor responses were overall speeded (in case of both congruent and incongruent stimuli). The explanation for the effect took into account the fact that the expectancy for incongruency (the *task set*) was high in these experiments, and that rTMS might have acted upon the attentional set by boosting the control system in its response selection component, with a resulting overall speeded RTs effect.

In a comprehensive review of the prefrontal specialization for action selection, response inhibition, performance monitoring and reward-based learning (Ridderinkhof *et al*., 2004), it was proposed that an evaluative component, crucial for monitoring the need for control and for signaling when adjustments are necessary, is implemented in the medial portions of the frontal cortex (ACC, SMA and pre-SMA); conversely, a more regulative component, responsible for the active implementation of executive control processes, relies predominantly upon more lateral and orbital portions of the frontal cortex (DLPFC, IFC). However, even when acknowledging a certain amount of frontal specialization, the high degree of overlap in the areas involved in the different subcomponents of the executive functions (response inhibition and activation, interference control, but also task switching, goal-directed action selection and performance monitoring) points towards a strongly integrated system for the control of adapted behavior, embedded in the prefrontal cortex. In summary, by means of the results obtained with several behavioral paradigms and research techniques, the functional differentiation *and* integration of the prefrontal cortices can be, to some extent, sustained and motivated.

Chapter 2.
The attentional networks theory

An influential account of the attentional function has been proposed by Posner and Petersen (1990), which presents a taxonomy of the attentional system as a complex network composed by at least three sub-components, with separate, although partly overlapping, functional and neural architectures. The three main constituents of the network are the *arousal* system, deputed to the achievement and maintenance of an adaptive alert state, the *spatial orienting* system, involved in the selection of information from the sensory input, and the *executive control* system, which detects and resolves conflicting aspects within the information processing stream. Since this model of the attentional networks has been used as the theoretical reference framework for the experimental part of this project, it will be shortly outlined in its details in this chapter.

2.1 Alertness

The most basic aspect of attentional intensity is constituted by the *arousal* system, which sustains the more complex and demanding components of selective attention. The *alertness* function, other name for the arousal system, is characterized by two separate and different subsystems: on the one hand, it refers to the ability to achieve and maintain an adaptive state of wakefulness (tonic arousal, or vigilance), which is characterized by a circadian oscillation that interacts with the top-down capacity to modulate our own internal state; on the other hand, it also concerns the ability to increase response readiness for short periods of time, in a bottom-up modality, subsequent to external cues or salient arousing stimuli (phasic alertness).

A typical task for the assessment of intrinsic (or tonic) alertness is the simple reaction time (RT) measurement in response to visual, auditory or somatosensory stimuli: in these situations a general level of response readiness has to be maintained for a rather short period of time in a resource-demanding modality, requiring the top-down control of sustained attention. At the same time, this kind of task is well suited for identifying the time course of the arousal function (or vigilance) in respect to the circadian rhythm, which is known to strongly interact with the more top-down ability to maintain an adequate level of alertness in order to keep performance at high levels.

Conversely, in order to test the ability to *increase* response readiness following external warning signals, it is common practise to present the goal-related stimuli shortly after cues delivered in the same or in different sensory modality. The ability to use warning stimuli as triggers for the alerting signal is mostly bottom-up, and, as for the vigilance, has been shown to interact with a circadian variation (e.g., Matchock and Mordkoff, 2009).

As well as it is important to indicate differences in the tasks that better tackle the phasic and tonic components of the system responsible for the arousal, it is also crucial to recognize that these two modalities are subserved by different functional architectures, based upon interacting but separate neural circuits (Sturm & Willmes, 2001). The vigilance system has been suggested to rely upon a cortical and subcortical, mostly right-hemisphere network, based on noradrenergic (NA) projections from the locus coeruleus to the frontal lobes (Aston-Jones *et al*., 1984; Posner & Petersen, 1990; Pardo *et al*., 1991), and also involving activations in the parietal cortex (Sturm *et al*., 1999). The key role of NA-driven structures, and of the right hemisphere involvement in intrinsic alertness has been confirmed by several neuroimaging studies: two PET experiments (Kinomura *et al*., 1996 and Sturm *et al*., 1999) showed activations in the subcortical noradrenergic pontomesencephacil tegmentum (including the reticular formation) and in the thalamus, together with the right anterior cingulate gyrus (ACC), dorsolateral prefrontal cortex (DLPFC), inferior parietal lobule, and in the middle and superior temporal gyri. Sturm and coworkers proposed an interpretation of the results pattern based on a network in which the ACC and the DLPFC control the brain-stem NA activations via the reticular nucleus of the thalamus. An additional PET study, involving auditory target signals instead of visual stimuli (Weis *et al*., 2000), showed a very similar pattern of activation of the right DLPFC and ACC, together with thalamic foci, suggesting supra-modality for the right-hemisphere network. Lesion studies in animals (Robinson, 1985) and in human stroke patients (e.g. Làdavas, 1987) are in line with the neuroimaging results, confirming the crucial contributions of the noradrenergic structures and of the right hemisphere in subserving tonic alertness. Nevertheless, Posner and coworkers (1987) showed that patients with right hemisphere lesions, though showing impairments in the tonic component of alertness, still benefit from warning cues; moreover, studies attempting to establish rehabilitation programs for right hemisphere patients (both parietal and frontal) capitalized on a phasic alertness training in order to improve spatial attention performance (Làdavas *et al*., 1994; Robertson *et al*., 1995). All in all, this pattern of results indicates that the phasic component of alertness is not damaged after right hemisphere cerebral lesions, or at least not completely, and, more crucially, it can be used in order to compensate vigilance or spatial attention deficits.

These data fit well with a model of phasic and tonic alertness as separate but interacting systems: when a speeded response is required to a target shortly preceded by a warning stimulus, i.e. under phasic alertness conditions, the system relies only partially upon right hemisphere activations; more crucial is the activation of left hemisphere structures which were spared in the right hemisphere patients trained in the study by Robertson and colleagues (1995), and were found to be involved in neuroimaging studies on phasic alertness tasks. In a PET study (Weiss *et al*., 2000) the left superior and ventrolateral frontal gyri were found to be active, in concert with the thalamus, in visual and auditory warning tasks in healthy subjects; in line with this pattern, a more recent event-related fMRI study (Fan *et al*., 2005) on healthy participants showed warning-related activations in the superior and inferior parietal cortices, and in the frontal lobe, both stronger in the left hemisphere as compared to the right one.

In conclusion, a comprehensive model of the alerting system must take into account the different subcomponents of the circuit, involving separate but interrelated neural networks based upon the functional integrity of noradrenergic subcortical structures and cortical portions of the left and right parietal and frontal cortices.

2.2 Orienting

The spatial orienting function is defined as the cerebral system which enables the organism to selectively attend portions of the visual field in order to facilitate the analysis of any stimulus which falls at the expected location, at the cost of suppressing (or delaying) a fast detection and analysis of stimuli which might appear in the unattended parts of the visual area (Posner, 1980; Posner *et al*., 1980; Posner & Dehaene, 1994). Following the attention networks theory, the orienting system is, globally, sustained by a diffuse cholinergic system based on cortical and subcortical structures. In the same theoretical context, the orienting construct has been further broken down into three independent components, subserved by segregated brain circuits, on the basis of behavioral and neuropsychological data (Posner *et al*., 1984; Rafal & Posner, 1987; Friedrich *et al*., 1998): the right temporo-parietal junction is the area selectively responsible for the *disengagement* function, by which the system reacts to the abrupt onset of salient stimuli and makes possible the allocation of attentional resources for their analysis (as anticipated in Chapter 1, in the framework of the neuropsychology of the attentional system); second, the superior colliculus has been proposed to mediate the *attentional shifting* towards any bottom-up stimulated location; third, the thalamus, and plausibly the pulvinar subthalamic nucleus, is theorized to subserve the attentional *re-engagement* at the new location.

As diffusely evidenced in the section concerning the neural bases of the attentional system (Chapter 1), the spatial orienting system can be characterized by two distinct brain circuits, which allow the recording of *source* and *site* signals: first, one supra-modal network controls in a top-down fashion the selection of portions of the visual stream, and has its core in dorsal and ventral groups of fronto-parietal areas (see neuroimaging and and electrophysiological evidences in chapter 1); second, a modular system interfaces the fronto-parietal network in sensory cortices, and it is involved in the on-line preferential analysis of the attended locations or features (as mentioned above, for brevity we will discuss only visual orienting, but with specific adjustments in the definition of the modality-specific involved areas, the model can be applied to auditory or somatosensory stimuli as well as visual stimuli).

As earlier reviewed, the supra-modality system involved in the control of spatial attention is based on a complex architecture of cerebral areas: lesions of portions of this network can be the cause orienting (or re-orienting) deficits, as the unilateral neglect syndrome (Vallar & Perani, 1986 & 1987; Kinsbourne, 1987; Mesulam, 1999), mainly depending on lesions located at the right temporo-parietal junction (TPJ) or right ventrolateral cortices. Other portions of the parietal lobes have been related to spatial attention, in particular more dorsal cortices as intra-parietal sulcus (IPs) and the the superior parietal lobules (SPL), bilaterally, even though lesions of these portions of the parietal lobes do not directly cause severe attentional deficits, as for the right TPJ. These dorsal areas have been implicated in attentional phenomena by several influential neuroimaging studies in which healthy participants were tested during spatial cueing tasks (Kastner *et al*., 1999; Gitelman *et al*., 1999; Corbetta *et al*., 2000 and 2002; Hopfinger, Buonocore & Mangun, 2000; Vandenberghe *et al*., 2001); the implication of the parietal cortices was accompanied by activations of a frontal network involving the superior and middle frontal gyri and the superior frontal sulcus (SFs), that in humans often identifies the human homologous of the Frontal Eye Fields (FEFs). Those cortical components of the system are accompanied and sustained by sub-cortical elements of the system, as the pulvinar of the thalamus (Posner & Petersen, 1990).

As reviewed in Chapter 1, this system of areas which drives the control of attention exerts a biasing activity over modality-specific areas, situated in the secondary (and, in certain conditions,primary) sensory visual areas as the extrastriate cortices (lingual, fusiform and middle occipital gyri): this biasing activity has been first observed as enhanced early visual electrophysiological responses to targets preceded by valid spatial cues as compared to unattended target stimuli; only recently, by means of the event-related fMRI technique, the biasing activity of the top-down control over sensory areas has been recorded in numerous neuroimaging experiments, as pre-target activity in response to orienting cues (Kastner *et al*., 1999; Hopfinger, Buonocore, Mangun, 2000; Woldorff *et al*., 2004; Wilson, Woldorff and Mangun, 2005; Hahn *et al*., 2006; Giesbrecht *et al*., 2006; Sylvester *et al*., 2009).

Only in recent years, pre-target biasing activations have been the object of electrophysiological studies, which reported the ERP occipital component LDAP/BRN (*late directing attention positivity*, Harter *et al*., 1989; *Biasing Related Negativity*, Grent't-Jong & Woldorff, 2007) and the modulation of the posterior oscillatory rhythms in the pre-target interval (Capotosto *et al*., 2009).

All in all, neuropsychological, electrophysiological and functional imaging studies provide converging evidences pointing towards an integrated network of fronto-parietal areas which exerts control over specific sensory areas, which in turn are deputed to the analysis of any stimuli falling at attended locations: only the coordinated activation of the network allows an adaptive and effective shift of the spatial attention.

2.3 Executive control

The *executive control* system as theorized in Michael Posner's models (Posner & Petersen, 1990; Berger & Posner, 2000; Bush, Luu & Posner, 2000; Fan *et al*., 2002 and 2003) can also be recognized in the *cognitive control* and *conflict monitoring* systems, belonging to Matthew Botvinick and Jonathan Cohen's functional and neural models (Botvinick *et al*., 2001 and 2004; Van Veen *et al*., 2001; Van Veen & Carter, 2002; Carter & Van Veen, 2007). Both models find agreement in defining *control* as a subcomponent of the executive functions, and both lines of research suggest that the anterior cingulate cortex plays a crucial role in detecting (for Botvinick and coworkers) or in detecting *and* resolving (for models built upon Posner's theorizations) situations in which a conflict among stimulus dimensions is present, or, in other words, in situations which might lead the organism to negative outcomes if they are not correctly handled (Botvinick *et al*., 2001 & 2004).

All of the *control* tasks described in Chapter 1, in the section deputed to the executive control function, involve the operation of conflict detection (or conflict monitoring), which has been suggested to be carried out by the anterior cingulate cortex using behavioral and simulation models (Botvinick *et al*., 2001), and several fMRI paradigms. As representative examples, in the study carried out by van Veen and coworkers (2001) a modified flanker task including fully compatible, stimulus incompatible and response incompatible visual stimuli requiring a speeded reaction time was used in order to address the locus of conflict monitoring operations. The results indicated that only the response incompatibility elicited enhanced levels of activation in the ACC, with a focus centered in its dorsal component (together with bilateral dorsolateral prefrontal cortex activations and parietal foci); in addition, this study was aimed at disentangling the possible roles of the anterior cingulate cortex in conflict detection/response inhibition: following the authors' interpretation of the results, the ACC mediates response conflict detection, and is not involved in the later stage of response selection, nor in the active inhibition of the incorrect response. More recently, Fan and colleagues (2003) carried out a series of fMRI experiments addressing the common sources of activation in several types of conflict tasks (flanker task, color-word Stroop task and Simon task) and, furthermore, investigated the correlations among the behavioral indexes of the various types of conflict, together with conjunction analyses on the functional results in a within subjects design. As already reported in Chapter 1, the results showed only weak behavioral correlations among the incongruency costs, accompanied by a small focus of common activation in the dorsal ACC and several foci in the dorsolateral prefrontal cortex (DLPFC), specific for the diverse conflict types. In line with the results pattern, the authors' interpretation suggested the cingulate activation as the locus of the cognitive operation of conflict detection/monitoring, possibly the only common component of the different tasks; at the same time, the separate DLPFC foci could reflect the cerebral counterpart of the task-specific conflict resolution operations (thus, agreeing with the interpretation of van Veen and colleagues in respect to a very similar pattern of results). Moreover, in a subsequent event-related fMRI study centered on a task involving an executive control component (Fan *et al*., 2005), the pattern of anterior cingulate and DLPFC activations was again confirmed.

Additionally, the response inhibition requested in most of the tasks tapping at the executive control system elicits supplementary activations in inferior and ventral frontal regions, especially in the right hemisphere, as it has been shown in several neuroimaging studies (Fan *et al*., 2003; Aron *et al*., 2007; Forstmann *et al*., 2008), repeated *Transcranial Magnetic Stimulation* (rTMS) studies (Chambers *et al*., 2007) and in neuropsychological evidences (Walker *et al*., 1998; Aron *et al*., 2003; Hodgson *et al*., 2007) reported earlier.

All in all, the involvement of the dorsal component of the anterior cingulate cortex and of more dorsolateral and ventrolateral frontal regions as the supplementary motor area (SMA), pre-SMA and the inferior frontal gyrus (IFG) in the executive control function is strongly consistent in functional studies, neuropsychological evidences and cognitive models; wide consensus has also been reached in the notion that this control system is sustained by a cerebral and subcortical network of structures whose activations are mediated by dopamine (DA), as several genetic studies on the DA receptors variations confirmed (Fossella *et al*., 2002 & 2002a; Fan *et al*., 2003a; Bish *et al*., 2005).

2.4 Integrative accounts of the attentional systems

An integrative perspective of the attentional system, as the *attentional networks theory* (Posner & Petersen, 1990) has been sustained by evidences provided by many different experimental tasks, used in behavioral, electrophysiological, neuroimaging and TMS studies. However, the investigation of the functional and neural bases of the three separate networks with the use of completely independent tasks was recognized not sufficient to tackle the integrative aspects of the model. The use of spatial cueing tasks as the Posner paradigm (Posner, 1980) might be perfectly suited for addressing the orienting system, and it even involves a component of sustained attention, and a phasic arousal component; unfortunately, those aspects of the task are not systematically manipulated in a classical cueing procedure. Additionally, in lateralized cueing tasks, target location and hand of response side are often matched, introducing a confound in the interpretation of preparatory motor activations which are not easily disentangled from more attentional or arousal-related activations in the same temporal window. At the same time, also the classical conflict tasks as the color-word Stroop (Stroop, 1935) or the flanker task (Eriksen & Eriksen, 1974) include a vigilance and even an attentional component, since targets and flankers are usually presented at a rather rapid pace at the attended location: again, those aspects of the task are not object of systematic manipulation and therefore are not properly addressed in combination with analyses of processes mediated by the control system.

In order to overcome such difficulties and methodological shortcomings in the integrative dimension, in 2002 Posner's coworkers proposed an innovative paradigm, which enabled the experimenters to tackle all the attentional subsystems with the use of only one task, characterized by simple and robust manipulations: the *Attention Network Test* (ANT, Fan *et al*., 2002). This task is basically a spatial cueing paradigm, with targets falling above or below fixation and flanked by several distracters. The targets are complex stimuli (arrows pointing right- or leftwards) requiring a speeded reaction time response, such as a key press compatible with the direction of the arrowhead. With this orthogonal manipulation of attentional shift (upwards or downwards) and target directions (left- or rightwards), any motoric explanation of lateralized activations *prior* to target appearance can be ruled out, since no information about the hand of response is provided before the target arrow is presented. The arousal system is addressed by means of manipulations of the temporal information provided by cues presented shortly before the target arrows: in ¾ of the trials an arousing cue is time-locked to the target, anticipating its appearance of 500 ms; in the remaining ¼ of the trials, no cue anticipates target presentation. An additional manipulation of the cueing levels is utilized in order to differentiate trials on the bases of the spatial attention mechanisms which are selectively elicited by them: in ¼ of the trials a diffuse focus of attention is triggered by the presentation of two peripheral asterisks simultaneously presented above and below fixation; a small central focus of attention is elicited by one single asterisk presented at fixation in an additional ¼ of the trials; in the remaining trials a spatial shift of attention is expected to be triggered by the peripheral presentation of a single, spatially informative asterisk which carries (with 100% validity) precise information about the location of the immediately subsequent target. All the cues (spatially valid, central neutral and double neutral) share the arousing properties due to the temporal coupling with the target presented 500 ms after their appearance on the screen; at the same time, only the peripheral valid cue provides the spatial information which is necessary in order to elicit a shift of the attentional focus or, in a more physiological perspective, might elicit a biasing of the visual system activation which allows a faster and more effective analysis of the target stimuli falling at the attended location. The comparison between reaction times in response to targets preceded by no cue and targets preceded by double neutral cues allows to calculate the benefit elicited by the activation of an alerting system (in particular, a phasic alertness mechanism is engaged in this type of cueing manipulation); the comparison between reaction times in response to targets preceded by central neutral cues and peripheral valid cues results in an index of the profit elicited by the activation of the spatial orienting system. The costs of the involvement of the executive control system, engaged in order to detect and resolve the response conflict elicited by incongruent flankers, is robustly recorded by means of the comparison between reaction times to targets flanked by incongruent and congruent distracters. With this set of straightforward reaction times comparisons, deriving from the application of a simple behavioral paradigm, it has been possible to test all the subcomponents of the attention networks in several different populations.

An important research line deriving from the ANT application is the genetic mapping of the attentional networks (Posner *et al*., 2007). One of the first studies which used the ANT in an applied perspective addressed the heritability of the attentional networks, by means of studies on mono- and dizygotic twins (Fan *et al*., 2001): the alerting system showed some indications of heritability, while orienting scores showed no evidences of familiarity. Capitalizing on the DA implication in the efficiency of the executive control system, the ANT task was administered to healthy controls differentiated by polymorphisms in dopamine receptors, in a combined genetic and fMRI study (Fan *et al*., 2003a). No differences at the behavioral level were observed in the two groups based on the DRD4[1] and MAOA[2] genes polymorphisms which were previously associated with more efficient handling of conflict in reaction times experiments. In the fMRI part of the experiment, however, significantly stronger activations of the ACC were observed in the group carrying the 'advantageous' polymorphism of each of the two genes, demonstrating how genetic differences in neuromodulators and DA receptors can mediate the efficiency of the control aspects of the attentional networks. The evidences of reliable heritability scores for the executive functions system and of markers of genetic variations warranted sufficient bases for further studies on the genetic bases of the control system: a more recent behavioral study from Bish and colleagues (2005) compared children carrying a not well understood chromosomic depletion (22q11.2 deletion syndrome) with normally developing children: the patients suffered of deficits in the ability to monitor stimulus conflict; moreover, they showed abnormal performance adaptation in case of repeated stimuli flanked by incongruent distracters, not showing the micro-adjustment which have been steadily observed in several studies on healthy subjects (Ridderinkhof, 2002) and patients (Ridderinkhof *et al*., 2005).

In the context of a different research line, healthy children at different stages of development have been tested with a modified version of the ANT task in several studies (Rueda *et al*., 2004 with children between 6 and 9 years of age; Rueda 2004a with children of age 4 and a control group of adults; Mezzacappa, 2004 with children of age 7): the scope of these studies was describing in detail the time course of the attention networks maturation and the sociodemographic properties influencing it. Orienting did not show strong developmental tendencies in the age range present in the sample (6-9

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[1] DRD4 = Dopamine D4 receptor

[2] MAOA = monoamine oxidase A

years); the alerting system showed evidences of change through the whole age range, and warning cues were shown to influence the behavioral performance of boys and socially advantaged children more in respect to girls and socially disadvantaged children; additionally, the executive control system index was stable after the age of 7, and, as for the alerting system indexes, signs of resistance to interference were mostly present in older and socially advantaged children; intriguingly, the conflict resolution speed appeared to be maximal in Hispanic children as compared to Caucasian or African American children (Mezzacappa, 2004): the author suggested an explanation based rather on the bilingual environment in which the Hispanic children of the Chicago neighborhood were immersed, than on ethnic/ratial intrinsic differences. Crucially, these developmental data on differential efficiency in bilinguals versus monolinguals have been further validated in a recent behavioral study on Spanish adults (Costa *et al*., 2008). The bilingual sample showed behavioral characteristics which differentiated them from monolinguals: they were overall faster in responding to all trials, irrespective of whether the trial was congruent or incongruent; moreover, bilinguals showed enhanced benefits from alerting cues and smaller costs for incongruency and for trial switch. This pattern of results justified the authors' claim that the continuous involvement of attentional control mechanisms during bilingual speech production exerts strong effects on the efficiency upon their general attentional system, facilitating the engagement of vigilance and interference control systems. This kind of interpretation, which links together the executive functions and the alerting system in a somewhat coordinated system can be recognized also in data coming from a completely different population: individuals suffering of attention deficit/hyperactivity disorder (AD/HD). People affected by this disorder have been tested with the ANT in several studies (Oberlin *et al*., 2005; Konrad *et al*., 2006; Booth *et al*., 2007; Johnson *et al*., 2008), with controversial results. In two studies, no deficits in any of the sub-networks were found in combined-type or inattentive type ADHD patients (Oberlin *et al*., 2005 & Booth *et al*., 2007); however, in a combined behavioral and fMRI study on ADHD children, although the behavioral differences were observed in comparison to the control group only in the executive control system, fMRI hypo-activations were shown in the host of brain regions responsible for the alerting and the conflict detection and resolution networks. Capitalizing on the results of this series of studies, Johnson and coworkers tested a numerous group of children with AD/HD and an equally numerous control group, matched for age and gender distribution. The results resembled, although in a mirrored pattern, the findings of Costa and coworkers on bilinguals (2008): significant differences were detected in the overall reaction times, but also in the costs for incongruency; additional deficits were shown in the tonic alertness system, as indicated by abnormally high percentages of omissions. Several other lines of research investigated the performance in the ANT in groups characterized by executive control deficits, in particular patients affected by obsessive compulsive disorder and schizophrenia, which are known to suffer from imbalances in the dopaminergici system. In two independent studies, using different techniques, (Wang *et al*., 2005 with behavioral measures and Neuhaus *et al*., 2007 in an ERP study) the ANT was administered to schizophrenic patients and control groups. The main differences between patients and controls were observed in the executive control network, as shown by larger means of the incongruency scores, and by larger distributions of the same index. Interestingly, the behavioral results are also sustained by electrophysiological indications of poor functionality of the ACC, as reflected in a lack of modulation of the cognitive electrocortical potential P300 by incongruency in the patients group, and in much weaker activations in respect to the control group in cerebral areas, as the dorsal ACC, which were previously linked to the cognitive control system (Bush *et al*., 2000; Van Veen *et al*., 2001 and Van Veen & Carter, 2002; Fan *et al*., 2003 & 2005; Crottaz-Herbette & Menon, 2006). In all of the aforementioned studies, the ANT proved to be useful in the investigation of the neural bases of the attentional networks as composed by independent neural and functional subsystems.

Up to date, by means of additional manipulations applied to the original formula of the ANT, several studies tackled not only the functionality, but also the integration among the subcomponents of the attentional system. The review of the findings of these studies will be presented separately for the different integrative accounts. Noteworthy, the original study by Fan’s group claimed an almost complete independence of the three subsystems, sustained by the finding of weak or null correlation scores among the behavioral indexes of the three subcomponents (all r comprised between 0.10 and -0.16, all $p > .05$). Nonetheless, the analysis of variance performed on the reaction times as a function of cueing condition (none, double, central and spatial) and flanker type (neutral, congruent, incongruent) resulted in a significant interaction between the two factors, showing how the cost for incongruency was significantly enhanced for situations in which an alerting cue with no spatial value (i.e. in the central and double cue conditions), as compared to situations in which the cue carried also a spatial value or was not delivered at all (i.e. the spatial cue and the no cue conditions). This finding has been interpreted by the authors as a hampering role of the alerting system upon the executive control system or, alternatively, as a side effect of the parallel engagement of two completely independent processes: a non-specified facilitation exerted by the spatial orienting system activation upon the executive control system, and a concurrent reduced incongruency cost in the no cue trials due to the much slower reaction times which characterizes the responses to targets not anticipated by a warning signal. Although a line of research derived from the first hypothesis, and it will be further discussed in the next paragraphs, we tend to agree with the latter, because of several theoretical and practical reasons. First of all, spatial and non spatial alerting cues all share similar arousing properties (as will be further demonstrated with electrophysiological evidences in Chapter 4, concerning the first experimental study object of this dissertation): from this perspective, it is not clear which kind of arousing properties differences could sustain a significantly different modulation of the interference control system activation; in second instance, and crucially, theoretical reasons sustained by distributional analyses on similar behavioral effects (De Jong *et al*., 1994; Ridderinkhof, 2002 and 2002a) showed how the overall speed of response in certain categories of stimuli can influence the interference effect size, in a direction of a progressive reduction of interference costs with progressive slowing of go reaction times. Taken together, these notions challenge the hypothesis of a possible depression of the executive control system by means of the alerting system, as suggested by Fan and coworkers; more crucially, the hypothesis of a separate effect of the intrinsic properties of the reaction times in the 'slow' no-cue conditions and a facilitatory effect of the orienting system over the control system leave open the opportunity to further investigate this latter interactive aspect of the network, otherwise neglected.

2.4.1 Alertness and executive control

The possible explanations for the initial observation of an interaction between cueing condition and flanker type in the original work by Fan and colleagues (2002) inspired a series of works addressing the links between the noradrenergic arousal system and the dopaminergic executive control network (Callejas, Lupianez & Tudela, 2004). The starting hypothesis was straightforward: the attentional networks are not independent, but inter-dependent, and the way to operationalize the question is to break up the alerting component of the task and the spatial value of the valid cues. In order to do so, the authors substituted the visual central neutral cues with auditory warning tones, which could be coupled with a selection of visual cues: a no cue situation, a valid cue situation and an invalid cue situation (1/3 of the trials were uncued, 1/3 were validly cued and 1/3 of the trials were invalidly cued, thus transforming the original voluntary spatial attention task in a completely bottom-up, involuntary and exogenous attention task). This manipulation elicited strong effects of auditory warning, validity and congruency. The interaction between auditory warning and validity was in the expected direction, with enhanced costs for incongruency in the trials preceded by auditory warning signals (this interaction was replicated in Callejas *et al*., 2005). The effect was interpreted according to the "clearing of consciousness" hypothesis (Posner, 1994), claiming a shutdown of the control system when the system has to concentrate on the detection of external events, which are suggested by the warning signal. In line with this explanation of the phenomenon, functional data showed how the engagement in alerting tasks enhances the activations in the right hemisphere, but hampers signals coming from the anterior cingulate cortex (Cohen *et al*., 1988), thus possibly mediating a depression in the conflict monitoring system.

2.4.2 Orienting and executive control.

The series of experiments carried out by Callejas and coworkers (2004 & 2005) also indicated a significant interaction between orienting and executive control scores, in line with the original study by Fan and colleagues (2002), and with a recent study carried out by Luis Fuentes and Guillermo Campoy (2008). The original interaction between cueing condition and flanker type, further validated by the subsequent series of studies capitalizing on the modified ANT, indicated reduced interference effects in situations of pre-activation of the spatial orienting system; the interpretation of the behavioral effect proposed in all of the aforementioned studies suggests a reduction of the focus of attention around the attended location. This effect was suggested to act by boosting the filtering function of the executive control system and therefore reducing the behavioral cost for incongruency at the attended location. The fact that the behavioral benefit was present at the validly cued location, but not at the invalidly cued one, has been taken as indicative of the specificity of the exerted effect, which therefore was supposed to involve an adjustment of the attended area (most probably its reduction), and not an aspecific enhancement of the conflict detection or resolution in case of the orienting network activation. The observed interaction between spatial attention and executive control was also in line with previous studies using different paradigms tapping at the executive functions and at the attentional system, which demonstrated not only that the interaction is quite robust, but also that it can be bi-directional, with an impairment of the spatial orienting system when most of the resources were engaged in resolving an executive conflict task (Posner *et al*., 1987; Fuentes *et al*., 1999).

2.4.3 Alertness and orienting.

The interaction between the alerting and the orienting systems could be observed only in the series of studies implicating orthogonal manipulations between validity and warning properties of the cues (as in Callejas *et al*., 2004 & 2005 and in Fuentes & Campoy, 2008). With wide accordance among datasets, the orienting effect was increased in those trials in which the spatially valid cue was preceded by a warning tone. The interpretations of the effect, however, differed among studies: Callejas and coworkers (2005, Exp. 2 and 3), by the additional introduction of two levels of Stimulus-Onset-Asynchrony (SOA), tried to rule out one of the possible influences of the alertness activation over the orienting system: since the orienting towards a stimulus takes time to build up, the alerting network may increase the orienting function either by increasing its functioning, or by speeding it up. Since the effect of the alerting cue could be observed only at the short SOA, the authors concluded that the influence was exerted through a speeding-up of the orienting process, which didn’t affect the slower part of the distribution, which reached the same asymptotic levels regardless of the presentation of a warning signal. Moreover, on the bases of their SOA manipulation, they argued that the asymptote of the orienting function is normally reached within 500 ms from cue onset, regardless of the concurrent presentation of an alerting tone. In order to inspect with finer temporal resolution the time course of the orienting function and its relationships with the arousal activation, Fuentes and Campoy (2008) increased the SOA values from 2 to 5 levels, ranging from 100 to 1200 ms. In their study (different from the one by Callejas *et al*., 2005 also in the exclusion of no cue trials) the effect of alertness over orienting was strong and stable up to 500 ms SOA, in contrast with previous findings. This evidence sustained an explanation of the effect in terms of an *increasing* of the orienting effect, as an alternative for the speeding-up hypothesis proposed by Callejas and colleagues (2005). The methodological differences between the two studies, however, may be among the causes for the differences in results found between the two groups. Further analyses might be necessary to clarify the orienting/alertness interaction more in detail.

2.5 Conclusions

In an influential prefatory essay for the 2007 volume of the Annual Reviews of Psychology, Michael Posner and Mary Rothbart presented an inspired review of the research on the attention networks as a model for integration of psychological science. They provided a categorization of several studies performed capitalizing on the attention network theory and test (ANT) by means of their relevance for diverse psychological domains and applicative fields, and acknowledged the need for the psychological science to use a common approach in order to account for genetic and environmental influences, developmental properties, temperamental variations and neuropsychological deficits of cognitive functions. In this respect, as can be also recognized by the number and variety of the studies reviewed in this chapter, the attention network theory has proved to be a useful, unifying tool for the study of the attentional functions. Its major qualities, in our point of view, are the robustness of the indexes used for analyses, the behavioral relevance and the strong neural foundation of the anatomical model sustaining the theory; at the same time, and even more intriguingly, the orthogonal approach of the theory and task guarantees space for applied studies on the most diverse populations which, in turn, will provide further specifications in the highly debated integrative aspects of the spatial orienting function with the arousal system in its two-fold nature, and with the *per se* complex and multi-componential executive functions domain.

Chapter 3.
Aims of the project

3.1 Unresolved problems and open questions

Several unresolved issues, derived from the theoretical and empirical state of the art in neurofunctional research investigating the attentional networks, contributed to stimulate the questions upon which this research project is based. These questions will be listed here, together with the objectives that the experimental studies presented in this work aimed to address.

As reviewed in the previous chapters, based on functional and neuropsychological evidences, the neuroscientific research addressing the control of the attentional processing has indicated, based on functional and neuropsychological evidences, a widely distributed anatomical network which is sustained by tight communications between a dorsal system for the top-down control of attention, and a more ventral system which subserves bottom-up shifts in response to the onset of peripheral, salient stimuli (Corbetta & Shulman, 2002). In addition, the modulations of the baseline firing rate in task-selective occipito-temporal sensory cortices in anticipation to attended stimuli has been demonstrated with several paradigms and techniques (e.g., Kastner *et al*., 1999; Hopfinger, Buonocore & Mangun, 2000; Giesbrecht *et al*., 2006).

On the other hand, the electrophysiological research addressing the *site* signals in sensory areas (i.e., the enhancement of visual responses to previously cued or top-down attended stimuli) found countless evidences in favor of modulatory effects upon processing stages as early as the sensory responses in extrastriate cortices (Heinze *et al*., 1994; Mangun *et al*., 1997; Zani & Proverbio, 1997 & 1999; Natale *et al*., 2009); however, the control of these modulations, driven by the aforementioned fronto-parietal networks, has been rather poorly addressed. The main research lines tackling the attentional control have been strongly influenced by the need to compare their results, obtained by means of modified cueing paradigms, with the pioneering work by Harter and coworkers (1989), which reported early and late contralateral components of different polarities (EDAN, LDAP) in response to attention-directing cues. Therefore, even the latest ERP studies which addressed the attentional control system descend from research lines stemming from Harter's approach: either they attempted to develop new analysis techniques in order to better express ipsi- versus contralateral activations in response to lateralized attention-directing cues (as in Hopf & Mangun, 2000, or in Green *et al*., 2005), or they experimented innovative cueing modalities in order to balance the lateralized visual stimulation carried by the cues themselves (Nobre, Sebestyen and Miniussi, 2000; Van Velzen & Eimer, 2003; Grent-'t-Jong & Woldorff, 2007; McDonald & Green, 2008; Brignani *et al*., 2009) or, again, they tried to test the supramodality of the control system, introducing cues and/or targets delivered in different modalities (through tactile and/or auditory stimuli, as in Green *et al*., 2005 & 2008; Mc Donald & Green, 2008; Eimer & Van Velzen, 2002; Van Velzen, Forster & Eimer 2002; Eimer, Van Velzen & Driver, 2002). All the aforementioned studies derived from a theorization of the contralateral components of the attentional control system as symmetrically distributed across the two hemispheres, in particular between the two parietal and occipital lobes. However, several neuropsychological evidences (Mesulam *et al*., 1999, for a review; Vallar, 2001), functional imaging and ERP studies (e.g., Proverbio *et al*., 1994; Corbetta *et al*., 2000 and 2002), reviewed in a highly influential work by Corbetta & Shulman (2002) provided evidences supporting the existence of non-symmetrical attentional vectors in the two hemispheres, consistent with a rightward bias for spatial orienting. More in detail, while the *ventral* system (TPJ and IFG) non selectively responds to salient stimulation in either of the hemifields with activations consistently found in the right hemisphere and coupled with reflexive orienting and/or re-orienting mechanisms, the *dorsal* component of the network (IPs and FEF) repeatedly showed spatial selectivity (i.e., right-hemisphere responses for attentional shifts towards both directions, and left-hemisphere activations coupled only with rightward shifts). Up to date, this non-symmetrical account of the attentional system has been sustained by several converging evidences, as reviewed in Chapter 1. In light of this account, the widely used ERP analyses utilized in studies addressing cue-related activities, i.e., the arbitrary subtraction between ERP responses to left- from rightward cues, or the averaging across ipsilateral versus contralateral responses, might cancel out any electrophysiological index reflecting spatially selective responses in the frontal or parietal lobes. This possible confound, in fact, has been acknowledged by Hopf & Mangun (2000) in their discussion section, in which they sought to find a possible explanation for their left-sided activations in response to centrally presented cues (analyzed following the traditional subtraction between the cues pointing towards the two different directions). A different solution for this methodological problem, which might enable the experimenters to investigate plausible hemispheric asymmetries in response to attention-directing cues, might be the comparison of left- and rightward cues with neutral cues, which do not carry any intrinsic spatial information, and are not supposed to elicit any attentional shifts.

Second, the theoretical interpretation of the observed contralateral components recorded over parietal and frontal cortices (which might be bilateral, left, right, symmetric or non-symmetric), could be easily confounded by the intrinsic spatial value carried by the cues themselves, which are usually lateralized peripheral stimuli or centrally presented arrows or shapes. An orthogonal manipulation of the attentional shifts (i.e., upwards or downwards, instead of left- and rightwards) might be a possible solution for these protocol flaws and possibly misled interpretations, resulting in a much more flawless experimental design and straightforward interpretations of the findings, especially as hemispheric asymmetries are concerned.

Third, the introduction of invalid cues, necessary for capturing in behavioral measures the benefit exerted by the cueing procedure upon the processing of attended (as compared to unattended) targets, might cause additional confounds precisely because it diminishes the informative value of the cues themselves. Indeed, the manipulation of the validity ratio has been proven to influence (i.e., reduce) the size of the behavioral validity effect (Jonides, 1980 & 1983; Riggio & Kirsner, 1997; Vossel Thiel & Fink, 2006): therefore, it is also plausible to argue that the power of attentional effects recorded in response to cues might be significantly hampered in case of manipulated validity ratios. In other words, concurrent non-spatial strategies might be utilized by a subgroup of the participants, or by some participants in a subset of trials, in order to overcome the possible presentation of invalidly cued trials, thus reducing the signal-to-noise ratio of the ERP differential responses.

Fourth, the ERP addressing the cue-related responses elicited by endogenous and exogenous cues have been seldom compared directly, and never, to our knowledge, in combination with the previously proposed contrast neutral/valid: thus, a more systematic investigation of this aspect of the electrophysiological research would be highly desirable, when aiming at an integration or at comparisons among studies which used various cueing techniques.

Fifth, the previously reported behavioral interactions between alertness, executive control and spatial orienting (Fan et al., 2002; Callejas et al., 2004 & 2005) raised several questions. The explanation of the interaction has been proposed in terms of hampered functioning of the executive system in case of activations of the alerting system, and facilitation of the same system by concurrent spatial orienting activations. These interpretations, however, have been circumstantiated only with behavioral evidences or on the basis of theoretical positions (e.g., the *clearing of consciousness* hypothesis proposed by Posner, 1994). It would be extremely useful, both theoretically and practically, to clarify whether any arousal differences are truly present between spatially neutral alerting cues (which do not carry any orienting value), and spatially valid cues (which, naturally, also stimulate the phasic arousal system): any differences in the alerting value might support the proposed *clearing of consciousness* explanation, which is supposed to act in case of *purely* arousing stimuli only; on the other hand, where differences in the alerting value of neutral and valid cues might not be recorded, this evidence might help in ruling out the possibility that the two categories of cues are qualitatively different in their arousing properties, as proposed by Callejas and coworkers (2004 & 2005).

Another extremely intriguing interaction observed in the context of the attention networks theory (as based on the integrated cueing/flanker paradigms called the Attention Networks Test) is the facilitation of the executive system by means of previous engagement of the spatial orienting system. The behavioral effect is, however, only the last step of a very long processing stream which ranges from the attentional modulation, through the sensory perception of the target stimuli and their distracters, till the interpretation of the target arrow-point direction and the subsequent response selection, which is the last cognitive operation preceding the motoric activation and the key-press. An electrophysiological approach, with its fine temporal resolution reaching the millisecond, is indeed a suitable tool for addressing the question concerning the step at which the functional interaction takes place. Secondarily, after additional corroboration of the existence and robustness of the behavioral interaction effect, the question could be taken forward: for a comprehensive theory of the integrated system of attention and control, it would be crucial to test whether the interactive effect is task-specific of cueing-tasks only or whether it involves, in a broader perspective, also other tasks tapping at the executive functions (such as the go/no-go task or the stop-signal task, for instance).

From there, it descends that, if the interactive nature of the attentional and executive control system holds with more than one executive task, it would be of extreme interest to test the possible uni- vs. bi-directionality of this interaction.

Additionally, although, on the one hand, countless studies addressed with functional imaging techniques the nature of the executive function and the attentional networks, and, on the other hand, a growing body of evidences coming from the electrophysiological literature concerned the temporal dynamics of the attentional networks activations, there is nonetheless a lack of integration between the spatial and temporal domains, in particular in the more interactive aspects between the three interdependent systems of arousal, attention and control. Directly descending from this lack of meta-integrative approaches, a systematic use of high density recording and source reconstruction methods, in combination with tasks designed in an integrative perspective, is highly desirable, in the perspective of an attentional control theory which is able to explain and incorporate both the spatial and temporal domains of the cerebral systems for attention, alertness and control.

3.2 Study 1

The first study presented in this work has been designed to specifically investigate the ERP activations in response to attention-directing cues. The chosen paradigm was the Attention Network Test (ANT, Fan *et al*., 2002), because of its simple design and for the robustness of the behavioral effects previously reported for all the three networks and for their interactions. However, the task was adapted in order to be better suitable for electrophysiological recording.

The experimental manipulations and the high-density EEG recording allowed fine comparison between the spatio-temporal dynamics elicited in the brain systems for the control of attention in response to neutral and spatially valid cues (Aim 1). The additional presence of runs in which no cues were interspersed with the presentations of the targets permitted the recording of tonic arousal responses in anticipation to the targets: these responses could be therefore compared to the brain reactions to phasically arousing cues, which anticipated target delivery with a predictive temporal coupling (Aim 2).

The presence of complex target patterns, which required responses choices (made even more difficult by the presence of salient distracters), allowed the experimental investigation of the spatio-temporal dynamics of the interactions among the three systems (Aim 3). Moreover, the attentional shifts required by the task took place along the vertical meridian: this procedure allowed the decoupling of the expected lateralized activations due to the engagement of the (ventral and dorsal) attentional control systems in response to attention-directing cues, from the direction of the attentional shift itself, overcoming the methodological difficulties reported in previous studies (Aim 4). Additionally, the comparison between neutral and valid cues allowed the experimenters to investigate the spatial specialization of the left and right hemispheres, at early and late temporal latencies in response to cues (endogenous control of attention), as well as in response to the peripherally presented targets (exogenous capturing of attention in case of no-cue or neutral cue conditions, Aim 5).

3.3 Study 2

The second study capitalized on the results obtained in Study 1. The investigation of the contralateral components in response to spatial cues (valid or neutral) was further investigated by means of two different types of cueing: a central endogenous spatial cueing and an exogenous peripheral one. Keeping the informative values and the temporal parameters of the cues identical to the ones used in study 1, it has been possible to compare directly the brain mechanisms involved in orthogonal shifts of attention, i.e., along the vertical and horizontal meridians (Aim 1). Moreover, the within-subjects design utilized in the comparison between endogenous and exogenous cueing modalities (together with the identical temporal and spatial parameters used for the two modalities) allowed the direct comparison of the spatio-temporal dynamics of the brain related to each of the cueing types, as well as the commonalities and differences among them (Aim 2). Moreover, this design allowed comparisons among the cerebral responses to validly and neutrally cued targets, within and across the two modalities (Aim 3).

Additionally, and differently from Experiment 1, it was theorized the possibility to compare the plausible lateralized activations in response to cues directing attention to the left or right visual fields with the results of the traditional ERP studies which addressed the attentional control system, as the EDAN, the ADAN and the LDAP components (Aim 4).

Last but not least, the behavioral task coupled with both the endogenous or the exogenous cueing paradigms was a Go/Nogo task, in which a speeded reaction time was required in response to one category of stimuli, whereas the motor response to the other type of visual stimuli was to be withheld. The adoption of this combined paradigm (cued Go/no-go task) enabled the investigation of the interactions between the alertness/orienting systems and the executive control system, in its motoric inhibition component (Aim 5), in order to test the hypothesis of task-specificity of the interactive functionality of the executive control and attentional systems.

3.4 Study 3

The approach of the third experimental study was sustained by the results obtained in Study 1 and 2. The fact that robust interactions were observed between the executive control and the attentional control systems in both of the electrophysiological studies, raised the question about the directionality of the effect. The expected nature of the relationship between the two system was a bidirectional communication, and we tested this hypothesis by means of a combined stop task/flanker task. The operational measure utilized in this task was the analysis of the ERP responses to the stop-signal, which are known to be modulated by attention, besides several other stimulus-centered variables. If the relationship between the conflict monitoring system and the attentional system is indeed bidirectional, the experimental manipulation of the difficulty of the primary task (the speeded reaction times to the visual target stimuli, accompanied by diverse categories of flankers) should selectively modulate the amplitude of the auditory components recorded in response to the stop-signals (Aim 1). The manipulation of the flanker categories included three levels of conflict, thus enabling a fine investigation of the selective involvement of stimulus and response incompatibility in interaction with the attentional modulation (Aim 2). If present, this modulation was expected to be mediated by the frontal right-hemisphere structures responsible for the re-orienting of attention, which are also supposed to be among the anatomical regions involved in response selection and motor inhibition (Aim 3). The investigation of possible interactions between response selection and response inhibition measures was also included in the scopes of this electrophysiological study (Aim 4), in order to clarify some inconsistencies in the behavioral literature concerning the functional systems for the cognitive control and motor inhibition.

Chapter 4.
Study 1: Spatio-temporal dynamics of the neural mechanisms for spatial orienting, executive control and alertness

4.1 Introduction

An influential model of the attentional system (Posner & Petersen, 1990) postulates that, in order to selectively pay heed to relevant portions of the input stream, biological systems rely upon the reciprocal communications among multiple neural structures, widely distributed in the brain. These large-scale neural networks (Mesulam, 1981; Posner & Petersen, 1990; Gitelman *et al*., 1999) have been proposed to sustain the attentional control, since they respond with strong activations during tasks requiring attention (Corbetta *et al*., 2000 & 2002; Fan *et al*., 2005; Hopfinger, Buonocore & Mangun; Kastner *et al*., 1999), and are related to attentional deficits when damaged (Posner *et al*., 1984; Vallar & Perani, 1986 & 1987; Mesulam, 1999; Corbetta & Shulman, 2002).

Furthermore, wide agreement has been reached in the notion that the attentional function is not a unitary construct, whereas it can be broken down into multiple, anatomically defined, mechanisms, deputed to the interdependent functions of *arousal*, *spatial orienting* and *executive control* (Posner & Petersen, 1990; Fan *et al*., 2002). Supporting this theoretical position, functional imaging, neurophysiological and neuropsychological studies (Pardo, Fox & Raichle, 1991; Marrocco, Witte & Davidson, 1994; Coull *et al*., 1996; Làdavas, 1987) revealed a specific anatomical network responsible for the achievement and maintenance of an adaptive state of wakefulness, sustained by the cerebral distribution of norepinephrine (NE, Aston-Jones *et al*., 1984). This system, selectively activated by the need to reach an alert state, can be further differentiated into a tonic, or intrinsic, component, implemented by a right-hemisphere cerebral circuit (Làdavas, 1987; Sturm *et al*., 1989 & 1999) and a left-hemisphere system (Posner *et al*., 1987; Sturm & Willmes, 2001), which sustains the ability to phasically react to salient events increasing for brief periods the responsivity of the cognitive system (see chapter 2 for a more detailed description of the construct). Similarly, a body of converging evidences sustained the existence of a specific network deputed to the monitoring and resolution of conflict situations and to the control of performance (Bush, Luu & Posner, 2000; Botvinick *et al*., 2001 & 2004; di Pellegrino *et al*., 2007; Cole & Schneider, 2007; Koechlin & Summerfield, 2007), implemented in various frontal and prefrontal medial and lateral dopaminergic structures. Additionally, on the basis of neuropsychological (Posner *et al*., 1984; Friedrich *et al*., 1998) and neuroimaging studies (Gitelman *et al*., 1999; Corbetta *et al*, 2000), influential theorizations proposed that parietal and frontal regions, in a coordinated network (Corbetta & Shulman, 2002), act as sources of top-down attentional modulations of extrastriate activity (Kastner *et al*., 1999; Hopfinger, Buonocore & Mangun, 2000), facilitating processing of stimuli at attended locations, and therefore mediating spatial deployment of attention.

However, all the reported evidences in favor of an integrative perspective of the attentional system, as the *attentional networks theory* (Posner & Petersen, 1990), were obtained by means of different and independent experimental tasks, utilized in various behavioral, electrophysiological, neuroimaging and TMS studies. A further step toward an integration of the attentional networks in a unitary perspective was reached with the development of an innovative behavioral paradigm, the Attention Network Test (ANT, Fan *et al*., 2002), which enabled the testing of the three attentional subsystems in one integrated and simple task. The ANT combines a spatial cueing reaction time task (Posner, 1980) with an arrow version of the flanker task (Eriksen & Eriksen, 1974). As described in detail in Chapter 2, the ANT requires participants to determine the pointing direction of a target arrow, surrounded by irrelevant congruent or incongruent distracters. The patterns of arrows are presented above or below fixation in random order, and may or may not be preceded by neutral or valid cues: with this manipulation of the cueing levels it has been possible to observe the modulation of the alerting and spatial orienting systems by means of simple overt measures (RTs and error rates in response to targets). Up to now, several studies have been conducted using the ANT to test the behavioral performance of many populations as children (Rueda *et al*., 2004 and 2004a; Mezzacappa, 2004; Sobin *et al*., 2004; Bish *et al*., 2005; Johnson *et al*., 2008), patients with disorders of various types (Posner *et al*., 2002; Klein, 2003; Wang *et al*., 2005) and in combination with neuroscientific techniques as event-related functional neuroimaging (Fan *et al*., 2005) and electrophysiology (Neuhaus *et al*., 2007, with schizophrenic patients and matched controls). In particular, one fMRI study (Fan *et al*., 2005) aimed at describing and integrating in a functional model the anatomical dissociation among the three subcomponents of the networks, selectively activated by the ANT manipulations. Independently, the ERP study carried out by Neuhaus and coworkers addressed the responses to congruently and incongruently flanked targets, collapsing together the different cueing levels. Thus, to our knowledge, no study addressed the electrocortical responses to the different cue types used in the ANT. This type of study would be extremely informative, in many respects.

First, the traditional approach in the study of the electrophysiological responses to attention-directing cues involves the comparison of ERP waveforms elicited by left- and rightward directing cues (Harter *et al*., 1989; Hopf & Mangun, 2000; Nobre *et al*., 2000), or the comparison between responses elicited by the attention-directing cues in the ipsilateral or contralateral hemispheres (Green *et al*., 2005 & 2008). This traditional approach has several limitations: first, it doesn't take into account the possibility to record bilateral activations (i.e., spatially nonspecific activities, which are cancelled out in the subtraction or averaging procedures). Since the lateralization of the attentional-control, especially in the dorsal component of the fronto-parietal network, is not yet clear (see chapter 1 for a more detailed review of the evidences concerning this issue), it would be desirable to complement the traditional lateralized comparison with a different technique, which could enable a less biased recording of the activities related to the spatial deployment of attention. Moreover, the body of evidences indicating an asymmetrical distribution of the attentional control systems in the fronto-parietal networks (Mesulam, 1999; Spiers *et al*., 1990) strongly calls for a research approach which doesn't assume perfect contralaterality and symmetry.

Therefore, the ANT cueing manipulations, including peripheral valid cues, which are completely informative in respect to the position of the coupled target (i.e., 100% validity, vertical shifts), and central neutral cues, which do not provide any spatial information in respect to the needed vertical shift of attention, might be a useful tool to address these questions. At the same time, the neutral cues share with the spatially valid cues the warning properties, since the temporal coupling between each cue and subsequent target is always fixed at 500 ms. This manipulation allows the direct comparison between a situation in which the spatial orienting system is most likely activated (because of the maximal predictive value of the spatial cues), with trials in which this system is not engaged (because of the null spatial predictive value of the neutral central cues), balanced for the arousing properties. Two recent ERP studies addressed the differences between attention-directing cues and neutral cues (Grent-'t-Jong & Woldorff, 2007, with *interpret* cues; McDonald & Green, 2008 with central colored cues). The results of the first study indicated that no differences between the two types of cues took place until 400 ms after cue onset. However, both the neutral and the attention-directing cues were letters, which might have required longer interpretation intervals than other symbolic cues (e.g., arrowheads). Alternatively, the fact that the cue-target asynchrony was very long (900-1900 ms) might have influenced the speed of the cognitive processes engaged by the orienting cues. The use of a fixed stimulus-onset-asynchrony as in the ANT (500 ms), accompanied by the nature of the cues (simple asterisks) might be a better strategy to address the cerebral responses related to the activation of the spatial attention control system. The second study, by McDonald & Green (2008), addressed the same question by comparing the ERPs elicited by lateralized cues with aspecific neutral cues: the research technique implicated the computation of difference waves (dERPs) between lateralized and neutral cues, and a remapping of the two dERPs before averaging, in order to avoid the loss of spatial information. However, this technique, by definition, canceled out possible differences between the responses elicited by cues orienting attention towards the left and right hemifields, thus assuming symmetrical processes in the attentional mechanisms.

Therefore, a different technique, involving the statistical comparison between attention-directing and neutral cues, without the application of difference waves selectively for right and left cues, might be a more useful tool in order to shed light upon the cerebral lateralization of the system. Moreover, the vertical shifts of attention required by the ANT might enable straightforward interpretations of the expected lateralized (symmetrical or asymmetrical) activations linked to the activity of the fronto-parietal network for the control of spatial orienting, eliminating a possible confound introduced by the lateralized shifts traditionally required in spatial cueing tasks. At the same time, the arousing properties of the two types of warning signals (spatially valid and neutral) are completely balanced in the ANT, thus allowing a direct comparison of the electrophysiological responses elicited by the two categories, simultaneously ruling out possible interpretations of the attentional effects in terms of alerting differences.

Second, the cueing manipulation which is a distinctive trait of the ANT also incorporates uncued targets, which are presented on the screen above or below fixation without being anticipated by any warning signal. Several studies suggested that structures in the frontal and parietal lobes, especially in the right hemisphere, are involved in the sustained aspect of attention, which maximizes the responsivity of the system during expectancy periods (Posner & Petersen, 1990; Robertson *et al*., 1995; Sturm *et al*., 1999). On the other hand, a growing body of evidences indicates the involvement of the left frontal and parietal lobes in case of phasic enhancements of the system's responsivity in response to external warning signals (Sturm & Willmes, 2001; Coull *et al*., 2001). In the context of electrophysiological literature, the Contingent Negative Variation (CNV) is generated when the preparation for an imperative stimulus is induced by a warning stimulus (Walter *et al*., 1964; Eimer, 1993a; Brunia, 1993; Brunia & Damen, 1988; Gomez, Marco & Grau, 2003). One ERP study (Gomez, Flores & Ledesma, 2007) addressed the preparatory signals (CNV) in response to warning cues which directed with 80% validity the attentional shifts along the vertical meridian. Because of the cueing manipulation, however, all the cues elicited similar potentials, because no neutral cues were inserted in the design, and no trials were uncued. The results indicated a fronto-central distribution for the CNV, with a tendency towards a left-hemisphere maximum, compatible with the phasic preparation value of the warning signals. However, the fact that the required responses for the target stimuli were key-presses with the right hand was somehow a confound for a straightforward interpretation of the left-hemisphere biased pattern. A different ERP study, carried out on a group of children and a control group of adults, used peripheral cueing in order to elicit CNV responses, introducing also a small percentage (20%) of uncued trials (Perchet & Garcia-Larrea, 2005). The results indicated strong CNVs for the valid and invalid cues in the adult group, while the children showed enhanced fronto-central negativities only in the uncued trials: the interpretation proposed by the authors claimed that the preparatory activity in response to cues required the maturity of the control system, which was plausibly not fully developed in the children (age 6-9). However, the lateralization of the CNV for cued and uncued trials was not considered in the analyses, thus not allowing any speculation about the neural generators of the components (similar results were also reported in Perchet et al., 2001). Conversely, the use of the Attention Networks Test, in combination with high-density EEG recording, is expected to be a useful tool in the investigation of the lateralized preparatory activities in the expectation period. The analysis of the ERP responses in the interval preceding the uncued targets, and its comparison with the cue-target interval activations in case of valid or neutral cues, allows a detailed investigation of the alerting system. More specifically, we expected to be able to observe strong selective activations of the phasic arousal system (in case of warning signals, both neutral and valid), and smaller effects of the tonic arousal system (in case of uncued trials). This comparison, which doesn’t require the traditional subtractive method, usually applied in the fMRI studies addressing the alerting system (Fan *et al*., 2005; Thiel, Zilles & Fink, 2004), is assumed to be a useful tool in the investigation of the cerebral bases of the arousal system. The combination of traditional analyses (including amplitude and latency of the ERP responses) with diffuse source reconstruction algorithms as the low resolution brain electromagnetic tomography (LORETA, Pascual-Marqui *et al*., 1994), will enable the investigation of the spatio-temporal dynamics of the alerting system activations elicited by the ANT.

Third, the introduction, in the ANT, of distracters flanking the target arrows permits the modulation of the conflict monitoring system responses (Bush, Luu & Posner, 2000; Botvinick *et al*., 2001): in particular, the contrast between targets flanked by congruent and incongruent distracters (Eriksen & Eriksen, 1974) provides, at the behavioral level, a reliable index for the costs introduced by the necessary cognitive operations of conflict monitoring and response selection under effortful cognitive control (Fan *et al*., 2003). Moreover, in line with previous reports (Fan *et al*., 2002; Callejas *et al*., 2004 & 2005) behavioral interactions are expected between orienting and executive control measures (as expressed in a significant decrease of the incongruency costs in case of valid cues anticipating the incompatibly flanked targets). One of the interpretations for the reported interaction has been proposed in terms of boosting of the activity of the executive control system by means of the activation of the spatial orienting system. Unfortunately, the repeated observation of the behavioral interaction hasn’t yet been substantiated by neurofunctional indications of the locus of the integration of the two systems. The analysis of the ERP components in response to targets of different categories, anticipated by cues carrying different amount of information (null, temporal, or spatial and temporal) is used in this study in order to shed light upon this unclear aspect of the literature.

In summary, the goal of the study was to clarify the spatiotemporal dynamics of the arousal, orienting and executive control mechanisms, further specifying the cerebral bases of the inteactions among these distributed subsystems, by means of the combination of the ANT with high-density EEG recording and distributed source reconstruction techniques (LORETA).

4.2 Methods

4.2.1 Participants

21 healthy students received university credits for their participation in the study. All participants had normal or corrected-to-normal vision, no history of neurological or psychological diseases and were unaware of the purpose of the study. Two participants were successively excluded from the statistical analyses because of an excessive percentage of ocular or muscle tension-related artifacts in the task-related EEG signal, resulting in a sample of 19 volunteers (age range 19-31 years, mean 22.95 years, S.D. 4.20 years, 7 males).

4.2.2 Task

The experimental session consisted in several blocks of a modified version of the ANT spatial cueing/flanker task combined paradigm (Fan *et al*., 2002). Stimuli, presented on a black background, consisted in horizontal lines of five grey arrows, pointing either left- or rightwards. Only the central arrow, aligned with the principal vertical meridian, acted as target for the participants' task, while the four surrounding arrows were to be ignored. Noteworthy, all the four flanking arrows always pointed towards one direction, which could be either congruent (Congruent Flankers, CF) or incongruent (Incongruent Flankers, IF) with the target direction (see figure 4.1, left lower panel, for a graphic illustration of targets and flankers). Participants' goal was to detect the pointing direction of the target arrow, and to press a response button on a joy-pad with their correspondent index finger (i.e., left hand pressure for leftward arrows, and right hand for rightward-pointing arrows) as fast and as accurately as possible. Participants were instructed to accomplish the task regardless of the position of the stimuli on the screen, and ignoring the direction of the flanking arrows. Stimuli were presented above or below a small fixation cross (subtending 0.25 degrees of visual angle, at a distance from the screen of 114 cm), with a vertical eccentricity of 1.25 degrees of visual angle. Targets and flankers subtended 1.5 degrees of visual angle each, and were interspaced by 0.3 degrees of visual angle, for a total length of 8.7 degrees of visual angle for each group of stimuli. Considering all the possible target positions (above or below fixation), directions (left- or rightwards), and flankers category (CF, IF), eight possible stimuli were randomly presented to the subjects in each of the cueing conditions. The eight stimulus types were equally represented in each of the experimental blocks and cueing conditions. Figure 4.1 (middle panel) shows an example of the temporal structure of a trial: each trial started with the presentation of the fixation cross in the center of the screen, then a cue (S1) was presented for 100 ms, and, after a Stimulus-Onset-

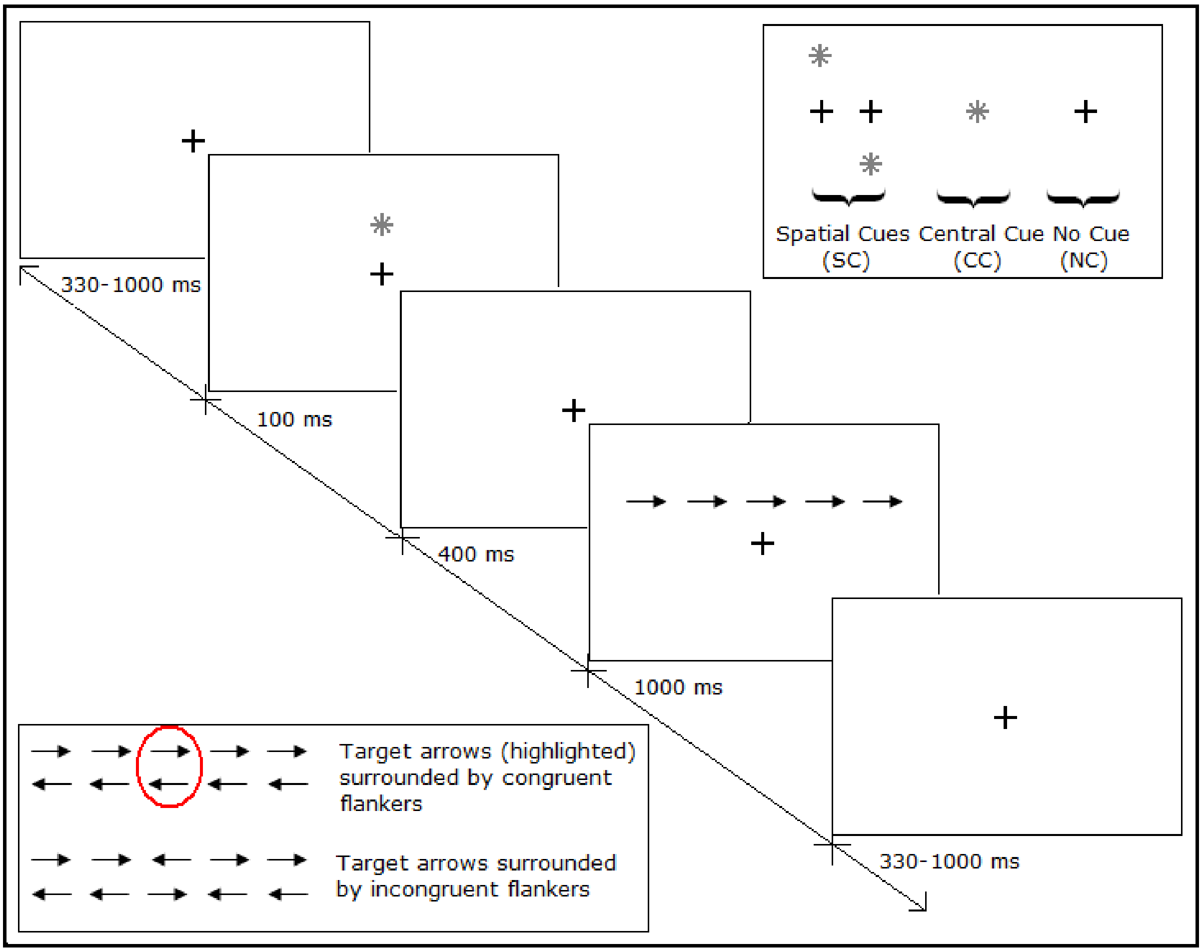


Fig. 4.1. Right upper panel: examples of the different cue types. Cues fell in one of the two vertical hemispaces (SC condition, temporally and spatially informative in respect to target appearance), or were presented superimposed to the fixation cross (CC condition, temporally but not spatially informative in respect to S2) or were missing (NC, control condition). Middle panel: example of the temporal structure of a spatially informative (SC), congruent flankers (CF) trial in the ANT task; note that in case of NC condition the temporal structure of the trial is non-affected, because a dummy (invisible for the participant) stimulus is coded and presented in place of the cueing asterisk. Left lower panel: illustration of the four possible combination of target/flankers directions and compatibility levels.

Asynchrony (SOA) of 500 ms, in which only the fixation cross was present on the screen, the target/flankers combination (S2) appeared above or below fixation. Cues could be either dummy stimuli, in case of the baseline No Cue condition (1/3 of the total amount of trials), or a small grey asterisk subtending 0.25 degrees of visual angle (2/3 of the trials). Cueing asterisks appeared either superimposed to the fixation cross (neutral Central Cue condition, CC, 1/3 of the trials), or anticipated with 100% validity the location of the coupled S2 (Spatial Cue, SC), above or below the fixation cross. In line with previous reports, the three cueing conditions were expected to elicit activations in different attentional networks, depending on the amount of information that each kind of cue provided to the participants. In case of SC condition, each S1 was both temporally and spatially informative in respect to the appearance of the coupled S2: cues under this condition were therefore expected to activate both the alerting and the orienting networks. Each central cue was temporally informative in respect to the presentation of the coupled S2, but, since it fell at fixation, it was considered neutral in the spatial domain, and expected to activate only a phasic alertness; in the NC condition no information whatsoever was given to the subjects regarding the presentation of the target stimuli, thereby the NC condition was not expected to be coupled to activations in any of the attentional networks, except for small activations in the sustained attention (intrinsic alertness) system. In order to avoid the use of rhythmic strategies (especially in the NC condition), the inter-stimulus interval (ISI) between two subsequent stimuli was randomized in a 330-1000 ms range. Stimuli belonging to the same attentional condition were grouped in four homogeneous runs of 120 stimuli, following a blocked design, for a total of 12 experimental blocks.

4.2.3 Procedure

Participants were required to sign a consent form, performed the Italian version (Salmaso & Longoni, 1985) of the Edinburgh Handedness Inventory (Oldfield, 1971) and were then prepared for the EEG recording. After preparation they were positioned in a dimly lit and electrically shielded Faraday cabin, comfortably sitting at a 114 cm distance from a computer screen and from an infra-red closed-circuit video-camera used to monitor their state during the whole EEG session; impedances of the EEG signals were then checked, and subsequently volunteers were asked to perform the 12 blocks of the cueing task. The order of the cueing conditions was counterbalanced across participants, as well as the order of the 4 blocks within each cueing condition. Short breaks were given to the volunteers among the four homogeneous blocks, while longer breaks, instructions and a short practice block were administered before each attentional condition. Stimuli were presented to the volunteers on a computer screen driven by a stimulator computer, controlled by the experimenter through a stimulation program (Eevoke 1.5, 2002, A.N.T. Software, Enschedee, The Netherlands).

4.2.4 EEG recording and processing

EEG was continuously recorded at 512 Hz with ASAlab (vers. 4.1.0.4, 2006, A.N.T. Software, Enschedee, The Netherlands) from tin electrodes mounted in an elastic ‘Electro-Cap’; the 128 recording leads were distributed over the whole surface of the scalp according to the 10.05 International System (see Figure 4.2). An extra ground electrode was positioned on the forehead of the participants, while the linked earlobes were used as off-line reference leads. Eye movements were monitored through 4 additional electrodes positioned on the outer canthi of the eyes, and above and below the right eye. Impedances were kept below 4 KΩ. EEG signals were amplified and through an optical cable reached the recording computer, synchronized with the stimulator.

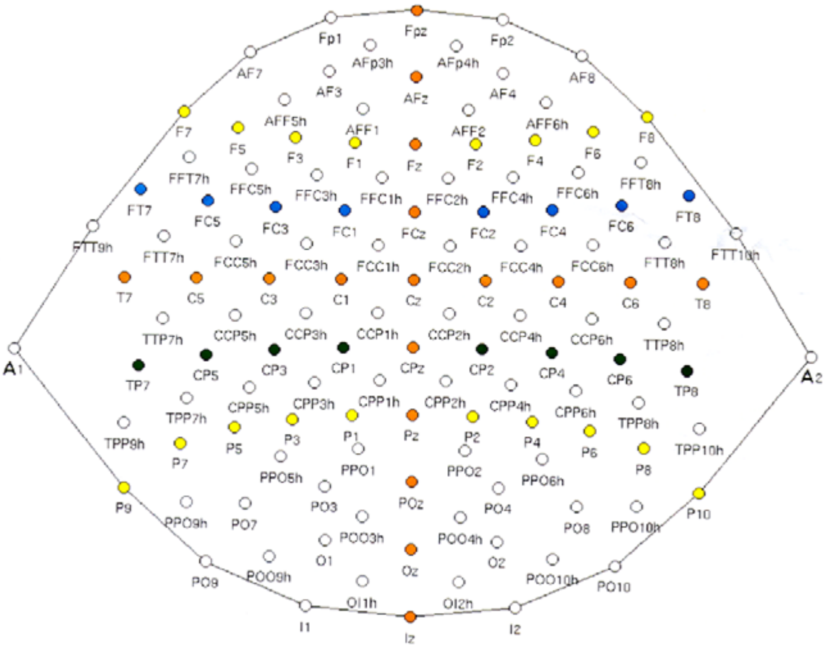


Fig. 4.2. EEG recording layout, with 128 electrodes distributed over the whole scalp surface following the 10.05 I.S.

Electrophysiological data were continuously recorded and off-line analyzed using ASAlab (vers 4.1.0.4, 2006, A.N.T. Software, Enschedee, The Netherlands). EEG signals were off-line band-passed (0.016-70 Hz), and a notch filter of 50 Hz was applied, in order to correct for possible artifacts derived from electrical interference.

Artifact rejection was performed with a criterion of difference in respect to the mean signal (±75 μV for the EEG channels and ±150 μV for the ocular ones). For each subject, epochs were computed from -100 ms prior cue presentation till 1000 ms after target presentation as a function of attention condition, target direction and position and flanker type (total length of each epoch: 1600 ms, from -100 to +1500 ms relating to cue onset). Epochs were then referred to the 100 ms period before cue onset and averaged as a function of attention condition (SC, CC, NC) and flanker type (CF, IF).

4.2.5 Behavioral and electrophysiological analyses

Behavioral data in response to targets were collected during the EEG recording from Eevoke (vers. 1.5, 2002, ANT Software, Enschedee, The Netherlands) and analyzed separately in a 4 ways repeated measure ANOVA with Cue Type (SC, CC, NC), Target Position (above fixation, below fixation), Target Direction (which corresponds with hand of response: left, right) and Flanker type (CF, IF) as factors. Responses faster than 150 ms (anticipations), slower than 1500 ms or falling outside the interval comprised between ±2 S.D from the mean (outliers) were discarded and non included in any further analysis. Accuracy data were also analyzed: error percentages were converted in arcsin degrees and analyzed with a 4 ways repeated measures ANOVA with Cue Type

(SC, CC, NC), Target Position (above fixation, below fixation), Hand (left, right) and Flanker type (CF, IF) as factors.

The electrophysiological components which were scored, analyzed and localized for the purposes of this experiment were the occipito-parietal P1 and N1, the frontal orienting-N1, the parietal P300, the fronto-central Contingent Negative Variation (CNV) and the parietal Late Directing Attention Positivity (LDAP) in response to the different cues; moreover, analyses were carried out on the P300 and on the frontal conflict negativity in response to targets accompanied by different flanker types.

The P1 was scored as the mean amplitude of the ERP response to cues in the time range comprised between 125 and 160 ms after cue presentation, for SC and CC attention conditions. It was measured at occipital and occipito-parietal leads (O1/O2, PO3/4, PO7/PO8, PO9/PO10).

The anterior orienting N1 was scored as the mean amplitude of the ERP response to spatial and central cues at frontal electrodes (AF7/AF8, F7/F8, FT7/FT8) in a time window comprised between 130 and 170 ms.

The posterior N1 was scored at occipito-parietal leads (O1/O2, PO3/4, PO7/PO8, PO9/PO10), as the peak amplitude of the ERP response in the time range comprised between 160 and 200 ms.

While the early, visual and orienting responses to cues were scored primarily on the conditions in which a visual stimulation was present (SC and CC), the longer-latency components P300, CNV and LDAP were scored for all the three conditions, in order to disentangle responses due to alertness mechanisms from specific correlates of the spatial orienting of attention. More specifically, the P300 was scored as the mean amplitude of the cerebral response between 290 and 380 ms, at a selection of frontal, central and parietal homologous electrodes (FFC3h/FFC4h, C3/C4 and P3/P4); the CNV and the LDAP were scored in the same time window (430-500 ms after cue onset), but at different leads: for the CNV the scoring procedure was performed at central leads (FC1/FC2, C1/C2, FP1/FP2), while the posterior LDAP was scored at parietal and occipital homologous sites (P3/P4, PO3/PO4, O1/2).

The cerebral responses to targets were scored at a selection of centro-parieto-occipital sites along the midline for the P300 (Cz, CPz, Pz, POz, amplitude and latency of the peak scored semi-automatically between 800 and 1100 ms), and at fronto-central sites for the conflict-N2 (peak amplitude scored semi automatically between 820 and 860 ms at frontal electrodes AFp3h, AFp4h, F4, F5, FFC3h, FFC4h).

The statistical analyses performed on the measures of the ERP components consisted in repeated measures ANOVAs with Cue Type (SC, CC, NC when scored), Lead (dependent upon the specific component distribution) and hemisphere (Left, Right) as factors. For all the reported significant effects, the Greenhouse-Geisser correction was applied in case the sphericity assumption was violated, and only significant main-effects/interactions will be discussed. All the significant interactions will be interpreted in light of the results of post-hoc (Tuckey) tests.

4.3 Results

4.3.1 Behavioral Results

For the reaction times analyses, highly significant main effects of Cue Type ($F_{2,36} = 54.21$, $p < 0.0001$) and Congruency ($F_{1,18} = 139.59$, $p < 0.0001$) emerged. Post-hoc tests indicated significant differences among the three levels of attentional cueing: the temporal information provided by the alerting cues (CC and SC) was sufficient to elicit a gain in respect to the baseline NC condition (mean RT for NC was 464 ms, S.E. 10 ms) in the speed of the motor responses to S2; moreover, the spatial information provided by the Spatial Cues only, elicited facilitation (31 ms) in respect to the neutral condition CC (mean RT for SC: 411 ms, S.E. 8 ms; mean RT for CC: 442 ms, S.E. 9 ms). The presence of incongruent flankers was sufficient to introduce a 39 ms cost in the speed of response to targets (CF: 420 ms, S.E. 8 ms; IF: 459 ms, S.E. 9 ms).

Significant interactions emerged between Cue Type and Congruency ($F_{2,36} = 17.88$, $p < 0.0001$), and between Cue Type and Position ($F_{2,36} = 5.25$, $p < 0.05$). Table 4.1 and Chart 4.1 show the mean RTs for the interaction Cue Type x Congruency. Follow up-analyses performed on the differences Incongruent-Congruent flankers for the three cueing types showed a main effect of Cue Type ($F_{2,36} = 18.52$, $p < 0.0001$), with SC showing a significantly smaller cost for incongruency than both CC and NC, which in turn did not show any internal difference (see Chart 4.1, right panel).

Post-hoc tests on the Cue Type x Position interaction showed (as can be seen in Table 4.2) that responses to targets appearing above fixation were faster than responses to targets presented below fixation, but only in case information was given prior target appearance about its position (i.e., in case of spatially informative cues); in case of simple alert (CC) or in the control condition (completely bottom-up, NC), no difference in speed emerged between the two possible target positions. When this interaction is interpreted taking into account the significant triple interaction Cue Type x Position x Hand ($F_{2,36} = 3.62$, $p < 0.05$), it becomes clear that only responses given in the SC condition *and* with the right hand are faster in the upper hemispace than in the lower one (8 ms difference), while the left hand and the other two attentional conditions do not differentiate between positions.

Accuracy analyses on the transformed error percentages showed main effects of Position ($F_{1,18} = 12.24$, $p < 0.01$), Hand of Response ($F_{1,18} = 4.91$, $p < 0.05$), and a highly significant effect of Congruency ($F_{1,18} = 35.59$, $p < 0.0001$). Also significant were the interactions between Cue Type and Position ($F_{2,36} = 5.46$, $p < 0.01$) and between Hand and Congruency ($F_{1,18} = 8.61$, $p < 0.01$).More in detail, errors were more numerous in the lower hemispace (2.05% as compared with 1.44% for stimuli presented in the upper field), in responses emitted with the right hand (1.96% vs 1.54% for the left hand), and when targets were accompanied by incongruent flankers (2.80% vs 0.69% for targets flanked by congruent arrows). More interestingly, errors were more common in the lower hemispace only in interaction with the CC condition, but not in the SC or NC conditions (see table 4.2), and the higher percentage of errors with the right hand was significant for incongruent flankers only, while targets flanked by congruent arrows elicited comparable percentages of errors with the two response hands (see table 4.3).

	Spatial Cue	**Central Cue**	**No Cue**
Congruent Flankers	396 (8)	420 (9)	442 (10)
Incongruent Flankers	425 (8)	465 (10)	486 (10)
Difference (IF-CF)	29 (3)	45 (4)	44 (4)

Table 4.1. Mean RTs (S.E) for the three cue types in interaction with flanker category, and (IF-CF) differences (S.E.); values are expressed in ms.

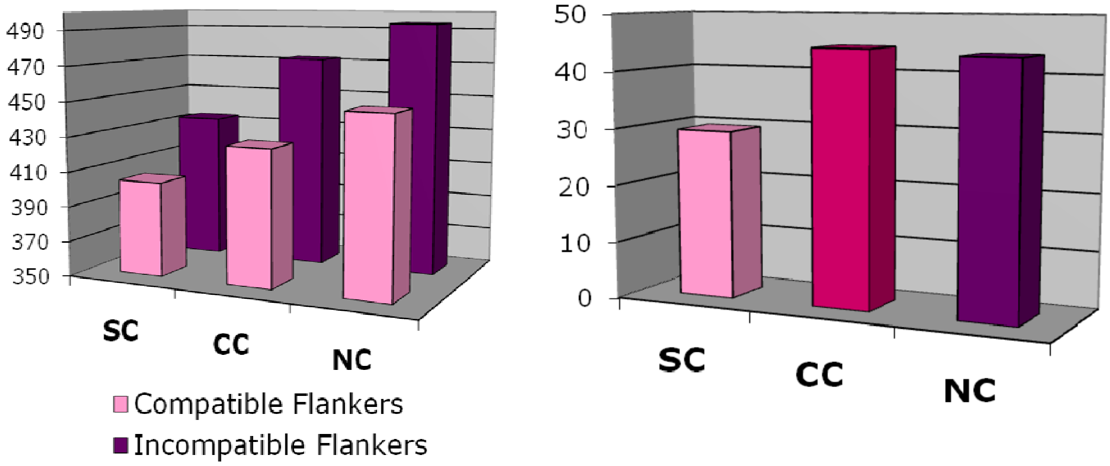


Chart 4.1. Left panel: mean RTs for the three cue types in interaction with flanker category. The differences between the three cueing levels are significant, as well as the congruency difference within each of the cue types. Right panel: RT differences between incongruent and congruent flankers for the three cueing types; the (I-C) difference is significantly smaller for SC than both CC and NC. All values are expressed in ms.

	Spatial Cue	**Central Cue**	**No Cue**
Above fixation	408 (8)	443 (9)	464 (10)
Accuracy	1.4 (0.3)	1.3 (0.2)	1.6 (0.3)
Below fixation	414 (8)	442 (10)	464 (10)
Accuracy	2.0 (0.4)	2.5 (0.4)	1.6 (0.3)

Table 4.2. Mean RTs (S.E) in milliseconds, and Accuracy (S.E.) in percentage, for the three attentional conditions in interaction with target positions.

	Left Hand	**Right Hand**	**Sig**
Congruent Flankers	0.73 (0.1)	0.66 (0.1)	n.s.
Incongruent Flankers	2.34 (0.4)	3.26 (0.5)	*

Table 4.3. Accuracy in error percentage (S.E.), for the two flanker types in interaction with Hand of response (always correspondent to target direction). Incongruent flankers elicit significantly higher error percentages than congruent flankers (with both hands), but within the incongruent flankers stimuli significantly more errors were committed with the right hand.

4.3.2 Electrophysiological Results

An overview of the ERP responses, sysnchronized with the presentation of the cues, is presented in Figure 4.3.

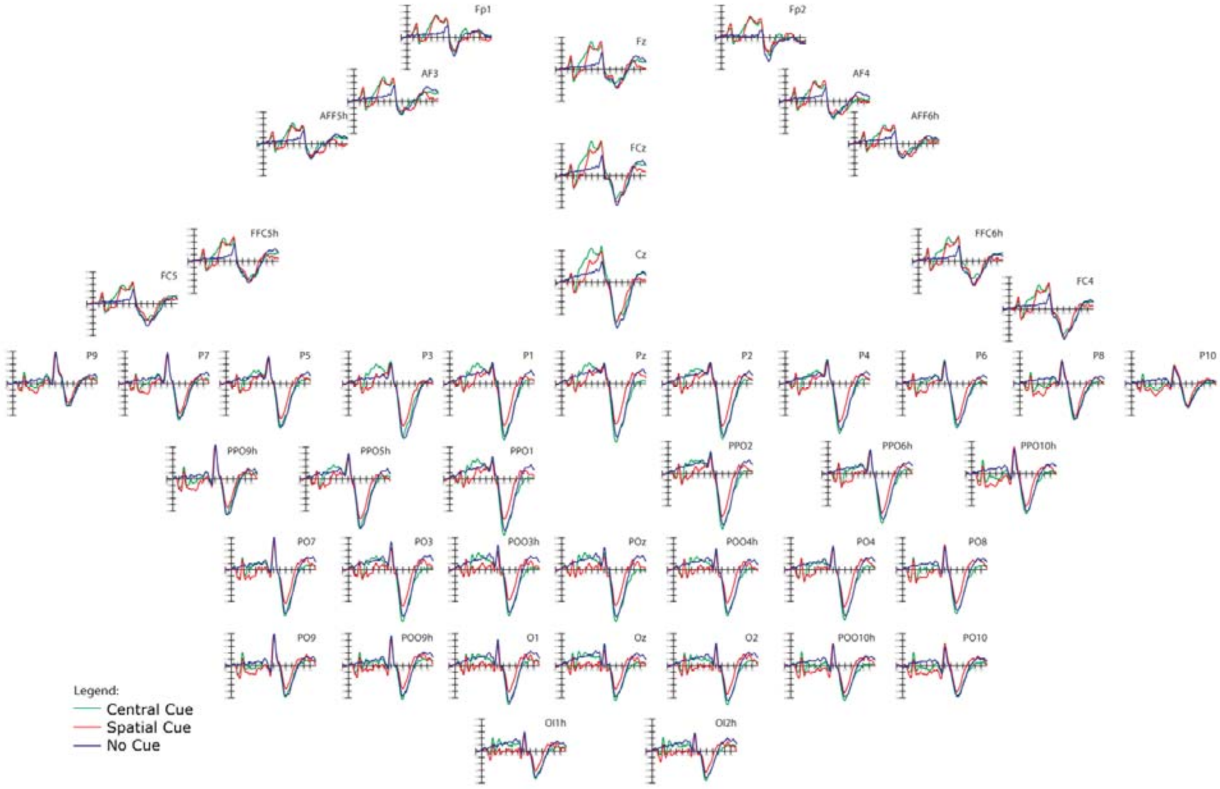


Figure 4.3. Overview of the ERP responses elicited by the three cueing types. The waveforms are synchronized with cue onset, therefore the onset of the target stimuli falls at 500 ms for the three cueing categories. It is possible to note the posterior, occipital and occipito-temporal visual components in response to the presentation of the cues, absent for the No Cue condition. Moreover, also the frontal orienting N1 and a robust fronto-central CNV are evident for SC and CC, and absent for NC, which, in turn, shows a slow negative drift in the cue-target interval.

P1 (125-160 ms). The ANOVA performed on the P1 response to central and peripheral cues resulted in a significant interaction between Cue Type and Lead ($F_{3,54} = 8.75$, $p < 0.01$). Post-hoc tests revealed that the P1 in response to peripheral (spatially valid) cues was significantly enhanced in respect to the P1 in response to the foveally presented Central Cues at the occipital and occipito-temporal sites (O1, O2 and PO9, PO10), but not at more parieto-occipital electrodes (PO3, PO4 and PO7, PO8), where the electrophysiological responses to different types of cue were not significantly different (the waveforms for the cue-target interval at representative occipital electrodes are depicted in Figure 4.4, and the P1 mean amplitude values at different leads are presented in Table 4.4).

Anterior orienting N1 (130-170 ms). Analyses performed on the orienting N1 revealed main effects of Cue Type ($F_{1,18} = 5.96$, $p < 0.05$), and Lead ($F_{2,36} = 13.07$, $p < 0.001$). The orienting N1 in response to spatially valid cues showed higher amplitudes (-1.39 μV, S.E. 0.3 μV) as compared to the responses to central, neutral cues (-0.82 μV, S.E. 0.3 μV). Post-hoc tests performed on the Lead main effect revealed that the frontal N1 response is overall stronger at fronto-polar electrodes as AF7 /AF8 (-1.48 μV, S.E. 0.3 μV) than at more fronto-lateral sites as F7/8 and FT7/8 (-1.02 μV, S.E. 0.2 μV and -0.81 μV, S.E. 0.2 μV, respectively). No other main effects or interactions were

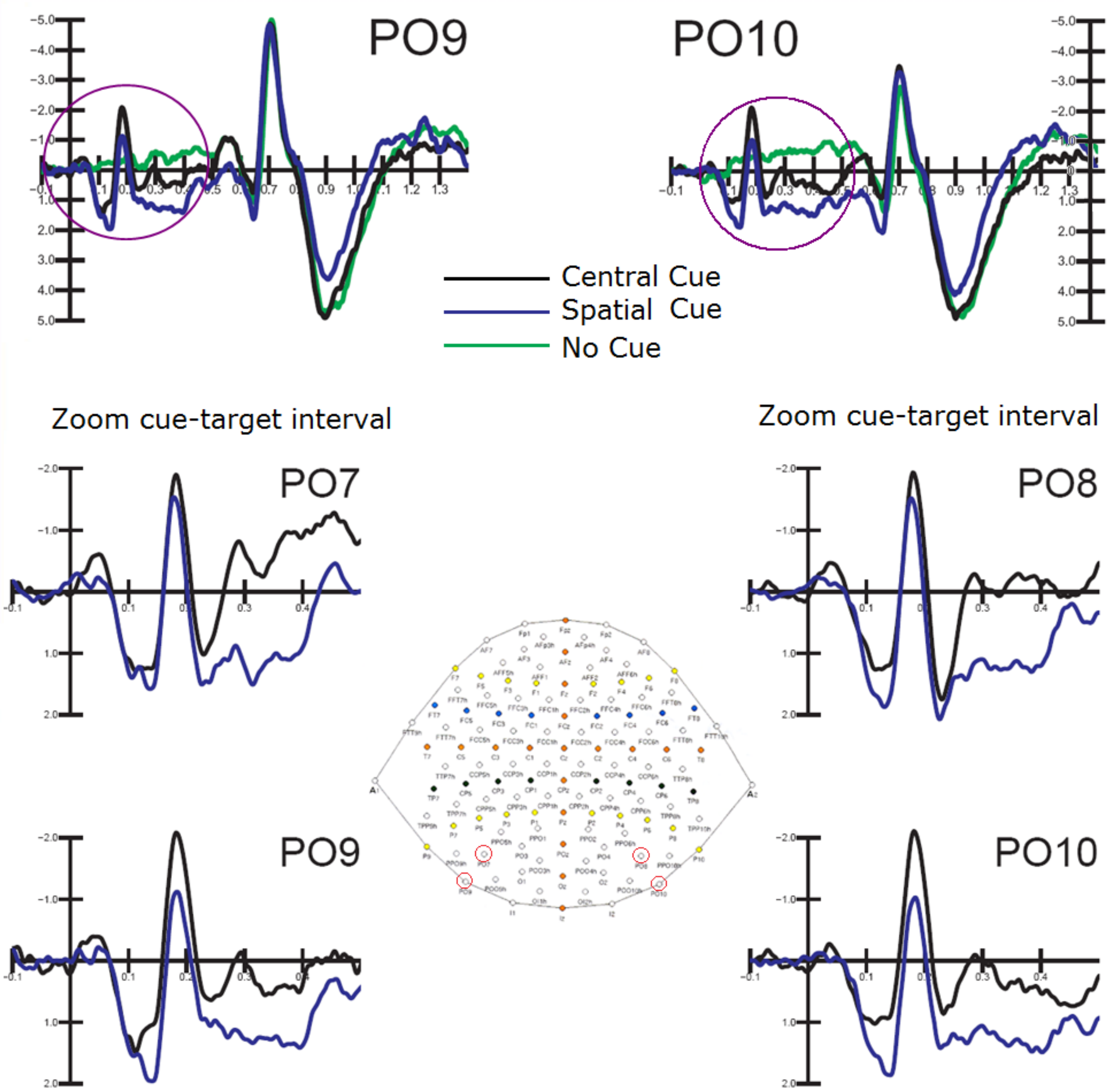


Figure 4.4. Upper panel: posterior view of the ERP responses elicited by the Spatial and Central cueing types. The No Cue trace, in green, shows no ERP components, as expected. The highlight points out the cue-target interval.
Lower panel: blow-up of the cue-target interval. It is possible to notice, in the zoom, the enhanced advantage of SC in respect to CC at more occipito-temporal sites (PO9/PO10), as compared to more occipital electrodes (PO7/PO8), and the N1 advantage for CC.

significant.

Posterior N1 (160-200 ms). The ANOVA performed on the N1 response to central and peripheral cues resulted in a significant interaction between Cue Type and Lead ($F_{3,54}$ = 7.70, $p < 0.01$). Post-hocs revealed that the N1 in response to central cues showed significantly higher amplitudes than the N1 in response to peripheral valid cues only at occipito-temporal sites (PO9 and PO10), but not at occipital and parieto-occipital electrodes O1, O2, PO3, PO4 and PO7, PO8, where the electrophysiological responses were statistically comparable (values are presented in Table 4.4).

P300 (290-380 ms). The ANOVA performed on the P300 response to the different categories of cues, including the control condition NoCue (in order to exclude any possible influences of the tonic arousal caused by the blocked design, in which the three attentional conditions were presented segregated from each other) showed only a highly significant main effect of Cue Type ($F_{2,36}$ = 10.99, $p < 0.001$). Post-hoc Tuckey tests revealed a significant difference between the spatially valid condition SC, which elicited a P300 (0.58 µV, S.E. 0.3 µV), and the other two conditions (CC and NC, -1.23 µV, S.E. 0.6 µV and -0.69 µV, S.E. 0.2 µV respectively), which failed to elicit such cognitive response and did not differ from each other (see Figure 4.3).

CNV (430-500 ms). The ANOVA performed on the CNV response to the different categories of cues included all the three conditions (SC, CC and NC), in order to compare the possible different types of alertness (phasic vs tonic) which might have

		O1/O2	**PO9/PO10**	**PO7/PO8**	**PO3/PO4**
P1 (125-160)	**Spatial cue**	1.52 (0.4)	1.84 (0.4)	1.61 (0.4)	1.18 (0.4)
	Central cue	1.0 (0.5)	0.93 (0.4)	1.25 (0.4)	1.21 (0.4)
N1 (160-200)	**Spatial cue**	-2.48 (0.5)	-1.94 (0.5)	-2.33 (0.5)	-2.34 (0.5)
	Central cue	-2.59 (0.5)	-2.78 (0.5)	-2.57 (0.5)	-2.14 (0.5)
		O1/O2	**PO3/PO4**	**P3/P4**	
LDAP(430-500)	**Spatial cue**	-0.15 (0.5)	-0.44 (0.5)	-1.08 (0.4)	
	Central cue	-1.08 (0.6)	-1.37 (0.5)	-2.15 (0.5)	
	No cue	-1.44 (0.4)	-1.38 (0.4)	-1.13 (0.3)	
		O1/O2	**POO9h/10h**	**PPO9h/10h**	**PO7/PO8**
LDAP(480-500)	**Spatial cue**	0.12 (0.5)	0.57 (0.5)	0.79 (0.4)	0.28 (0.5)
	Central cue	-0.96 (0.6)	-0.10 (0.5)	0.21 (0.4)	-0.48 (0.6)
	No cue	-1.37 (0.4)	-0.81 (0.3)	-0.65 (0.3)	-1.31 (0.4)

Table 4.4. Upper panel. Mean amplitude (S.E.) in microvolts, for the P1 component, and peak amplitude values (S.E.) in microvolts, for the occipital N1. The cueing condition significantly interacts with Lead in both time ranges. The difference between spatial and neutral cues is significant at occipital and occipito-temporal electrodes (O1/O2 and PO9/PO10) for the P1 interval (in favor of SC), and only at occipito-temporal electrodes (PO9/PO10) in the N1 interval (in favor of CC). Lower panel. Mean amplitude (S.E.) in microvolts, for the LDAP. The LDAP is more positive for SC at all leads as compared to both CC and NC in the interval 430-500 ms; the difference between CC and NC is significant only at the parietal electrodes P3/P4, suggesting the absence of the LDAP component in the latter two conditions, and a CNV spreading backwards for volume conduction only in the CC condition, where the CNV is present. Concerning the narrow interval (480-500 ms) the LDAP was more positive for SC at all leads, in respect to both CC and NC; the latter cue types were significantly different only at occipito-temporal leads (POO9h/POO10h; PPO9h/PPO10h).

been elicited by the use of differential strategies in the different attention condition blocks. Significant main effects of Cue Type ($F_{2,36} = 23.31$, $p < 0.00001$) and Lead ($F_{2,36} = 5.48$, $p < 0.05$) were observed, and might be better explained by the highly significant Cue Type x Lead interaction ($F_{4,72} = 16.11$, $p < 0.0001$). Post-hoc Tuckey tests performed on the interaction revealed a significant difference between the arousing conditions (SC and CC), which both elicited a strong CNV (-2.78 μV, S.E. 0.4 μV and -3.74 μV, S.E. 0.6 μV, respectively), and the control condition NC, which failed to elicit such cognitive response and elicited only a mild negative drift (-0.70 μV, S.E. 0.3 μV), more compatible with an aspecific, tonic increase of the arousal mediated by the right frontal and parietal noradrenergic structures (see Figures 4.3, 4.5 and 4.6). Interestingly, in line with this interpretation, the attention condition interacted with the electrode site, demonstrating how the control condition did not show a topographical differentiation in the distribution of this mild negativity, while both the alerting conditions showed stronger negativities over the fronto-central and central selection of leads included in the analyses (the couples of homologous electrodes FC1, FC2 and C1 and C2) as compared to the more centro-parietal CP1 and CP2 (see chart 4.2 for a graphical depiction of the interaction effect).

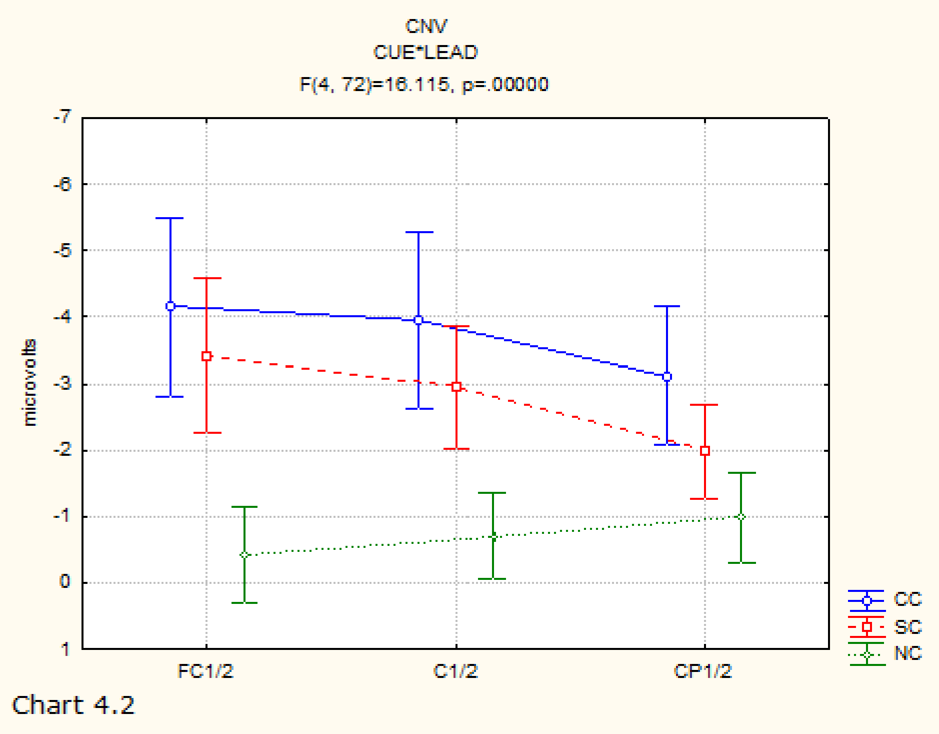


Chart 4.2. Interaction between cue type and lead in the CNV time range, at the fronto-central electrodes.

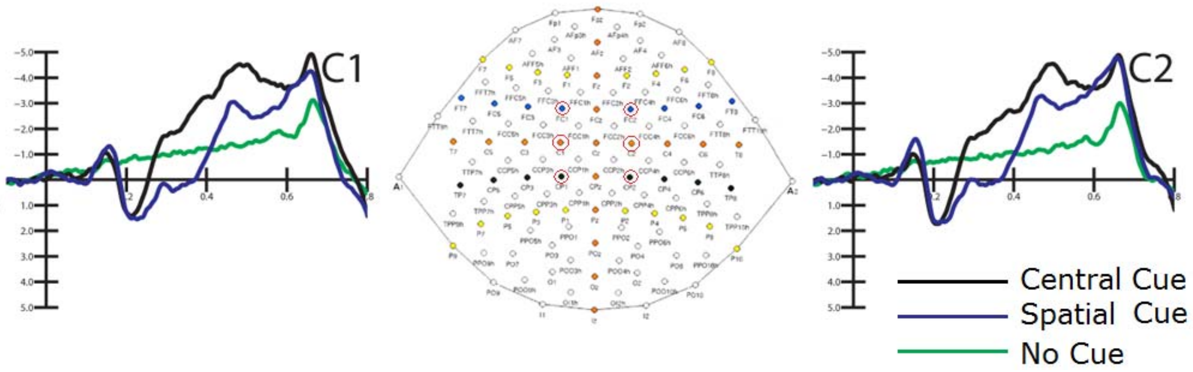
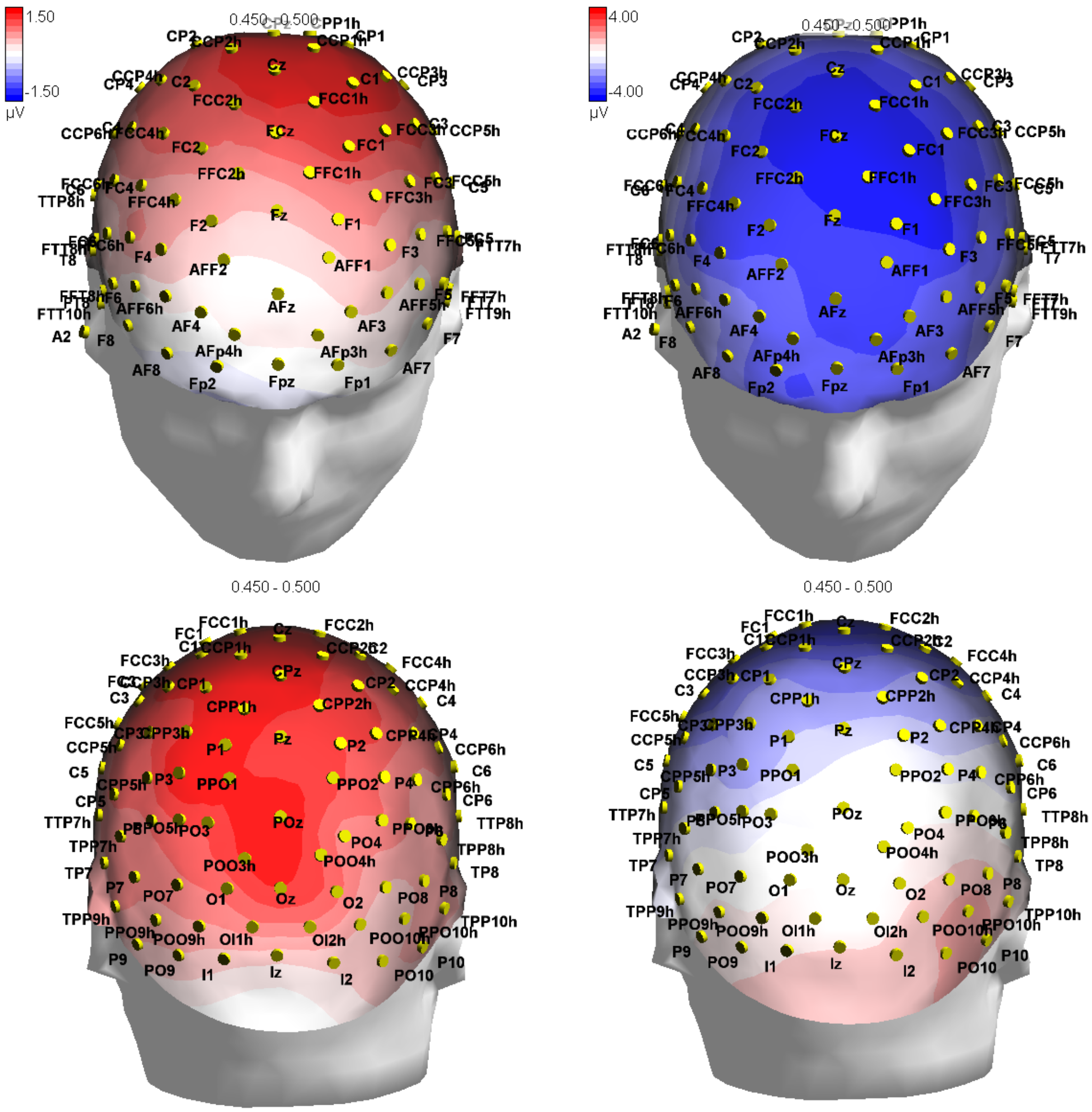


Figure 4.5. ERP responses elicited by the Spatial and Central cueing types. The No Cue trace, in green, shows no ERP components, except for a slight negative drift, plausibly elicited by a sustained attention modality.

LDAP (430-500 ms). In the same time-range in which the fronto-central CNV was analyzed, a positive component was present at more posterior electrode sites (see Figure 4.6 for the comparison between CNV and LDAP voltage distributions). The significant effects resulting from the ANOVA performed on the posterior LDAP were main effects of Lead ($F_{2,36} = 6.13$, $p < 0.05$), Hemisphere ($F_{1,18} = 5.79$, $p < 0.05$) and the more informative interactions between Cue Type and Lead ($F_{4,72} = 7.43$, $p < 0.01$) and between Cue Type and Hemisphere ($F_{2,36} = 4.70$, $p < 0.05$). Post-hoc tests revealed that the LDAP was stronger over occipital sites than at more parietal ones (O1/O2: -0.89 μV, S.E. 0.4 μV different from P3/P4: -1.45 μV, S.E. 0.4 μV, with PO3/PO4 being intermediate and not different from any of the other sites: -1.06 μV, S.E. 0.4 μV). The component was also more represented over the right hemisphere, overall (-0.92 μV, S.E. 0.4 μV vs -1.35 μV, S.E. 0.3 μV for the right hemisphere). The Lead x Hemisphere interaction indicated that the orienting condition SC elicited significantly more positive values than both the other conditions over both hemispheres, while the alerting condition CC showed even more negative values than the control condition only over the left hemisphere, effect that might be attributed to the stronger fronto-central negativity, maximal for the alerting condition, spreading for volume conduction towards the posterior regions. A graphic depiction of the Cue Type x Lead interaction is presented in Chart 4.3. Post-hoc tests performed on this interaction confirmed that the spatially valid cues showed more positive values than the alerting condition CC at all leads, while the latter showed values that were significantly more negative than the control condition NC only at the parietal leads P3 and P4, but not at more occipito-parietal sites as PO3, PO4 and O1/O2, further supporting the interpretation in terms of volume conduction. Follow-up analyses were performed on the LDAP, including a pool of more occipito-temporal electrodes (O1, O2; POO9h, POO10h; PPO9h, PPO10h; PO7, PO8; PO3 and PO4), and narrowing the time window in which the component was scored to the very last moments anticipating targets comparison on the screen (480-500 ms following cue presentation, that is equivalent to



Spatial Cue - Central Cue
difference voltage map

Central Cue - No Cue
difference voltage map

Figure 4.6. Left panel: voltage maps for the difference waves (SC-CC), in the 450-500 ms interval. The difference between these cueing categories (which, functionally, reflects the orienting activation present in the valid but not in the neutral condition) is maximal over posterior areas. By comparing the two difference maps it is possible to seize the functional difference between the CNV and the LDAP components, respectively supported by frontal and parietal foci. Right Panel: voltage maps for the difference wave (CC-NC), in the 450-500 ms interval (CNV and LDAP interval). As might be evident in the maps, the difference between the two conditions is maximal over fronto-central and central areas, especially over the left hemisphere. The maps reflect the selective phenomenon of the phasic arousal negativity, which is present for the neutral cue condition, but not in the NC condition.

-20 to 0 ms relative to target onset). The results confirmed and completed the main analysis results, showing a main effect of Cue Type ($F_{2,36} = 3.37$, $p = 0.05$), a main effect of Lead ($F_{4,72} = 20.71$, $p < 0.0000001$), an interaction between Cue Type and Lead ($F_{8,144} = 3.75$, $p < 0.01$). The post-hoc analyses performed on the significant effects showed a differentiation between NC and the other two conditions (CC and SC),

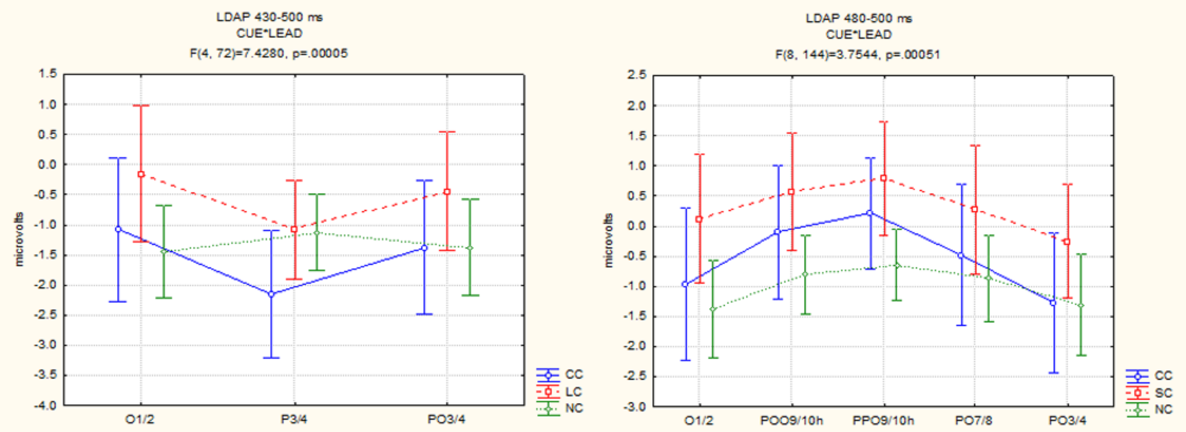


Chart 4.3 Chart 4.4

Chart 4.3 and 4.4. Interaction between cue type and lead in the LDAP time ranges, at posterior electrodes.

and a peak of the effect at occipito-temporal leads (POO9/10h and PPO9/10h) as compared to more occipital (O1 and O2) and occipito-parietal sites (PO3, PO4, PO7, PO8). The interaction between Cue Type and Lead indicates how SC results more positive than both CC and NC at all leads, while the alerting cue CC shows significantly more positive values in this time-window only at occipito-temporal electrodes as POO9h, POO10h, PPO9h and PPO10h (see Chart 4.4).

4.3.2.2 ERPs in response to targets

Fronto-central negativity (820-860 ms). The ANOVA performed on the peak amplitude values of the fronto-central negativity in response to the targets preceded by different categories of cues, and accompanied by different flanker types showed a significant main effect of Cue type ($F_{2,36} = 3.36$, $p = 0.051$, corrected). Fisher post-hoc tests revealed that the N2 elicited by SC was significantly more negative than the other two cue types (0.22 μV, S.E. 0.8 μV for SC; 1.19 μV, S.E. 1.0 μV for CC; 1.12 μV, S.E. 0.8 μV). Additional significant main effects were Congruency ($F_{1,18} = 8.53$, $p < 0.01$) and Lead ($F_{2,36} = 4.31$, $p < 0.05$), and their interaction (Congruency x Lead: $F_{2,36} = 3.63$, $p < 0.05$). Significantly enhanced negativities were recorded in response to targets flanked by incongruent distracters as compared with congruent ones (0.45 μV, S.E. 0.8 μV vs 1.23 μV, S.E. 0.9 μV), and the peak of the negativity was recorded at fronto-polar electrodes (AFp3h/AFp4h: -0.08 μV, S.E. 0.9 μV; F5/F6: 1.15 μV, S.E. 0.8 μV; FFC3h/FFC4h: 1.47 μV, S.E. 1.0 μV). The interaction indicated that within the incongruent condition the peak was more strongly centered at the frontal pole (AFp3h/AFp4h: -0.40 μV, S.E. 0.9 μV; F5/F6: 0.81 μV, S.E. 0.8 μV; FFC3h/FFC4h: 0.96 μV, S.E. 0.9 μV). After inspection of the difference waves performed between the incongruent and congruent flankers conditions (see Figure 4.7), and the source reconstruction algorithm (LORETA) results (see paragraph 4.3.3), additional analyses

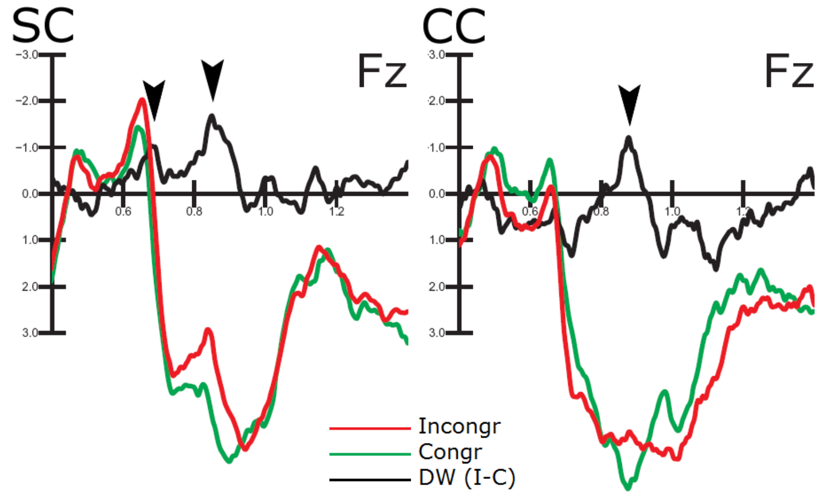


Figure 4.7. Target-locked waveforms elicited by stimuli flanked by incongruent (red) and congruent (green) distracters. In black, the difference wave (DW) calculated between incongruently and congruently flanked target stimuli. Noteworthy, the two different types of targets preceded by spatially valid cues were earlier differentiated, as indicated by the earlier negativities, as compared to the neutrally cued ones.

were performed on the difference waves Incongruent-Congruent for the two categories of spatial and neutral cues, in earlier intervals (650-700 ms) at midline sensors (Fz, FCz, Cz, CPz): the results showed a significant effect of cue type ($F_{1,18} = 4.99$, $p < 0.05$), with the spatially valid cues eliciting a stronger differentiation between the two flanker types at latencies as early as 150-200 ms after target onset at all leads (SC: -0.70 μV, S.E. 0.3 μV; CC: 0.03 μV, S.E. 0.3 μV).

P300 (800-1100 ms): peak amplitude. The ANOVA performed on the peak amplitude values of the P300 response to targets preceded by different categories of cues, and accompanied by different flankers showed significant a main effect of Congruency ($F_{1,18} = 12.15$, $p < 0.01$). Additionally, significant interactions were detected between Cue Type and Lead ($F_{6,108} = 2.87$, $p < 0.05$) and between Congruency level and Lead ($F_{3,54} = 8.12$, $p < 0.001$).

Significantly smaller P300s were recorded in response to targets flanked by incongruent distracters as compared with congruent ones (10.47 μV, S.E. 1.1 μV for congruent flankers, 9.57 μV, S.E. 1.1 μV for incongruent flankers), but this difference was not significant at central and centro-parietal electrodes; furthermore, post-hocs performed on the interaction between Cue Type x Lead revealed that SC elicited smaller P300s in respect to NC at all leads, and in respect to CC at all leads except Cz (see Chart 4.5), while no differences were significant in the comparison between CC and NC.

P300 (800-1100 ms): peak latency. The ANOVA performed on the latency of the P300 peak in response to the targets preceded by different categories of cues, and accompanied by different flankers showed significant main effects of Cue Type ($F_{2,36} = 5.32$, $p < 0.05$), Congruency ($F_{1,18} = 29.01$, $p < 0.0001$) and Lead ($F_{3,54} = 9.09$, $p < 0.01$). Follow-up analyses revealed faster-peaking P300s in response to targets anticipated by the arousing valid and neutral cues in respect to the uncued ones (926, 941 and 952 ms, respectively); moreover, earlier peaks were elicited by targets accompanied by congruent flankers, as compared to incongruent ones (925 ms vs 954 ms), and the faster P300s were recorded at parieto-occipital electrodes POz and Pz, as compared to more central electrodes (Cz and CPz).

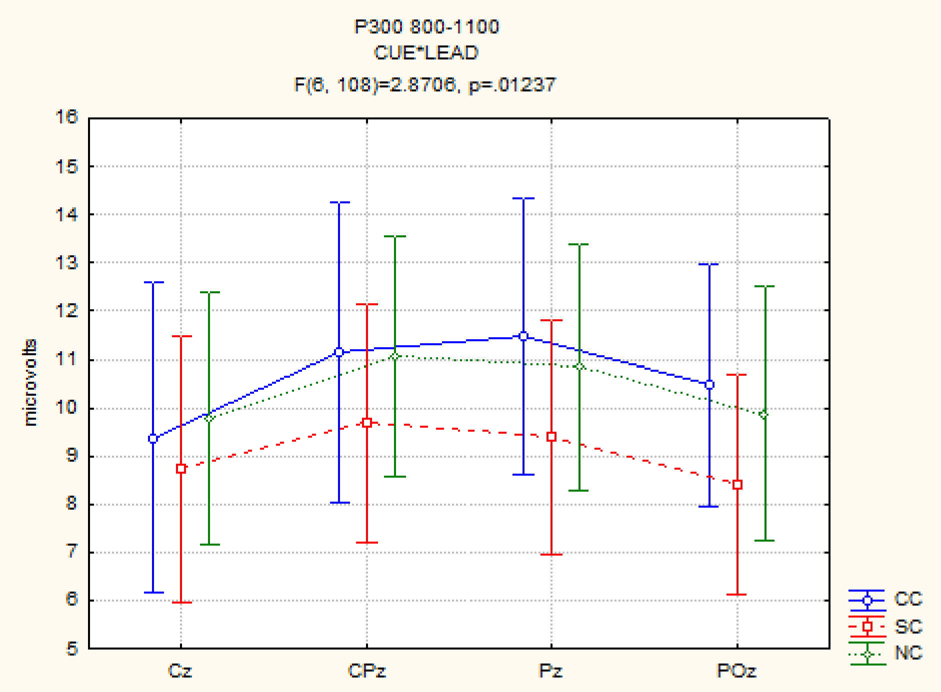


Chart 4.5

Chart 4.5. Interaction between cue type and lead in the P300 time range (800-1100 ms).

4.3.3 Source Reconstruction Results

P1 (125-160 ms). The P1 inverse solution, in line with the aforementioned significant differences in activation between SC and CC, especially at occipito-temporal electrodes, showed, among other activations, strong sources located in the right lingual gyrus (BA 18) and in the right middle temporal gyrus (BA 37) for the SC condition; in the same time window, the foveally presented cues elicited weaker sources only in the right cuneus (BA 17), with no temporal involvement. Besides the occipital dipoles, strong foci of activation were observed in the parietal lobe selectively for the spatially valid cue, in BA 7 bilaterally, suggesting an early construction (and later maintenance) of a spatial representation of the cued space, in order to make possible a later biasing in favor of the cued locations in visual areas. At the same time, early left prefrontal sources (BA 6 and 47) are commonly activated by the two arousing cues, indicating a possible early involvement of the phasic alertness system. The complete list of dipoles for the P1 interval is presented in Table 4.5.

Anterior N1(130-170 ms). Temporally, the frontal orienting N1 is, to a certain extent, overlapping with the posterior P1. Therefore, the occipital sources observed in concomitance with the frontal N1 will not be discussed further, while the attention will be focused on the more frontal display of activations. The main difference in the source distribution, between SC and CC conditions, lays in portions of the dorsolateral prefrontal cortex (right middle frontal gyrus, BA 6 and left precentral gyrus, BA 44), which is only weakly activated in the neutral condition. Conversely, a widely distributed pattern of frontal activations is commonly activate by the two types of cues (bilateral BA 10 and left middle and superior frontal gyri, BA 6 and 47), plausibly mediating the orienting reaction to cue onset.

Posterior N1 (160-200 ms). Mirroring the occipito-parietal N1 advantage for the foveally presented central cues resulting from the ERP analyses, the strongest activations in the occipital area are found in the neutral condition, with foci ranging from the left lingual and middle occipital gyri, to the superior temporal gyrus. Noteworthy, in the N1 latency range we can observe the onset of a bilateral activation of the Frontal Eye Fields (FEFs), corresponding to the Brodmann area 8, situated in the superior frontal sulcus, at the boundary between superior, middle and precentral frontal gyri.

SC_p1	Hemisphere	Lobe	Gyrus	BA	T-x	T-y	T-z	Magnitude
	Left	Frontal	Precentral Gyrus	44	-58	8	12	3 048
	Left	Frontal	Superior Frontal Gyrus	6	-14	27	54	4 682
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	3 325
	Left	Parietal	Superior Parietal Lobule	7	-29	-60	49	4 553
	Left	Temporal	Middle temporal gyrus	39	-43	-63	20	4 212
	Left	Cereb	Posterior Lobe, Declive		-29	-83	-16	6 326
	Midline	Cereb			0	-85	-26	6 631
	Right	Frontal	Middle frontal gyrus	6	29	12	56	4 976
	Right	Frontal	Superior Frontal Gyrus	10	29	55	22	8 947
	Right	Parietal	Precuneus	7	14	-60	49	3 756
	Right	Temporal	Middle temporal gyrus	37	58	-51	-8	6 367
	Right	Occipital	Lingual	18	14	-97	-5	8 528
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	7 116
CC_P1	Hemisphere	Lobe	Gyrus	BA	T-x	T-y	T-z	Magnitude
	Left	Frontal	Superior Frontal Gyrus	6	-14	27	54	7 149
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	4 301
	Left	Frontal	Middle Frontal Gyrus	46	-43	40	24	5 565
	Left	Frontal	Medial frontal gyrus	6	-14	-14	59	4 975
	Left	Temporal	Middle temporal gyrus	39	-43	-63	20	7 939
	Left	Cereb	Anterior Lobe, Culmen		-43	-54	-28	5 224
	Left	Cereb	Posterior Lobe, Declive		-29	-83	-16	7 245
	Right	Frontal	Middle frontal gyrus	8	43	26	40	7 502
	Right	Frontal	Superior Frontal Gyrus	10	29	55	22	7 966
	Right	Parietal	Postcentral gyrus	5	29	-43	62	12 629
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	8 504
	Right	Occipital	Cuneus	17	14	-80	7	6 753
	Right	Cereb	Posterior Lobe, Uvula		14	-85	-26	9 329

Table 4.5. Dipole list for the inverse solution (LORETA) performed for SC and CC in the P1 interval (125-160 ms).

P300 P300 (290-380 ms). The strongest difference revealed by the source reconstruction technique for the P300 interval is a strong and bilateral involvement of the superior parietal lobule in response to the spatially informative cue: this response is task-selective, because no activation in the area is recorded for the (equally arousing) neutral cue. At the same time, the common left prefrontal foci are still active for both the cue types involved in the phasic arousal system. Table 4.6 reports the full list of dipoles for the P300 interval for the SC and CC conditions.

CNV and LDAP (450-550 ms). The superior parietal involvement in case of spatially valid cues is still present in the last period before target onset, as testified by bilateral BA 7 foci for the SC condition. This parietal activation is also accompanied by occipital preactivation of the bilateral secondary visual areas (BA18), only for SC: the occipital

SC_P300	Hemisphere	Lobe	Gyrus	BA	T-x	T-y	T-z	Magnitude
	Left	Temporal	Superior Temporal Gyrus	22	-58	6	-2	4 534
	Left	Frontal	Superior Frontal Gyrus	8	-29	41	38	6 409
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	4 961
	Left	Frontal	Medial Frontal Gyrus	10	-14	52	-5	4 810
	Left	Frontal	Precentral Gyrus	6	-29	-14	59	4 542
	Left	Parietal	Superior Parietal Lobule	7	-14	-43	62	6 859
	Left	Parietal	Inferior Parietal Lobule	40	-43	-44	47	5 000
	Left	Temporal	Middle temporal gyrus	39	-43	-63	20	3 753
	Left	Parietal	Precuneus	7	-14	-77	36	5 718
	Left	Cereb	Posterior Lobe, Declive		-29	-83	-16	7 804
	Midline	Cereb			0	-85	-26	6 610
	Right	Frontal	Middle Frontal Gyrus	8	43	11	41	5 236
	Right	Frontal	Superior Frontal Gyrus	10	29	55	22	12 122
	Right	Temporal	Superior Temporal Gyrus	22	58	-47	18	3 877
	Right	Parietal	Superior Parietal Lobule	7	29	-60	49	6 384
	Right	Temporal	Inferior Temporal Gyrus	21	58	-8	-11	3 237
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	7 242
	Right	Occipital	Lingual	18	14	-97	-5	6 791
CC_P300	**Hemisphere**	**Lobe**	**Gyrus**	**BA**	**T-x**	**T-y**	**T-z**	**Magnitude**
	Left	Frontal	Middle Frontal gyrus	6	-29	12	56	15 841
	Left	Temporal	Superior Temporal Gyrus	22	-58	6	-2	7 294
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	8 277
	Left	Frontal	Middle Frontal Gyrus	46	-43	40	24	12 967
	Left	Frontal	Medial Frontal Gyrus	10	-14	52	-5	7 624
	Left	Frontal	Medial frontal gyrus	6	-14	-14	59	9 663
	Left	Parietal	Angular Gyrus	39	-43	-61	34	10 905
	Left	Occipital	Lingual Gyrus	18	-14	-97	-5	7 194
	Right	Frontal	Middle frontal gyrus	8	43	26	40	14 920
	Right	Frontal	Middle frontal gyrus	47	43	36	-4	12 358
	Right	Frontal	Medial frontal gyrus	10	14	52	-5	10 029
	Right	Parietal	Postcentral gyrus	5	29	-43	62	13 198
	Right	Temporal	Middle temporal gyrus	37	58	-51	-8	6 665
	Right	Cereb	Posterior Lobe, Declive		29	-83	-16	10 319
	Right	Occipital	Cuneus	18	14	-96	8	8 870

Table 4.6. Dipole list for the inverse solution (LORETA) performed for SC and CC in the P300 interval (290-380 ms).

SC	Hemisphere	Lobe	Gyrus	BA	T-x	T-y	T-z	Magnitude
	Left	Frontal	Middle Frontal gyrus	6	-29	12	56	17 037
	Left	Temporal	Superior Temporal Gyrus	22	-58	6	-2	8 811
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	10 281
	Left	Frontal	Middle Frontal Gyrus	46	-43	40	24	17 782
	Left	Frontal	Medial Frontal Gyrus	10	-14	52	-5	8 106
	Left	Parietal	Superior Parietal Lobule	7	-14	-43	62	10 058
	Left	Parietal	Inferior Parietal Lobule	40	-43	-44	47	8 708
	Left	Parietal	Precuneus	7	-14	-77	36	8 691
	Left	Occipital	Lingual Gyrus	18	-14	-97	-5	6 809
	Midline	Cereb			0	-85	-26	7 296
	Right	Frontal	Middle Frontal Gyrus	8	43	11	41	11 576
	Right	Frontal	Middle frontal gyrus	47	43	36	-4	14 487
	Right	Frontal	Superior Frontal Gyrus	10	29	55	22	13 048
	Right	Temporal	Superior Temporal Gyrus	22	58	-47	18	7 899
	Right	Parietal	Precuneus	7	14	-60	49	11 633
	Right	Temporal	Middle Temporal Gyrus	21	58	-20	-10	6 406
	Right	Temporal	Middle temporal gyrus	37	58	-51	-8	7 516
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	6 132
	Right	Occipital	Cuneus	18	14	-96	8	6 631
CC	**Hemisphere**	**Lobe**	**Gyrus**	**BA**	**T-x**	**T-y**	**T-z**	**Magnitude**
	Left	Frontal	Middle Frontal gyrus	6	-29	12	56	26 774
	Left	Frontal	Superior Frontal Gyrus	8	-29	41	38	21 856
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	14 362
	Left	Frontal	Medial Frontal Gyrus	10	-14	52	-5	11 115
	Left	Frontal	Medial frontal gyrus	6	-14	-14	59	14 862
	Left	Temporal	Middle temporal gyrus	39	-43	-63	20	8 185
	Left	Occipital	Lingual Gyrus	18	-14	-97	-5	6 598
	Right	Frontal	Middle frontal gyrus	8	43	26	40	21 202
	Right	Frontal	Middle frontal gyrus	47	43	36	-4	18 996
	Right	Frontal	Medial frontal gyrus	10	14	52	-5	14 131
	Right	Frontal	Superior Frontal Gyrus	9	14	55	22	14 683
	Right	Parietal	Postcentral gyrus	5	29	-43	62	20 175
	Right	Temporal	Middle temporal gyrus	37	58	-51	-8	6 800
	Right	Occipital	Middle Occipital Gyrus	19	29	-80	7	7 443
	Right	Cereb	Posterior Lobe, Declive		29	-83	-16	9 890
NC	**Hemisphere**	**Lobe**	**Gyrus**	**BA**	**T-x**	**T-y**	**T-z**	**Magnitude**
	Left	Frontal	Superior Frontal Gyrus	6	-14	12	56	11 403
	Left	Temporal	Superior Temporal Gyrus	22	-58	6	-2	6 853
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	5 425
	Left	Parietal	Superior Parietal Lobule	7	-29	-60	49	11 196
	Left	Occipital	Middle Occipital Gyrus	19	-29	-79	21	8 907
	Left	Cereb	Anterior Lobe, Culmen		-43	-52	-18	5 247
	Left	Cereb	Posterior Lobe, Declive		-29	-83	-16	7 386
	Midline	Frontal	Medial Frontal Gyrus	6	0	-27	60	5 991
	Midline	Cereb			0	-85	-26	6 483
	Right	Frontal	Middle frontal gyrus	47	43	36	-4	19 039
	Right	Frontal	Medial frontal gyrus	10	14	52	-5	17 660
	Right	Parietal	Postcentral gyrus	5	29	-43	62	9 474
	Right	Temporal	Inferior Temporal Gyrus	20	58	-21	-20	3 468
	Right	Temporal	Middle temporal gyrus	37	58	-51	-8	4 332
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	5 393
	Right	Occipital	Lingual	18	14	-97	-5	6 718

Table 4.7. Dipole list for the inverse solution (LORETA) performed for SC, CC and NC in the CNV/LDAP interval.

activation in case of CC and in the control condition is limited to unilateral BA 18 activations; an additional posterior differentiation is the strength of the right temporal biasing (BA 37), which is maximal for SC, intermediate for CC and minimal for NC.

Concerning the frontal pattern, more related to the alertness modulation, the bilateral activation of middle and superior frontal gyri, highly similar for SC and CC, is rather bilateral, in line with the hypothesis of an engagement of both the tonic and phasic arousal system in case of alerting cues; the ERP analyses, showing a fronto-central distribution of the CNV, but not a strong lateralization, point toward the same interpretation; on the other hand, in case no cue is delivered prior target appearance (NC), only the tonic aspect of the sustained attention system is activated, as reflected in more right-hemisphere lateralized foci (see Table 4.7).

Executive control activations. In order to clarify the interaction between congruency level and cueing condition, indicated by the behavioral results, the

LORETA source reconstruction was performed on the difference wave calculated between incongruent and congruent conditions for CC, subtracted from the same difference for SC (see Figure 4.7 and 4.8, upper panel). With this technique, the selective contribution of the orienting activation upon the executive control operations could be isolated. The intervals used for the calculations were hypothesis-directed, since preliminary solutions obtained for the gross subtraction SC-CC indicated early activations in the ACC, among other sources. Therefore, we expected to observe early anterior cingulate activations, and to be able, by means of the double subtraction technique, to highlight the ACC contributions. The results are depicted in Figure 4.8, lower panel. As it might appear evident, the anterior cingulate activation is characterized by an early onset and by a stable pattern of activation, peaking in the N1/N2 interval and decreasing in the P300 interval.

4.4 Discussion

Alertness

One of the aims of this study was to record cerebral responses to the different types of cues. First, we tackled those responses that selectively differentiated between conditions that carried an alerting value (both the central neutral cues and the peripheral spatially valid cues) and situations in which only a tonic level of arousal was maintained in order to achieve good levels of performance during the task (No Cue condition). The activation of the arousal system was reflected, at the behavioral level, in a reaction time benefit in respect to the uncued condition. At the electrophysiological level, the main deflection which selectively differentiated between these two situations was the Contingent Negative Variation (*CNV*), a cognitive component which is known to be related to orientation towards a warning stimulus (Weerts & Lang, 1973) expectancy of salient or goal-related events (Walter *et al.*, 1964; Eimer, 1993a; Brunia, 1993), and to motor preparation

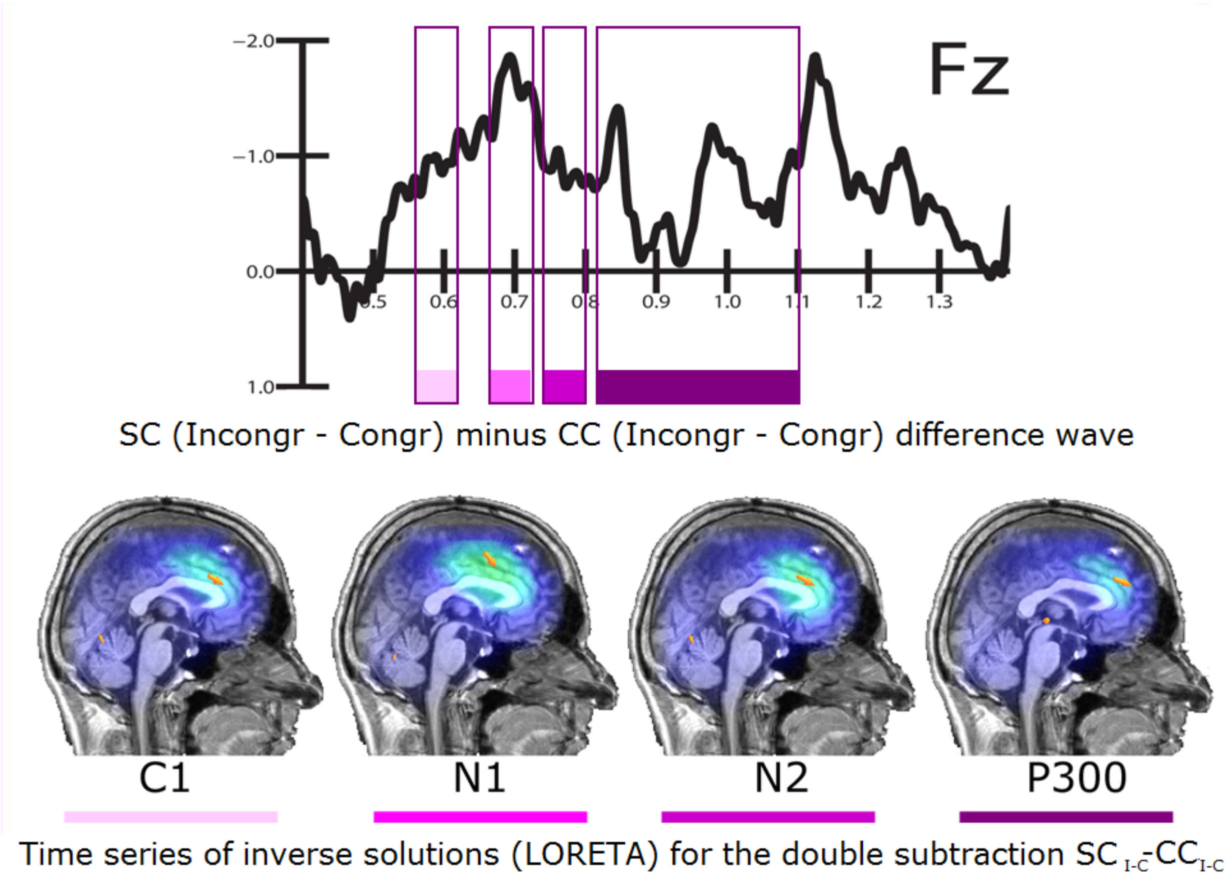


Figure 4.8. Upper Panel: Difference wave computed between the difference waves (Incongruent Flankers – Congruent Flankers) for the two cueing conditions Sc and CC. Superimposed on the waveforms are visible the time intervals of the principal ERP components, upon which the source reconstruction technique has been applied.
Lower panel: Time series of LORETA inverse solutions calculated upon the double difference SC(incon-con)-CC(incon-con). The main source in each time window is a dipole positioned in the anterior cingulate cortex (BA 24).

(Loveless and Sanford, 1974). In the ANT, the information provided by the alerting cues (even by the spatially informative cue SC) is not in any way related to the hand of response, because the direction in which the target arrow points, and which directly determines the hand to be used for the key-press, is not coded in the cues (Fan *et al*., 2002). In other words, knowing the temporal contingency (and even the position) of the target prior its appearance does not provide the participants with any information useful on order to trigger the motor preparation necessary to respond faster to the targets themselves. Therefore, the CNV response (present for both CC and SC, and not present for the No Cue condition) could not be selectively related to the activation of a response hand. The scalp distribution of the component reflected fronto-central sources centered around the Brodmann area 6, at the border between the superior and middle frontal gyri, accompanied by dorsal foci in the middle frontal gyri (BA 47 and 10). Previous literature suggested bilateral frontal involvement in the CNV generation, especially of the anterior cingulate cortex and of the SMA (Cui *et al*., 2000; Gomez *et al*., 2001; Gomez, Marco & Grau, 2003; Gomez, Flores & Ledesma, 2007). The present results are in line with previous reports. Moreover, and crucially for the multi-level manipulations utilized in our modified version of the ANT, all the fontal activations were bilateral in the alerting conditions, as indicated by the distributed sources resulting from the LORETA application. Conversely, the undifferentiated negative activation recorded in the NC condition showed, in the inverse solution, a rather more imbalanced (in detail, right-sided) distribution of the frontal dipoles, especially in the middle and middle frontal foci (BA 47 and 10), in line with the hypothesis that the sustained attention system is activated in the uncued trials. All in all, these findings show high accordance with haemodynamic functional neuroimaging (Coull *et al*., 1996; Sturm *et al*., 1989 & 1999; Sturm & Willmes, 2001) and neuropsychological literature (Làdavas, 1987; Posner *et al*., 1987) indicating two distributed anatomical networks responsible for the phasic and tonic aspects of the alerting system, embedded in the two separate hemispheres (left-sided for the phasic component, or for the orienting towards time intervals, as in Coull *et al*., 1996 & 1998; Sturm & Willmes, 2001; right-sided for tonic or sustained aspects, Sturm *et al*., 1989 & 1999; Sturm & Willmes, 2001).

In previous works, an interaction has been proposed between the alerting network and the executive control system. In detail, higher costs for incongruency were reported in case of warning signals, both in visual (Fan *et al*., 20002) and auditory (Callejas *et al*., 2004 & 2005; Fuentes & Campoy, 2008) modalities, in respect to orienting and control (uncued) situations. The explanation was proposed in terms of the *clearing of consciousness* hypothesis (Posner, 1994), which claims a shutdown of the control system when the organism has to concentrate on the detection of external salient events, which are suggested by the warning signals. The behavioral interaction between cueing type and flanker category was significant in our study, but the uncued and the neutrally cued targets showed non-different incongruency costs, and both significantly higher costs in respect to the validly cue targets. Therefore, in our case the *clearing of consciousness* hypothesis could be ruled out. Moreover, and crucially, we couldn’t find any ERP component or cerebral source which was significantly *decreased* in response to targets preceded by neutral cues, and could therefore be interpreted as indicators of a hampering of the control system in case of arousal increase.

Orienting

The spatial orienting system has been linked to a distributed fronto-parietal network (Gitelman *et al*., 1999; Corbetta & Shulman, 2002; Fan *et al*., 2005), with a dorsal component involving the superior and middle frontal gyri (and in detail the human homologous of the monkey frontal eye fields), the intraparietal sulcus and the superior parietal lobule. In the present study, the first activation that differentiated neutral and spatially valid cues was at the P1 latency. Such early effect could be motivated by the differential retinal position of the valid and neutral cues: however, the neutral cues were presented foveally, and the valid cues outside the foveal area; nonetheless, the valid cues, for which no magnification factor was used, elicited an enhanced P1in respect to the central cues. An attentional effect at this time latency has never been reported before, in the studies addressing the electrophysiological responses to attention-directing cues. To our knowledge, only two studies addressed the question comparing attention-directing cues and neutral cues. In one study (Grent-'t-Jong & Woldorff, 2007) the warning signals consisted in letters, which could either be attention directing cues (although the temporal coupling between cue and target was randomized) or interpret cues, which were not followed by any target. The earliest effects between the two cue types were reported around 400 ms, and consisted in frontal activations, which preceded the parietal contributions. The second, very recent, study (McDonald & Green, 2008) used complex colored pattern as valid and neutral cues. The authors reported the earliest differences between neutral and valid cues as positive peaks between 200 and 300 ms, at frontal and central electrodes. This effect appears significantly delayed in respect to the one we report here; however, the difference between the studies might be driven by the nature of the cues: in McDonald & Green’s study, the neutral cues were highly similar to the valid ones, but they were missing the color which was the to-be-attended one. Thereby, this complex patterns could have elicited similar visual components, and the later recognition of a missing feature could have caused an enhanced negativity (selection negativity) in response to the neutral cues, which resulted in the net positivity for valid cues at frontal electrodes, reported in the study. Our effect might be caused, on the other hand, by the vertical distribution of the valid cue position. The anisotropy of the cerebral representation of the visual hemifields along the vertical meridian (Fukusima & Flaubert, 2001; Sakaguchi, 2003), and the sensitivity of the ERP components to stimulus position (Clark & Hillyard, 1995) have been previously reported; however, the indications usually referred to differences among the upper and lower visual fields, which are both less represented than the fovea in the visual cortex. In consequence, the early effects reported in favor of the peripheral valid cues might, in our opinion, be attributed to attentional effects. The early onset of superior parietal activations (BA 7) near the intraparietal sulcus, selectively in response to spatial cues, further supports the explanation of the effect in attentional terms. The superior parietal activation in case of spatial orienting cues persists, bilaterally, until target appearance, sustaining the hypothesis of a role of the superior parietal cortices in maintaining the spatial representation of the cued location (Kastner *et al*., 1999; Corbetta *et al*., 2000). At the same time, during the LDAP/CNV onset and development, signs of bilateral occipital biasing are evident in extrastriate cortices (lingual gyrus, BA 18) in anticipation of the validly cued targets, in line with previous neurofunctional and electrophysiological reports (Kastner *et al*., 1999; Corbetta *et al*., 2000; Hopfinger, Buonocore & Mangun, 2000; Grent-'t-Jong & Woldorff, 2007; McDonald & Green, 2008).

Executive control

The engagement of the executive control system was testified by the behavioral costs recorded in the manual responses to targets flanked by incongruent distracters, as compared to congruent ones. Response selection, especially in case of response incompatibility, has been suggested to activate distributed networks embedded in frontal and prefrontal brain areas. Among the regions involved in the conflict monitoring and resolution operations, the anterior cingulate cortex, the SMA, pre-SMA and more dorsolateral and ventrolateral frontal cortices have been repeatedly reported (Bush, Luu, Posner, 2000; Botvinick *et al*., 2001; Van Veen *et al*., 2001; Fan *et al*., 2003 & 2005). Electrophysiological studies suggested fronto-central negativities (N200) as reflections of the engagement of these functional circuits in case of response conflict (Kopp, Rist & Mattler, 1996; Wang *et al*., 2000; Kenemans *et al*., 1993; Rueda *et al*., 2004a; Bartholow *et al*., 2005), with cingulate sources (Liotti *et al*., 2000; Lange *et al*., 1998; Van Veen & Carter, 2002, Crottaz-Herbette & Menon, 2006 with an oddball task). According to the *anterior attentional system* hypothesis the anterior cingulate exerts executive control by modulating the allocation of attentional resources (Posner & Petersen, 1990; Bush, Luu & Posner, 2000); on the other hand, the conflict monitoring hypothesis (Botvinick *et al*., 2001 & 2004) postulates a more limited role for the ACC, involved in the detection of response conflict, and in the recruitment of more dorsolateral areas for the effective cognitive control. In either case, the ACC involvement in cognitive control (either direct or indirect) is proposed by both theories. Our results, indicating ACC as the main source of the early and late frontal electrocortical negativities replicate previous reports; more crucially, the interaction between orienting response and conflict detection and resolution, as indicated by the converging behavioral data, ERP analyses and inverse solution patterns, strongly points towards an anatomical network which integrates the fronto-parietal network for attentional control (Corbetta & Shulman, 2002) and the executive control system (Bush, Luu & Posner, 2000). In our interpretation, the activation of the attentional control system exerts a biasing upon the posterior, visual areas, as reflected by the tonic positive shifts recorded upon occipito-parietal cortices prior target appearance (LDAP/BRN, Grent-‘t-Jong & Woldorff, 2007; Harter *et al*., 1989). At the same time, the need for detection of complex target features, required by the ANT, enabled the observation of a higher-order cognitive modulation: the attentional effect is reflected in a priming of the fronto-medial structures deputed to cognitive control, in turn reflected in smaller behavioral costs for incongruency in the valid condition. The early onset of the modulation (about 50 ms after target appearance in the inverse solutions, and about 150 ms in the ERP reflections of the cognitive activity) was a surprising finding, but somehow in line with previous reports of early enhanced negativities for incompatible targets presented at fixation, thus *within* the spatial orienting focus (Rueda et al., 2004a).

4.5 Conclusion and open questions

Our results provide compelling evidences for a dissociation between alerting and orienting systems, for internal dissociations between phasic and tonic alertness and for frontal integrations between attentional and control systems. Still open are the questions concerning the lateralization of the frontal and parietal components in the orienting system: the bilateral activations recorded with early onset in response to attention directing cues might be due to the intrinsic organization of the fronto-parietal networks, or, conversely, to the vertical distribution of the cue and target stimuli characteristic of the ANT. More research is needed to address this question; moreover, the new finding of an integration between attentional and control systems poses an issue concerning the specificity of the effect: additional studies addressing the question with the use of different *executive tasks* are desirable.

Chapter 5.
Study 2: Spatio-temporal dynamics of endogenous and exogenous spatial orienting, in interaction with the conflict monitoring / motor inhibition system

5.1 Introduction

In the electrophysiological literature, the traditional approach in the study of attentional control has been to provide participants with attention-directing cues and to record their differential cerebral responses to them. In particular, most of the studies presented so far made use of valid and invalid cues which were expected to elicit lateralized shifts of the attentional focus (Harter *et al.*, 1989; Yamaguchi, Tsuchiya & Kobayashi, 1994; Hopf & Mangun, 2000; Nobre, Sebestyen & Miniussi, 2000). Therefore, the theoretical debate concerning the electrophysiology of attentional control has been centered onto two main questions: first, at what latency it is possible to detect the onset of attentional effects, and, second, which kind of lateralization pattern characterizes the attention-related ERPs (Harter *et al.*, 1989; Yamaguchi *et al.*, 1994; Hopf & Mangun, 2000; McDonald & Green, 2008); more recently, the functional meaning and the cerebral sources of the traditionally recorded ERP components in response to attention-directing cues have been addressed (Van Velzen & Eimer, 2003; Green *et al.*, 2005; Grent-'t-Jong & Woldorff, 2007; McDonald & Green, 2008). The electrophysiological deflections which have been traditionally reported in case of attention-directing cues included an early negativity, recorded on the posterior scalp sites contralateral to cue direction (EDAN, *early directing attention negativity*, with onset at 200 ms after cue onset, Harter *et al.*, 1989), a late contralateral posterior positivity (LDAP, *late directing attention positivity*, Harter *et al.*, 1989) and an anterior negativity (ADAN, *anterior directing attention negativity*), recorded controlaterally to cue direction between 300 and 500 ms after cue onset (but which could be also considered an ipsilateral positivity, see Hopf & Mangun, 2000). Functionally, the EDAN has been considered the reflection of the initiation of voluntary shifts of attention implemented in the parietal lobes (Harter *et al.*, 1989; Hopf & Mangun, 2000; Nobre *et al.*, 2000), but later studies indicated that this component might be more plausibly generated in occipito-temporal cortices and may reflect the selection of relevant aspects of the cue itself (as its lateralization, Van Velzen & Eimer, 2003). Conversely, the ADAN has been proposed to reflect the drive of frontal structures upon attentional control (Hopf & Mangun, 2000), in particular because of some evidences of ADAN supramodality (e.g., Eimer, Van Velzen & Driver, 2002); however, these indications have not been replicated in paradigms involving auditory cues or targets (Green *et al.*, 2005 & 2008), which challenged the idea of the ADAN intended as the scalp reflection of the supramodal attentional control system activation. In turn, the LDAP has been suggested to reflect the maintenance of the attended location representation (Hopf & Mangun, 2000; Eimer, Van Velzen & Driver, 2002) or the modulation of excitability in cortical structures which are deputed to the processing of the upcoming visual information (Harter *et al.*, 1989; Hopf & Mangun, 2000; Green *et al.*, 2005). The fact that different accounts concerning these controversial components are still highly debated is most likely due, at least in part, to the methodological differences across studies, and, maybe even more crucially, to the conventional approach used to obtain, compute and score the lateralized components. The early studies used symbolic cues (e.g., arrowheads), which may have led, because of their asymmetric presentation, to lateralized sensory activity due to the crossed organization of the visual pathways: thereby, in order to resolve this methodological shortcoming, more symmetrical cues have been adopted, such as colored shapes (Nobre *et al.*, 2000; McDonald & Green, 2008), composed pointers (Van Velzen & Eimer, 2003; Brignani *et al.*, 2009), or letters (Grent-‵t-Jong & Woldorff, 2007). Since low level sensory responses are more balanced across the cerebral hemispheres in case of symmetric pointers, these cueing modalities enabled the researchers to couple lateralized activations with purely cognitive operations engaged by the stimuli, independently from sensory activations elicited by them. Nevertheless, the techniques which has been traditionally used in order to compute, visualize and score the lateralized components always included either comparisons or subtractions between the ERPs in response to cues directing attention toward the right and left hemifields (Harter *et al*., 1989; Yamaguchi *et al.*, 1994; Hopf & Mangun, 2000; Nobre *et al*., 2000; Van Velzen & Eimer, 2003), or comparisons between the cerebral responses recorded contralaterally and ipsilaterally in respect to cue direction (Green *et al*., 2005 & 2008). Unfortunately, the approach involving the subtraction of lateralized components, which led to the detection of the EDAN, ADAN and LDAP components, is not a suitable tool for detecting bilateral activations or spatially aspecific activations (i.e., lateralized responses elicited by cues directing attention to either hemifield), which are both canceled out by these analysis procedures. On the other hand, the comparison between contra- and ipsilateral activations (which includes spatial re-mapping an averaging across hemifields, as in McDonald & Green, 2008) doesn't take into account the possibility to record asymmetrical activities in response to attention-directing cues in the attentional control networks, which, conversely, have been repeatedly reported in the context of neuropsychological and hemodynamic-based functional imaging literature (e.g., Gitelman *et al.*, 1999; Mesulam, 1999; Corbetta *et al.*, 2002; Fan *et al.*, 2005). Therefore, in order to complement the functional explanations of the ERP components with the hemodynamic literature, a different approach is needed, which could seize both contra- or ipsilateral activations and asymmetrical or bilateral involvements, at the same time integrating these notions with precise information about the temporal dynamics of the attentional mechanisms. One possible solution could be the comparison between attention-directing cues and neutral cues, coupled with high-density EEG recording and inverse solutions techniques, as it has been proposed in study 1. Capitalizing on the results of the first experiment of this project, and being interested in addressing the questions which still remained unanswered after it, we designed a new ERP study. The goals of this experiment were multiple: first, we planned to further validate the *neutral versus valid cues* comparison utilized in study 1, additionally comparing the cerebral effects of vertical and horizontal shifts of attention.

Second, we were interested in a more direct comparison with previous ERP studies addressing attentional control, which all used lateralized cues and targets. Our goal was, then to integrate the previously reported literature with the investigation of plausible asymmetrical or bilateral activations of the system, by means of the introduction of neutral cues in combination with lateralized target stimuli. This kind of comparison has been previously used in ERP, in the context of the investigation of endogenous attention mechanisms studies (Grent-‘t-Jong & Woldorff, 2007; McDonald & Green, 2008). In these studies, however, the cues were either letters (Grent-‘t-Jong & Woldorff, 2007) or rather complex colored stimuli (McDonald & Green, 2008): in both cases, the cognitive operations needed in order to recognize or interpret the cues might have influenced the timing of attentional modulations, introducing between-subjects noise that may have acted as a confound upon early attentional effects (see Chapter 4 for a more detailed description of these studies). Therefore, we opted for rather simple stimuli, as asterisks and arrowheads, in order to elicit spatial shifts of attention.

Third, we were interested in direct comparison between the cognitive responses to central and peripheral attention-directing cues, sharing the predictive value. Hemodynamic-based studies sustained highly overlapping systems for endogenous and exogenous *orienting* (Kim *et al.*, 1999) or *facilitation* (Mayer *et al.*, 2004), with stronger involvement of the network in case of endogenous cueing (Kim *et al.*, 1999; Mayer *et al.*, 2004), with a more ventral distribution of activation in the fronto-parietal networks for exogenous processes (Corbetta & Shulman, 2002; Gitelman *et al.*, 1999). Within the framework of the electrophysiological literature, whereas many studies addressed the differential effects of attention upon the detection and processing of target stimuli (e.g., Eason *et al.*, 1969; Zani & Proverbio, 1997; Zani *et al.*, 1999; Fu *et al.*, 2001; Natale *et al.*, 2009), to our knowledge only one ERP study explicitly addressed the differential effects of endogenous and exogenous cueing modalities upon *attentional control* mechanisms (Yamaguchi *et al.*, 1994). The authors’ main goal was to shed light upon the temporal unfold of the exogenous and exogenous attentional deployment, by comparing the electrical activations driven by left- and rightwards attention-directing cues: the results indicated an earlier lateralized effect in case of exogenous cues (160 ms as compared to 240 ms for the endogenous ones, both recorded contralaterally), and a posterior onset for the attentional effects, centered at first over occipito-parietal leads and then spreading more anteriorly at longer latencies, in particular for endogenous cueing. An additional sustained negativity was reported for the exogenous cueing modality starting around 460 ms, and spreading more centrally and frontally at longer latencies (no LDAP was reported for either modality). These results indicated some common aspects between the two attentional control modalities (e.g., the presence of sustained contralateral negativities, and the posterior onset of the effects); however, as anticipated, no neutral baseline conditions were inserted in the design, and the electrophysiological recording was based only upon a limited number of sensors (14 leads). Following the approach of Yamaguchi and coworkers, but avoiding the conventional left/right cues comparison, we aimed at the integration of the authors' results and functional conclusions by means of the use of two cueing paradigms in a within-subject design: one task included the comparison between neutral and valid central cues, while the other modality involved the comparison between central neutral and lateralized (spatially informative) cues (similar to the ones used in experiment 1).

One additional goal of our study was to address the integration between endogenous and exogenous attentional control with the activity of the monitoring and control system, in particular in its inhibitory component. This aspect of the question was investigated by combining the two cueing modalities with a go/no-go task, which is known to require the engagement of the monitoring system (Donkers & Van Boxtel, 2004) and of the motor inhibition system, embedded in frontal and parietal structures as the ACC, the inferior frontal cortices and the posterior parietal areas (Garavan *et al.*, 2002; Watanabe *et al.*, 2002; Swainson *et al.*, 2003; Chambers *et al.*, 2007). Moreover, the go/no-go task has been reported to elicit specific ERP components, as the *NogoN2* (Kok, 1986; Pfefferbaum *et al.*, 1985; Nieuwenhuis *et al.*, 2003; Donkers & Van Boxtel, 2004; Smith, Johnstone & Barry, 2007), sensitive to the conflict dimension of the stimuli and to the need to withhold or delay or modulate behavioral responses. To our knowledge, no previous ERP study combined the attentional modulation with inhibitory control manipulations, thus, in order to design the study, we capitalized on the results of study 1.

In summary, out predictions involved the observation of early attentional modulations in response to valid cues, at least in the peripheral cueing modality (i.e., replicating the results of Study 1); furthermore, we were interested in the lateralization of later attention-related components (addressed by comparing neutral and valid cues, instead of left- versus rightwards attention-directing cues), in the perspective of an integration of the traditionally reported lateralized cue-related ERPs (EDAN, ADAN, LDAP). We also predicted that, during the cue-target interval, expectancy-related and preparation-related components as the Contingent Negative Variation (CNV, Walter *et al.*, 1964, Eimer, 1993a) would be generated, depending on the alerting value of the visual cues, shared by both neutral and valid cues in both modalities; however, since the hand of response was coded at the beginning of each block (thus, the motor preparation could be initiated prior target onset), we expected to observe stronger negativities following valid cues than following neutral ones. Furthermore, given that the task included no-go trials, we expected to observe a modulation of the conflict-related negativities on the basis of the cueing condition (valid versus neutral), replicating and further integrating the hypothesis proposed based on the results of study 1, suggesting a biasing of the monitoring functions exerted by the frontal lobes dependent upon the activation of the spatial orienting system.

5.2 Methods

5.2.1 Participants

20 healthy students received university credits for their participation in the study (age range 20-33 years, mean 23.16 years, S.D. 3.24 years, 9 males). All participants had normal or corrected-to-normal vision, no history of neurological or psychological diseases and were unaware of the purpose of the study. 6 participants were successively excluded from the statistical analyses because of an excessive percentage of ocular or muscular artifacts in the task-related EEG signal, resulting in a sample of 14 volunteers (age range 20-33 years, mean 23.0 years, S.D. 3.57 years,6 males).

5.2.2 Task

The experimental session consisted in two parts: an endogenous spatial cueing paradigm and an exogenous spatial cueing paradigm. In both tasks the volunteers’ goal and the target stimuli were identical: participants were asked to press a response button on a joy-pad with their left or right index fingers (counterbalanced across blocks) as fast and as accurately as possible, in response to the presentation of a visual target, regardless of its position on the screen; besides, they were required to withhold any response in case a non-target was presented. Targets and non-targets were both vertical grey bars, characterized by a certain length and width, which differentiated them. All targets were 5 cm in length and 0.5 cm in width, while non-targets were 3 cm tall and 0.8 cm wide. In each block, the proportion between randomly presented targets and non-targets was 80%-20%. All stimuli were presented on a black background, with a lateralization of 3.5 degrees of visual angle in respect of a small white fixation cross (subtending 0.25 degrees of visual angle, at a distance from the screen of 114 cm). The temporal structure of the trial was identical across conditions: both targets and non-targets were presented for 90 ms, 500 ms after the presentation of the cueing stimulus; cues were different in shape and position between the two conditions (endogenous vs exogenous), but commonly lasting 100 ms on the screen. The interval between the onsets of two succeeding trials was randomized between 800 and 1000 ms for both parts of the experimental session.

Endogenous task. In order to be able to compare the ERP responses to the endogenous cues to previous studies using similar paradigms, the endogenous task was constructed applying a randomized design. Neutral and valid cues (20%-80%) where thereby

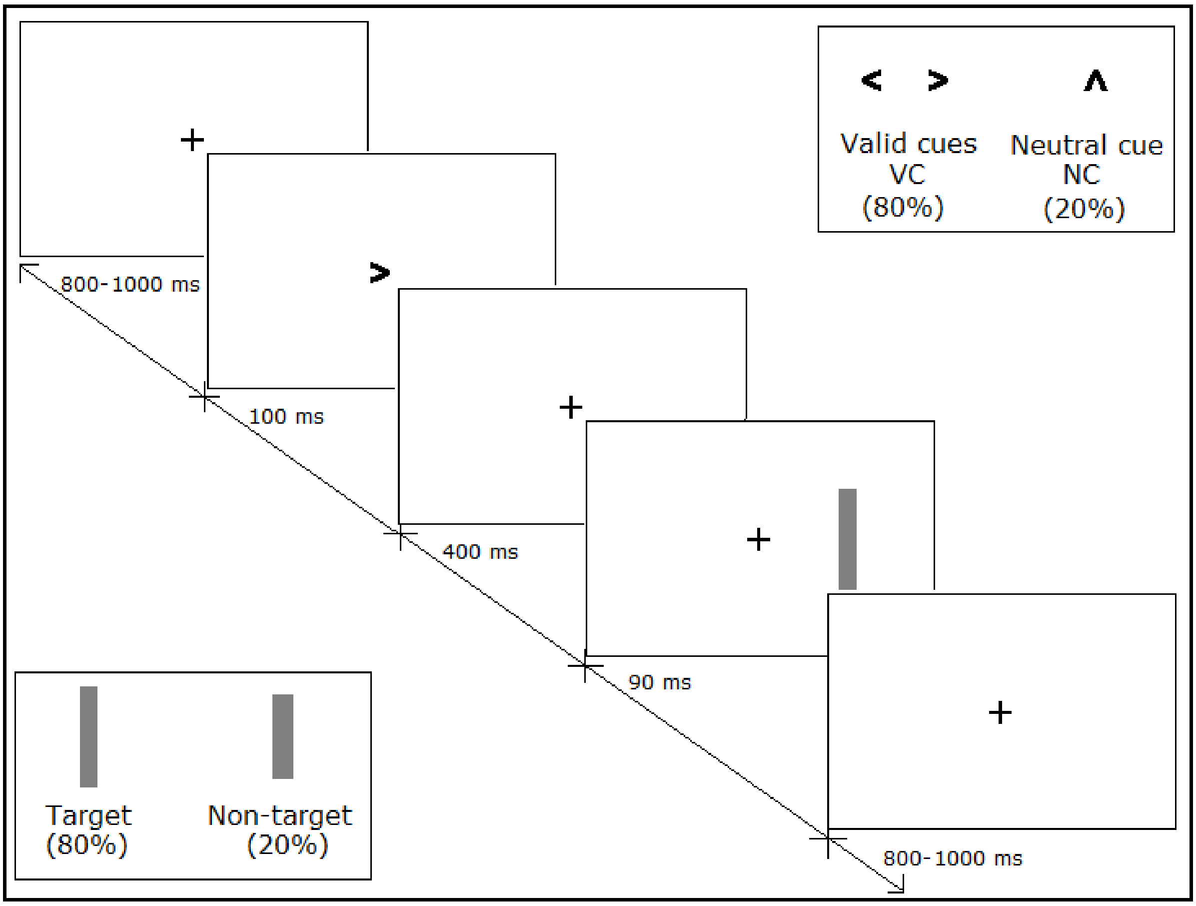


Fig. 5.1. Example of the temporal structure of a valid target trial in the endogenous cueing paradigm. In the right upper panel examples of the different cue types, either indicating one of the two hemifields, or pointing upwards; in the left lower panel is illustrated the difference in shape between target and non-target bars.

presented for each block in a randomized order, either of them followed in the majority of cases (80%) by a target stimulus and 20% of the times by a non-target stimulus (see fig 5.1 for an exemplification of the temporal structure of a valid trial, and for a graphic depiction of targets and cues). Cues (S1), presented at fixation for 100 ms, consisted in grey arrowheads pointing either upwards (neutral cues, NC, 20% of the total of the trials in each block) or left- or right-wards (valid cues, VC, always informative in respect to the location of appearance of the next stimulus). The valid cues were pointing towards the left hemifield in half of the valid cues (40% of the total amount of stimuli in each block) and rightwards in the rest of the cases (40% of the total amount of stimuli of each block). All the cues subtended $1^{o}x1^{o}$ of visual angle, and were centered around the fixation cross both vertically and horizontally, in order not to introduce any difference in the amount of visual stimulation across quadrants. Targets and non-targets (S2) followed the endogenous cues as described earlier. The total amount of stimuli in the exogenous task was 600, divided into 8 blocks: 480 valid trials (S1 + S2) were presented (384 targets and 96 non-targets, half of which in the left visual field and the other half in the right visual field); the total amount of neutral trials corresponded to 120 stimuli (96 targets and 24 non targets, again equally distributed

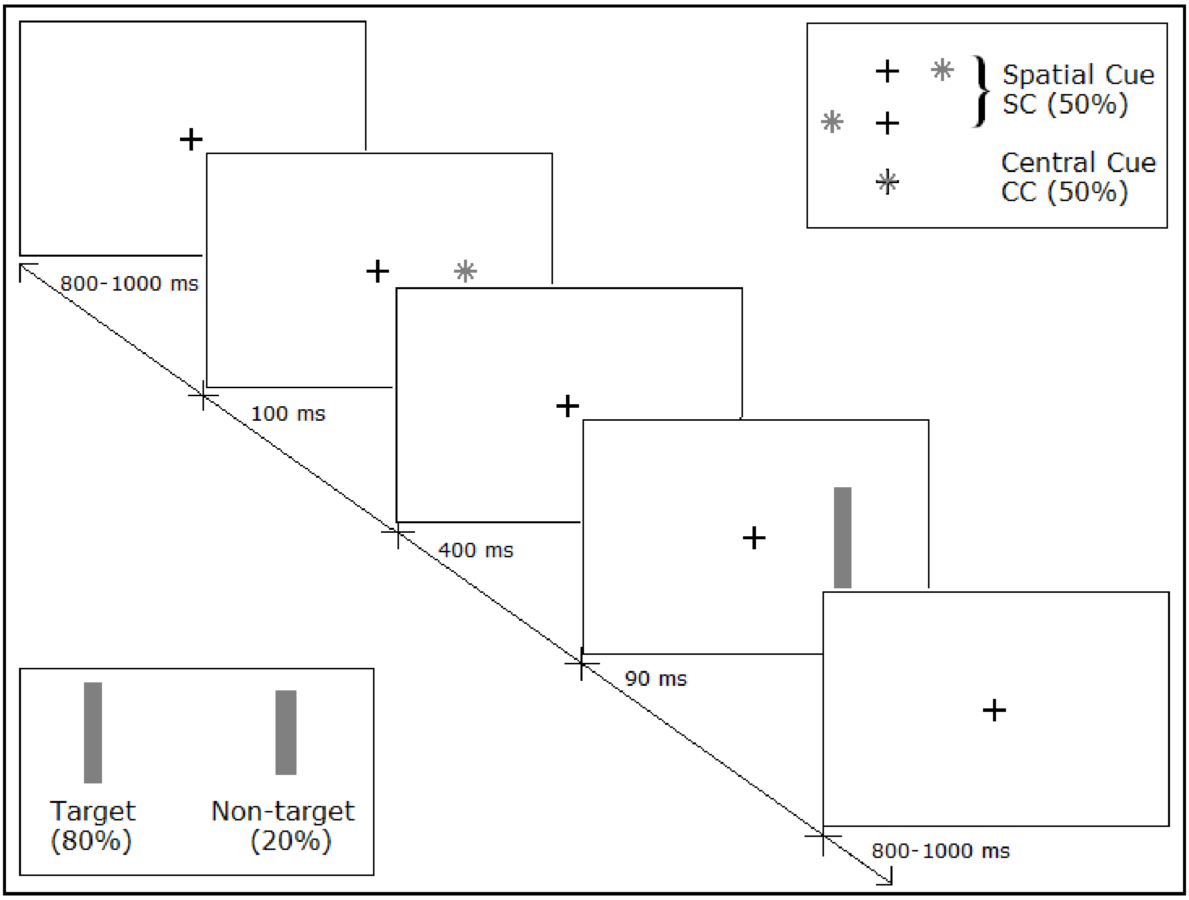


Fig. 5.2. Example of the temporal structure of a valid target trial in the exogenous cueing paradigm. In the right upper panel examples of the position of the different cue types in respect to the fixation cross; in the left lower panel is illustrated the difference between target and non-target bars.

among the two hemifields). Since the valid cues were predictive in respect to the hemifield of appearance of the subsequent stimulus, the volunteers were expected to be able to use this information for anticipating the attentional deployment towards the cued direction, while during a neutral trial we predicted that the orienting of the visual attention would be completely bottom up, only guided by the appearance of S2 (target or non-target). Since the temporal coupling between each S1 and its relative S2 was fixed, all cues (either neutral or valid) served also as a warning (alerting) signal for the participants. As described above, volunteers were asked to perform a simple go/no-go task, in which they had to respond to the appearance on the screen of the target bars with the index finger of one hand, which was indicated to them by the instructions at the beginning of each block, while withholding their response to the non-targets.

Exogenous task. In order to be able to compare the lateralized exogenous task with Study 1, in which the S2 stimuli followed the cue above or below fixation, the temporal structure and the block design as in the first experiment was maintained. Cues (S1) consisted in small grey asterisks presented in different positions, either at fixation or with a left or right eccentricity of 3.5^{o} of visual angle along the horizontal meridian (see Figure 5.2 for a graphic example of the trial temporal structure). All the trials in which

S1 was presented at fixation (central neutral cues, denominated CC) were grouped in 4 blocks, for a total of 332 stimuli (266 targets and 66 non-targets, half of them being presented in each hemifield). All the trials in which S1 anticipated the position of S2 (spatial valid trials, SC) were grouped in 4 blocks, for a total of 332 stimuli (266 targets and 66 non-targets, half of them falling in the left hemifield and the rest in the right hemifield). The position of each valid cue and the position of the coupled S2 was always identical, in a sense that the information given to the subject by each valid S1 was sufficient to determine the location of appearance of S2.

Again, a strict temporal coupling (500 ms SOA) was applied, and the task the volunteers were required to perform was to respond to the appearance of the target bars with the index finger of the hand which was indicated to them by the instructions at the beginning of each block, withholding the response in case of non-targets.

5.2.3 Procedure

Participants were required to sign a consent form, performed the Italian version (Salmaso & Longoni, 1985) of the Edinburgh Handedness Inventory (Oldfield, 1971) and were then prepared for the EEG recording. After preparation they were positioned in a dimly lit and electrically shielded Faraday cabin at a 114 cm distance from a computer screen and from an infra-red closed-circuit video-camera used to monitor their state during the session; the impedance of the EEG signal was then checked, and volunteers were subsequently asked to perform the two cueing tasks, in an order which was counterbalanced across participants. Each task was preceded by instructions and by a 50 trials practice block. Only if necessary, a second practice block was given. Stimuli were presented to the volunteers on a computer screen driven by a stimulator computer, controlled by the experimenter through a stimulation program (Eevoke 1.5, 2002, A.N.T. Software, Enschedee, The Netherlands). Short breaks divided the 8 blocks of each task, and a longer break was given between the two different paradigms.

5.2.4 EEG recording and processing

EEG was continuously recorded at 512 Hz with ASAlab (vers. 4.1.0.4, 2006, A.N.T. Software, Enschedee, The Netherlands) from tin electrodes mounted in an elastic ‘Electro-Cap’; the 128 recording leads were distributed over the whole surface of the scalp according to the 10.05 International System (cfr. Fig. 4.2 in Chapter 4). The ground electrode was positioned on the forehead of the participants, while the linked earlobes were used as reference leads. Eye movements were monitored through 4 additional unipolar electrodes positioned on the outer canthi of the eyes, and above and below the right eye. Impedances were kept below 4 KΩ. EEG signals were amplified and through an optical cable reached the recording computer, synchronized with the stimulator. Data were recorded and analyzed using ASAlab (vers 4.1.0.4, 2006, A.N.T.

Software, Enschedee, The Netherlands). EEG signals were off-line band-passed (0.016-70 Hz), and a notch filter of 50 Hz was applied, in order to cut possible artifacts derived from electrical interference. Artifact rejection was performed with a criterion of difference in respect to the mean signal (±75 μV for the EEG channels and ±150 μV for the ocular ones). For each subject, epochs were computed from -100 ms before the cues till 800 ms after target presentation for each task, S1 category and position, and S2 targetness (total length of each epoch: 1400 ms, from -100 to +1300 ms relating to cue onset). Epochs were then baseline corrected (-100, 0 ms) and averaged as a function of task, cue category and position, separately for targets and non-targets.

5.2.5 Behavioral and electrophysiological analyses

Behavioral data in response to targets were collected during the EEg recording from Eevoke (vers. 1.5, ANT Software, Enschedee, The Netherlands) and analyzed separately for task (endogenous, exogenous), cue type (VC, NC, SC, CC) and target position (left hemifield, right hemifield). Responses collected with the right and left hands were collapsed. Responses faster than 150 ms (anticipations) or slower than 1500 ms (omissions) were discarded.

Accuracy data were also analyzed: false alarms percentages were calculated and analyzed with a 4 ways repeated measures ANOVA with Task (endogenous, exogenous), Cue Type (spatially valid, spatially neutral) and Target position (left hemifield, right hemifield) as factors.

We analyzed several EEG components in response to the attention-directing or neutral cues: the occipital P1, the frontal orienting N1, the occipito-parietal N1, the P300 and the Contingent Negative Variation (CNV).

P1. The occipital P1 was scored as the mean amplitude of the ERP signal in response to the various cues. The time interval for the scoring procedure was comprised between 130 and 150 ms for the exogenous task, and between 110 and 140 ms for the endogenous task, depending on visual inspection of the grand average waveforms for the two tasks. For both tasks, the mean amplitude was scored at the occipito-temporal electrodes PO7, PO8; POO9h, POO10h; O1, O2. Because of the physical differences in shape and position of the cues used in the two tasks, reflected in the latency differences already reported, the analyses were carried out separately for the two paradigms, comparing within each of them the occipital response to informative vs uninformative cues. The two separate repeated measures three ways ANOVAs followed the same design, with Cue Type (VC vs NC and SC vs CC), Lead (PO7/8; POO9/10h; O1/2) and Hemisphere (Left vs Right) as factors.

Anterior (orienting) N1. The anterior (orienting) N1 was scored as the mean amplitude of the signal in response to cues at the fronto-polar leads AF7, AF8; F7, F8; FT7, FT8 in the time window 130-170 ms after cue onset. Since the synchronization among cue types and tasks is clearly visible in the grand averages at this latency window and leads (see Figure 5.3, anterior leads), a single 5 ways repeated measure ANOVA was used in order to contrast Task (Exogenous; Endogenous), Cue Type (SC/Valid; CC/Neutral), Hemifield of appearance of the cue (Left; Right), Lead (AF7/8; F7/8; FT7/8) and Hemisphere (Left vs Right). The introduction of the Hemifield as factor was necessary to take into account the strong contralateral pattern of the responses to the spatially informative cues, as might be seen in figure 5.5; noteworthy, for the endogenous Neutral Cue and for the Exogenous Central Cue no difference was expected among the differently coded, but otherwise identical, stimuli.

Posterior N1. The occipital N1 was scored as the mean amplitude of the ERP response to the cues over the posterior leads PO7, PO8; O1, O2; POO9h, POO10h, in the time range 160-210 ms after cue onset (see Figure 5.6). As for the frontal N1, a single 5 ways repeated measure ANOVA was used in order to contrast Task (Exogenous; Endogenous), Cue Type (SC/Valid; CC/Neutral), Hemifield of appearance of the cue (Left; Right), Lead (PO7/8, POO9/10h,O1/2) and Hemisphere (Left vs Right). Again, posterior N1s in response to left and right cues were scored separately, in order to take into account the scalp distribution of the electrical signal, strongly contralateral for lateralized cues; as for the frontal N1, for NC and CC no differences were expected among the identical stimuli.

P300. The mean amplitude of the P300 was scored at a fronto-central-parietal pool of electrodes (FFC3h, FFC4h; C3, C4; P3, P4) in a time window ranging between 290 and 420 ms. The 4 ways repeated measures ANOVA contrasted Task (Exogenous; Endogenous), Cue Type (SC/Valid; CC/Neutral), Lead (FFC3/4h; C3/4; P3/4) and Hemisphere (Left vs Right). In figure 5.7, a time series of voltage maps can be observed, highlighting the latency difference between the cerebral P300 in response to endogenous and exogenous cues, and the dissociation between parietal and more frontal areas. In order to correctly measure the amplitude of the responses around the component peak, the scoring procedure was applied in different time windows for the two tasks, as highlighted in the picture, after grand average inspection (note that the same windows were applied for both valid and neutral cues within paradigm).

CNV. For the Contingent Negative Variation, the mean amplitude of the electrophysiological response to cues was measured between 450 and 550 ms at fronto-central, central and centro-parietal leads (FC1, FC2; C1, C2; CP1, CP2). As for the P300, the 4 ways repeated measures ANOVA contrasted Task (Exogenous; Endogenous), Cue Type (SC/Valid; CC/Neutral), Lead (FC1/2; C1/2; CP1/2) and Hemisphere (Left vs Right). In Figure 5.3 and 5.8 the strong negative drift of the CNV can be observed.

Central NoGo N2. In order to score the cerebral responses to target and non-target stimuli preceded by different cues, a difference wave (DW) was calculated between these two categories of visual stimuli (in detail, no-target stimuli minus target stimuli). This procedure was applied in order to cancel out the CNV contribution upon the responses to targets, since the amplitude of the fronto-central negativities resulted significantly enhanced for valid cues (see results section), and could therefore create a confound on the interpretation of the frontal negativities in response to target and non-target stimuli (see also Figure 5.9). The scoring procedure measured the peak amplitude and latency of the DW at selection of fronto-central sites (F1, F2; FC1, FC2; C1, C2; CP1, CP2) between 750 and 850 ms. As for the CNV, the 4 ways repeated measures ANOVA contrasted Task (Exogenous; Endogenous), Cue Type (SC/Valid; CC/Neutral), Lead (F1/2; FC1/2; C1/2; CP1/2) and Hemisphere (Left vs Right) as factors.

For the entire results section, all the reported significant results were Greenhouse-Geisser corrected in case of violations of the sphericity assumptions, and only significant main-effect/interactions will be discussed. All the significant interactions will be interpreted in light of the results of post-hoc (Tuckey) tests.

5.3 Results

5.3.1 Behavioral Results

Behavioral data were analyzed for the 14 participants with a 3 ways repeated measures ANOVA as a function of Task (Endogenous, Exogenous), Cue Type (NC/CC; VC/SC) and Target Position (Left Hemifield; Right Hemifield). Only a highly significant main effect of Cue Type emerged from the analyses ($F_{1,13} = 19.51$, $p < 0.001$), indicating that the information provided by the valid cues (both in an endogenous and in an exogenous modality) elicited a benefit in the speed of response to the subsequent S2, regardless of its position. Average reaction time for the Neutral/Central cueing type was 353 ms,

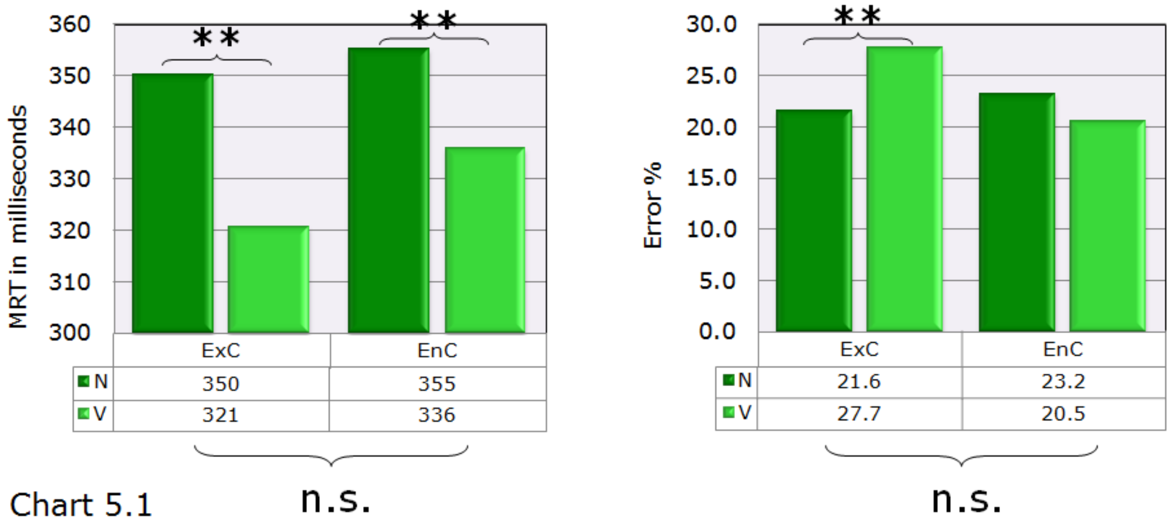


Chart 5.1

Chart 5.1. Left panel: behavioral effects of the cueing modality and validity upon the RTs. Right panel: behavioral effects the cueing modality and validity upon the error (false alarms) rate.

while the mean reaction time for the target stimuli coupled with Valid/Spatial cues was 328 ms: the benefit for informative cueing was therefore correspondent to 25 ms (see Chart 5.1).

Accuracy analyses on the false alarms percentages showed an interactive effects between Task and Cue Type ($F_{1,13} = 13.23$, $p < 0.01$). Post-hoc tests showed that, in case of endogenous cueing, valid and neutral cues elicited the same proportion of false alarms; on the other hand, in case of exogenous cueing the central cues were followed by lower percentages of false alarms (see Chart 5.1, right panel).

5.3.2 Electrophysiological Results

An overview of the ERP responses, sysnchronized with the presentation of the cues, is presented in Figure 5.3.

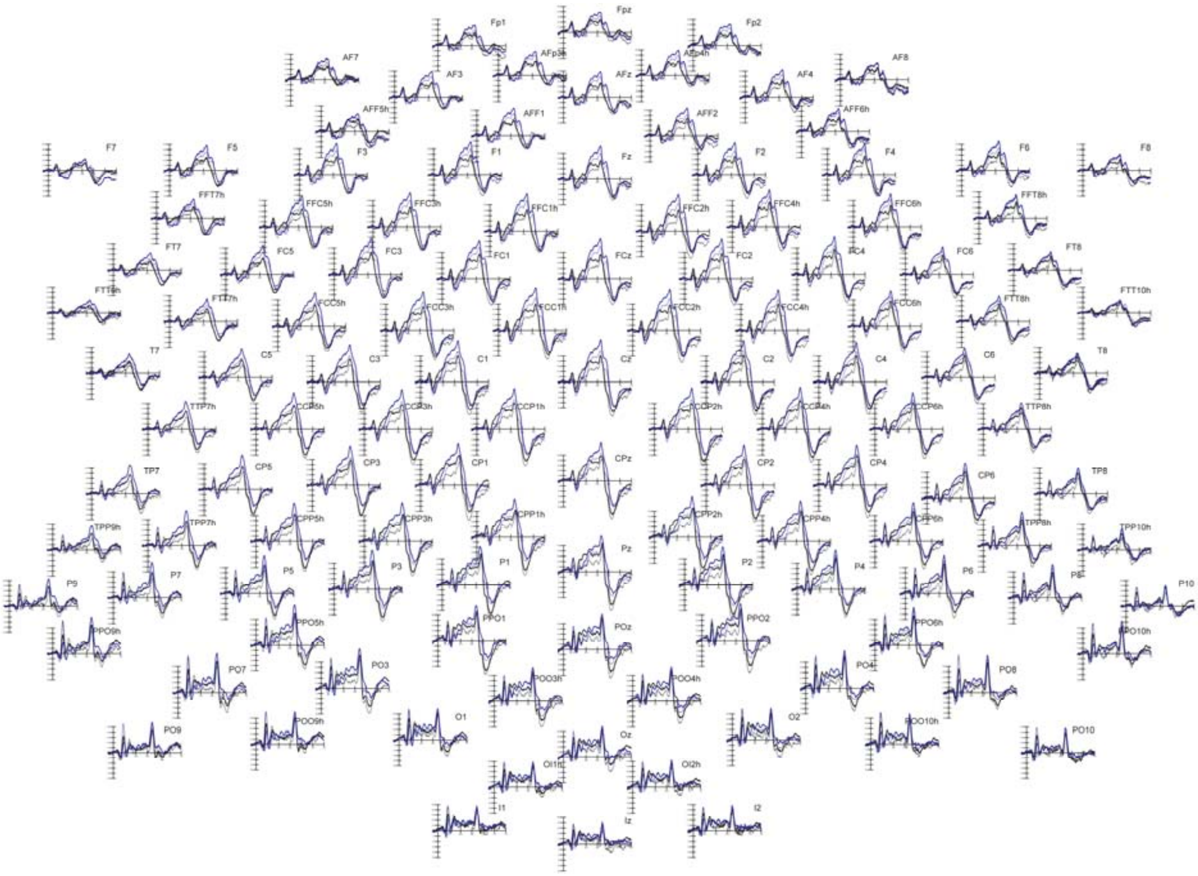


Fig. 5.3. Overview of the waveforms elicited by the four categories of cues and by the target stimuli. The epochs are synchronized with the onsets of the cues, therefore the target appearance falls at 500 ms. **Solid lines**: exogenous task. **Dotted lines**: endogenous task. **Blue traces**: spatially valid cues (VC, SC); **black traces**: spatially neutral cues (NC, CC).

5.3.2.1 ERPs in response to cues

P1 Endogenous task. The ANOVA resulted in main effects of Cue Type ($F_{1,13} = 5.54$, $p < 0.05$) and Lead ($F_{2,26} = 5.82$, $p < 0.05$). Post-hoc tests revealed that the P1 reached significantly higher amplitudes following valid cues, as compared to neutral ones, and peaked at more lateral sites (PO7/8, mean 0.74 µV, S.E. 0.34 µV) as compared to more medial sites (O1/2 mean amplitude 0.09 µV, S.E. 0.40 µV). The occipito-temporal leads

POO9/10h didn’t show any difference with any of the other electrodes (mean amplitude 0.35 µV, S.E. 0.37 µV). No other main effect or interaction was observed.

P1 Exogenous task. The ANOVA resulted in a main effect of Cue Type ($F_{1,13}$ = 7.64, $p < 0.05$). Interestingly for our analyses, CC was centrally presented, while SC was lateralized and therefore presented out of the fovea (no magnification factor was used, as in experiment 1): nonetheless, plausibly because of its intrinsic spatially informative characteristics, SC reached higher amplitudes than the non-informative cue, as expressed in a mean amplitude for SC of 1.17 µV (S.E. 0.29 µV), while CC reached only 0.08 µV (S.E. 0.38 µV).

In Figure 5.4, the visual responses for the two tasks and cue types are presented at a selection of posterior electrodes, and the respective voltage maps in posterior view. Additionally, the indication of the electrode set at which the P1 component has been scored is provided in the electrode layout.

Anterior N1, endogenous and exogenous tasks. The ANOVA on the anterior N1 resulted in a main effect of Lead ($F_{2,26}$ = 19.91, $p < 0.0001$). The Post-Hoc tests revealed a significant difference between the pair of more fronto-polar leads AF7 /AF8 (-1.5 µV, S.E. 0.24 µV) and all the more lateralized ones F7/F8 and FT7/FT8 (-0.90 µV, S.E. 0.20 µV and -0.71 µV, S.E. 0.15 µV, respectively). The interactions between Cue Type and Hemifield ($F_{1,13}$ = 9.66, $p < 0.01$) and Hemifield with Hemisphere ($F_{1,13}$ = 11.32, $p < 0.01$) were also significant. Since these interactions were also significant in triple or 4 factors interactions, they will be discussed in light of these effects. As for the triple interactions, resulted significant Cue Type x Hemifield x Lead ($F_{2,26}$ = 6.92, $p < 0.01$), Task x Hemifield x Hemisphere ($F_{1,13}$ = 11.27, $p < 0.01$) and Cue Type x Hemifield x Hemisphere ($F_{1,13}$ = 17.59, $p < 0.01$). Moreover, was significant the 4 factors interaction Task x Cue Type x Hemifield x Hemisphere ($F_{1,13}$ = 7.23, $p < 0.05$), which showed that the SC elicited different activations across the two hemispheres, depending on the stimulated hemifield, while the CC and all the endogenous cues (centrally presented) did not show differentiation among the cerebral hemisphere responses (see Table 5.1 for mean amplitude and standard error values of this interaction). Also significant was the interaction among Task, Hemifield, Lead and Hemisphere ($F_{2,26}$ = 7.23, $p < 0.01$), showing that the lateralized exogenous cues elicited significantly different activations over the two hemispheres (especially at more lateral sites for left-sided cues, and at more fronto-polar sites for right-sided cues), while the endogenous cues did not elicit inter-hemispheric asymmetries.

Posterior N1, endogenous and exogenous tasks (graphic depiction in Figure 5.6). The repeated measures ANOVA computed on the mean amplitude values for the posterior N1 showed main effects of Task ($F_{1,13}$ = 12.08, $p < 0.01$) and Cue Type ($F_{1,13}$ = 7.79,

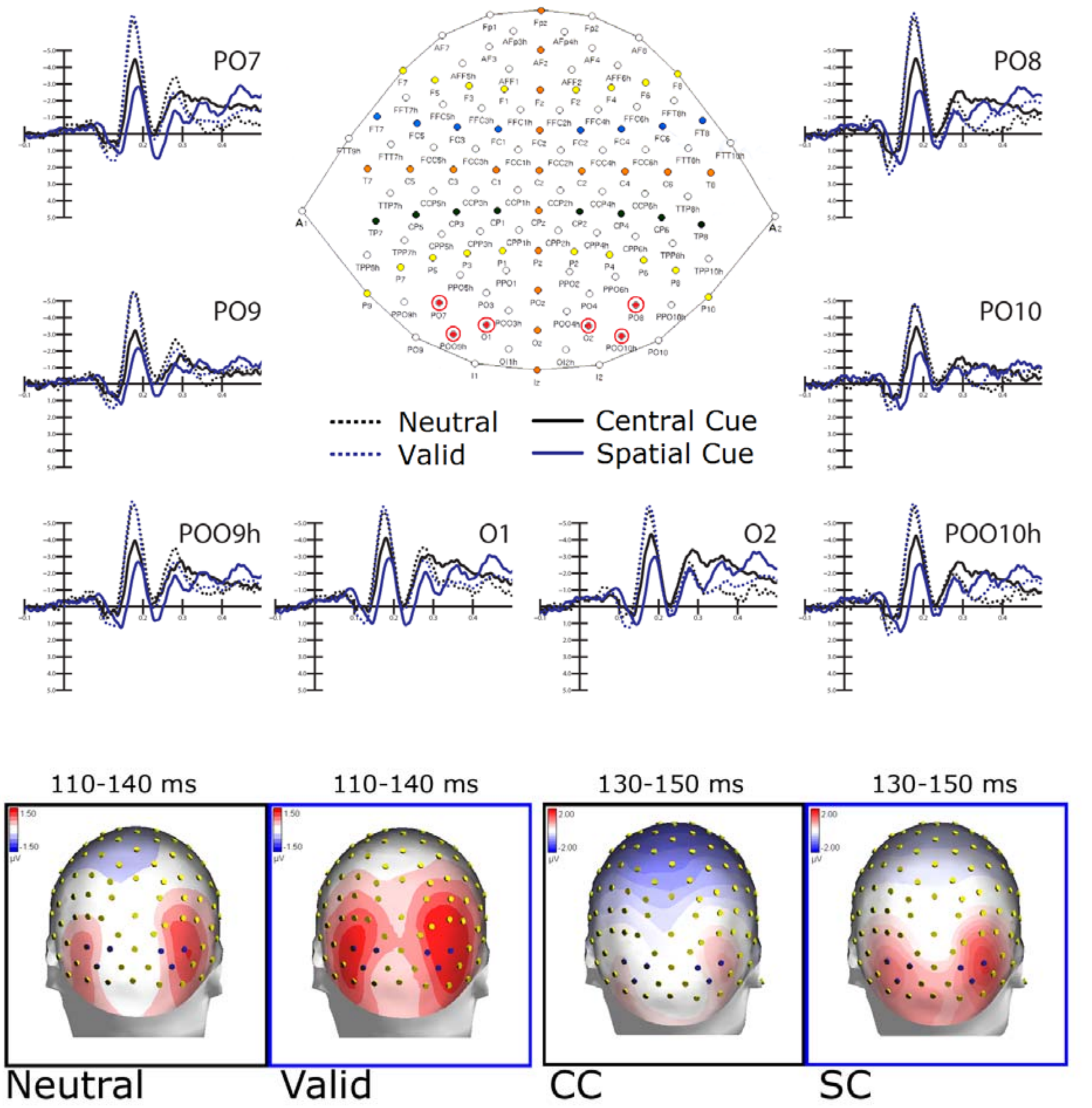


Fig. 5.4 Upper panel: electrophysiological responses elicited by the four types of cues (symbolic valid, symbolic neutral, lateralized valid, central neutral) at a selection of occipital electrodes. The electrodes at which the P1 and N1 components were scored are highlighted in the electrode layout. In the ERP waveforms it is visible the significant effect of cue validity, besides the slight latency difference between the P1s elicited in the separate paradigms. Lower panel: voltage maps correspondent to the P1 responses in the four cue types.

Ant	**N1**	**Exogenous**	**paradigm**	**Endogenous**	**paradigm**	
		Left Hemisphere	***Right Hemisphere***	***Left Hemisphere***	***Right Hemisphere***	
SC	***Left cue***	-0.57 (0.34)	-1.61 (0.37)	-0.76 (0.22)	-1.05 (0.24)	**VC**
	Right cue	-1.28 (0.48)	-0.26 (0.41)	-0.97 (0.31)	-0.79 (0.30)	
CC	***Left cue***	-1.31 (0.30)	-1.10 (0.26)	-1.23 (0.45)	-0.66 (0.28)	**NC**
	Right cue	-1.19 (0.29)	-1.50 (0.22)	-1.35 (0.37)	-1.08 (0.32)	

Table 5.1. Anterior N1 Task x Cue Type x Hemifield x Hemisphere interaction. Values are expressed in μV, as Mean Amplitude (S.E.).

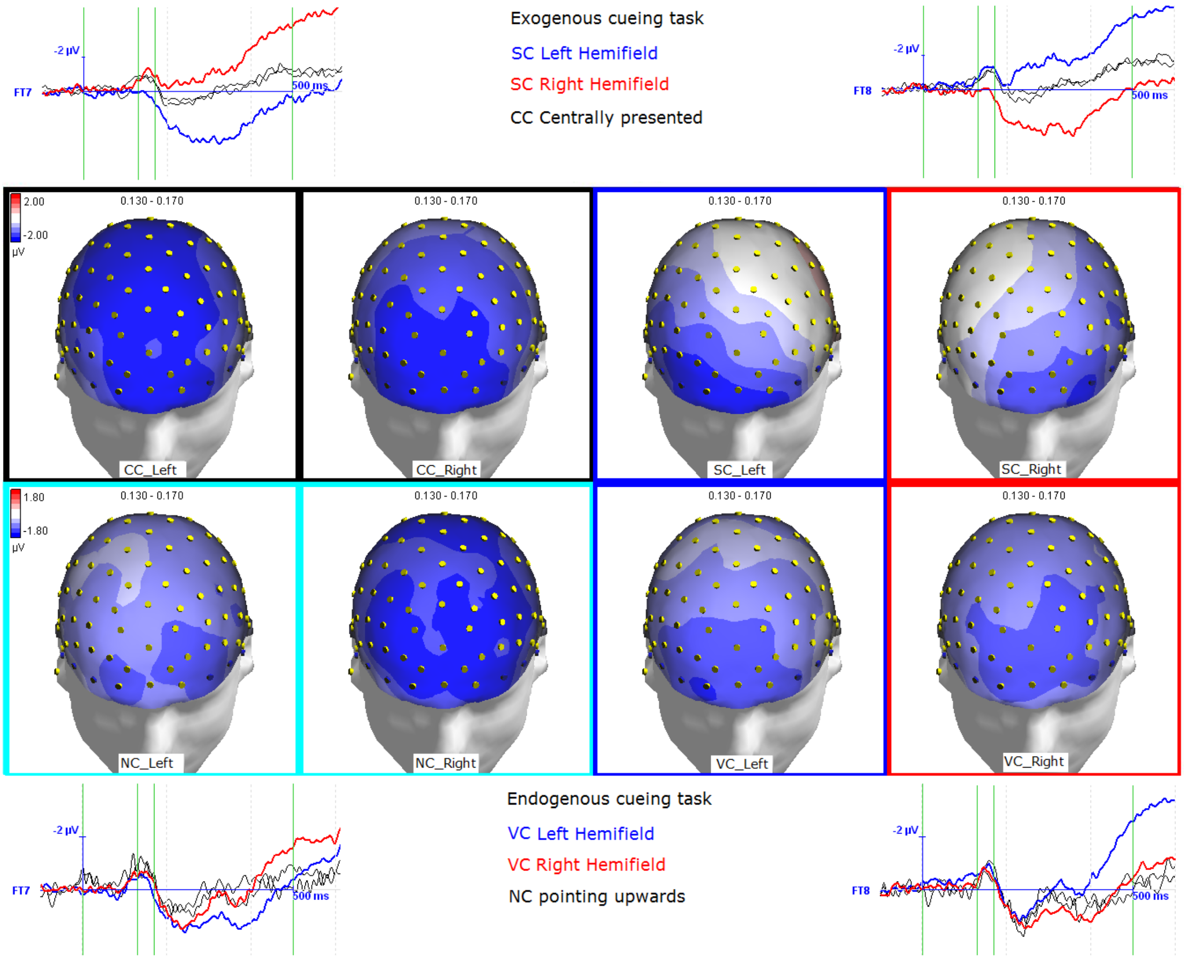


Fig. 5.5. Cerebral responses to the different cueing modalities (endogenous and exogenous), cue types (spatially predictive and spatially neutral) and directions (left, right, central). Highlighted is the 130-170 ms time window, in which the Anterior N1 component was scored, and in which the voltage maps were computed.

$p < 0.05$), indicating a stronger N1 component for the endogenous task over the exogenous one (mean amplitudes were -5.34 µV, S.E. 1.19 µV, and -2.82 µV, S.E. 0.62 µV, respectively), and higher amplitudes for the spatially non-informative cues over the informative ones (possibly because their foveal position in the visual field). Significant were also the interactions between Task and Cue Type ($F_{1,13} = 6.12$, $p < 0.05$), Task x Lead ($F_{2,26} = 7.51$, $p < 0.01$) and Hemifield x Hemisphere ($F_{1,13} = 9.97$, $p < 0.01$). In line with the interpretation that the position of the stimulus influences the N1 amplitude, the Post-Hoc tests computed over the interaction between Task and Cue Type showed that the endogenous task didn’t differentiate (in amplitude values) between Valid and Neutral cues (mean values were -5.35 µV, S.E. 1.25 µV, and -5.32 µV, S.E. 1.14 µV, respectively), while the exogenous task showed significantly higher amplitudes for the Central Cues (-3.46 µV, S.E. 0.62 µV) than for the lateralized Spatially informative ones (-2.20 µV, S.E. 0.68 µV). The Task x Lead interaction Post-Hoc showed that the exogenous task didn’t elicit any differentiation in activation among different leads, while the endogenous task N1 peaked at PO7/PO8 (-5.91 µV, S.E. 1.32

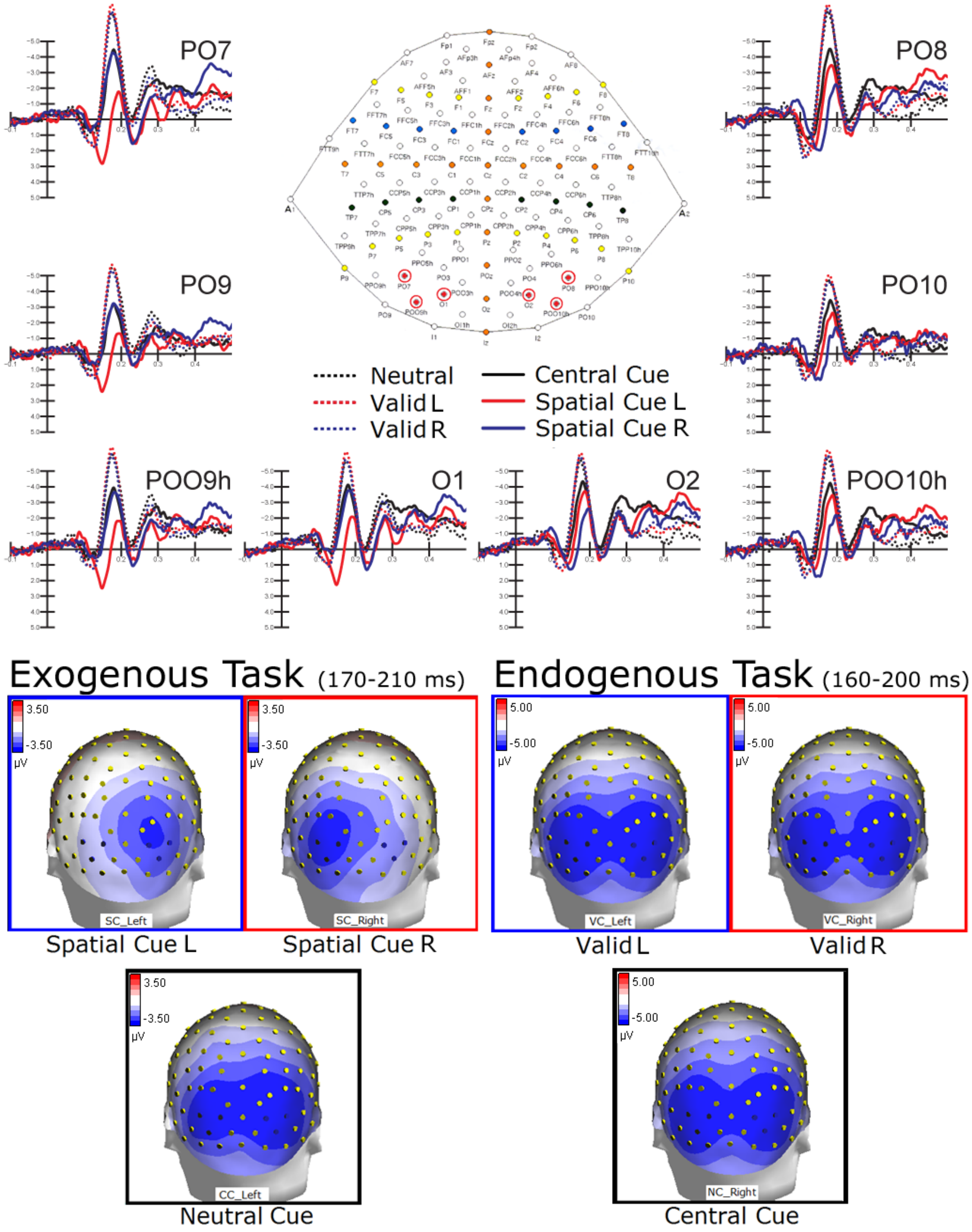


Fig 5.6 Upper panel: electrophysiological responses elicited by the four types of cues (symbolic valid, symbolic neutral, lateralized valid, central neutral), in interaction with cue direction (left, right, neutral) at a selection of occipital electrodes. The electrodes at which the N1 was scored are highlighted in the electrode layout. In the ERP waveforms it is visible how the N1 in response to endogenous cues is equivalent for the three cue directions, while a pattern of contralaterality characterizes the N1 responses to exogenous cues positions (left, right), with a bilateral activation for the central (neutral) cues.
Lower panel: voltage maps correspondent to the N1 responses in the two cueing modalities, in interaction with attention-direction.

µV), with significantly higher amplitudes than POO9/10h and O1/2, which in turn didn’t show any internal differentiation (mean values: POO9/10h -5.13 µV, S.E. 1.11 µV; O1/2

-4.96 µV, S.E. 1.18 µV). The significant triple interactions that this ANOVA resulted in, were Task x Hemifield x Hemisphere ($F_{1,13} = 11.99$, $p < 0.01$) and Cue x Hemifield x Hemisphere ($F_{1,13} = 15.83$, $p < 0.01$). They will not be discussed any further because converged in the significant 4 factors interaction Task x Cue Type x Hemifield x Hemisphere ($F_{1,13} = 9.59$, $p < 0.01$). The tests performed on this interaction showed an interesting pattern of inter-hemispheric asymmetries for the exogenous task: cues presented in the left hemispace elicited significantly different responses over the two hemispheres (in particular, the strongest activation being contralateral, with an average amplitude of -2.91 µV with a S.E. of 0.83 µV, versus an ipsilateral activation of -1.37 µV, with a S.E. of -1.36 µV), while cues presented in the right hemisphere elicited comparable response in both hemispheres (left hemisphere: -2.94 µV, S.E. 0.76 µV; right hemisphere: -1.58 µV, S.E. 0.67 µV, n.s.). For the complete overview on mean amplitude and standard error values see Table 5.2, and Chart 5.2 for a graphic illustration of the interaction, also evident in Figure 5.6.

These results suggested an attentional involvement in the generation of the occipito-parietal N1, in line with neuropsychological models of the hemispheric asymmetries of spatial representations. This interpretation is further reinforced by the observation that the left hemisphere shows a significant difference in the response to stimuli falling in the contralateral vs ipsilateral hemifields (-2.94 µV with a S.E. of 0.76 µV for the contralateral cues, while only -1.37 µV, with a S.E. of -1.36 µV for the ipsilateral stimuli); the right hemisphere, conversely, doesn’t respond selectively to contralateral stimuli, but is equally sensitive to the stimulation of both hemifields (-2.91 µV with a S.E. of 0.83 µV for left-sided cues; -1.58 µV, with a S.E. of 0.67 µV for right-sided cues, n.s.). No differences were observed in the CC condition, as expected (the central cues, even though coded in a different way in order to couple them with their respective left- or right-sided S2s, were identical, therefore eliciting highly similar cerebral responses). No difference whatsoever was observed in the electrophysiological responses during the endogenous paradigm at the posterior N1 latency. An interesting differentiation among posterior and anterior N1 responses is that only the posterior N1 shows a strong asymmetry in the responses to lateralized stimuli, while the frontal component seems to be simply contralateral to the stimulated hemispace (in a more symmetric pattern). The source reconstruction patterns, separately computed for the two tasks, for the different cues and for different stimulation hemifields, will furthermore clarify the

Post	**N1**	**Exogenous**	**paradigm**	**Endogenous**	**paradigm**	
		Left Hemisphere	***Right Hemisphere***	***Left Hemisphere***	***Right Hemisphere***	
SC	***Left cue***	-1.37 (0.72)	-2.91 (0.83)	-5.49 (1.26)	-5.54 (1.18)	**VC**
	Right cue	-2.94 (0.76)	-1.58 (0.67)	-4.99 (1.36)	-5.39 (1.31)	
CC	***Left cue***	-3.49 (0.73)	-3.84 (0.70)	-4.73 (1.39)	-4.79 (1.31)	**NC**
	Right cue	-3.09 (0.62)	-3.42 (0.68)	-5.83 (1.08)	-5.92 (1.08)	

Table 5.2. Posterior N1 Task x Cue Type x Hemifield x Hemisphere interaction. Values are expressed in µV, as Mean Amplitude (S.E.).

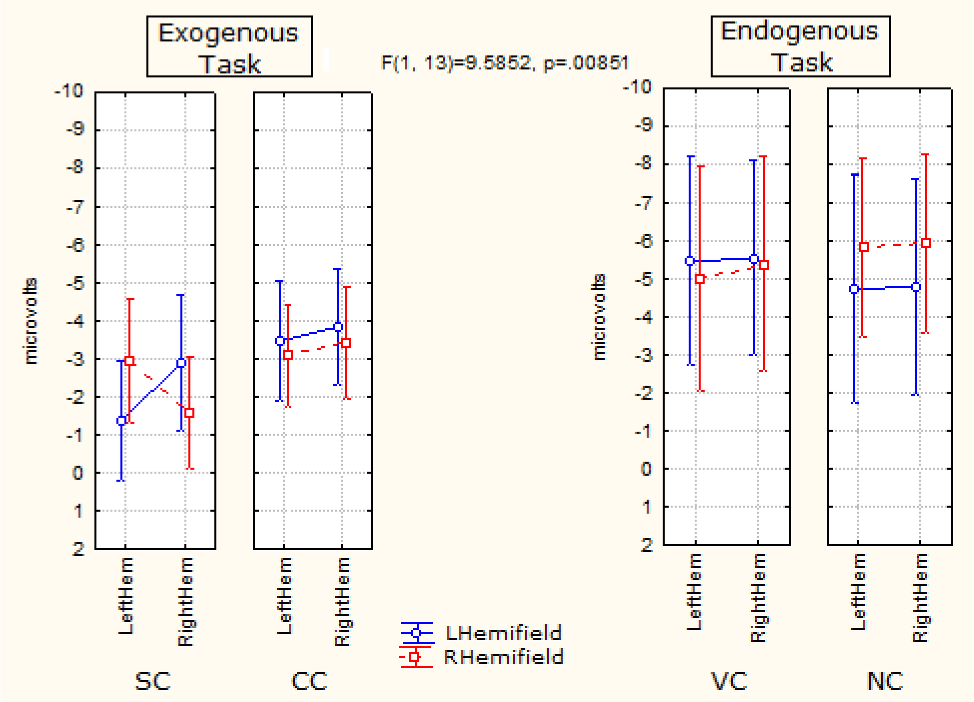


Chart 5.2. Posterior N1 statistical interaction Task x Cue Type x Hemifield x Hemisphere. The vertical bars indicate a .95 confidence interval.

pattern already suggested by the statistics calculated on the electrophysiological components.

P300, endogenous and exogenous tasks. The ANOVA calculated on the P300 time windows (see Figure 5.7) showed a main effect of Cue Type ($F_{1,13}$ = 9.64, p < 0.01). The spatially informative cues elicited a significantly stronger P300 (-0.09 µV, S.E. 0.55 µV) than the spatially non-informative ones (-0.91 µV, S.E. 0.65 µV). Note that the P300 values are all negative or around zero because at this latency, starting at central leads, a strong negative drift (CNV) is starting to develop, causing a displacement of the positive components around the baseline or in the negative quadrants. Also significant resulted the interaction between Cue Type and Hemisphere ($F_{1,13}$ = 24.06, p < 0.001), that indicates how the Neutral/Central cues did not show hemispheric differentiation (-0.97 µV, S.E. 0.66 µV over the left hemisphere and -0.86 µV, S.E. 0.64 µV over the right hemisphere, not significant at the Tuckey post-hoc test), while the Valid/Spatial cues showed a significantly stronger response over the left hemisphere (0.01 µV, S.E. 0.57 µV) than over the right one (-0.18 µV, S.E. 0.53 µV). Furthermore, analyzing the significant triple interaction Task x Cue x Hemisphere ($F_{1,13}$ = 4.88, p < 0.05), the pattern shows that the P300 is significantly more positive for the endogenous task over the exogenous one except for the left Valid/Spatial cues, which did not differentiate between paradigms (the left informative cues show the strongest P3 within both paradigms). The mean amplitude and standard error values are presented in Table 5.3.

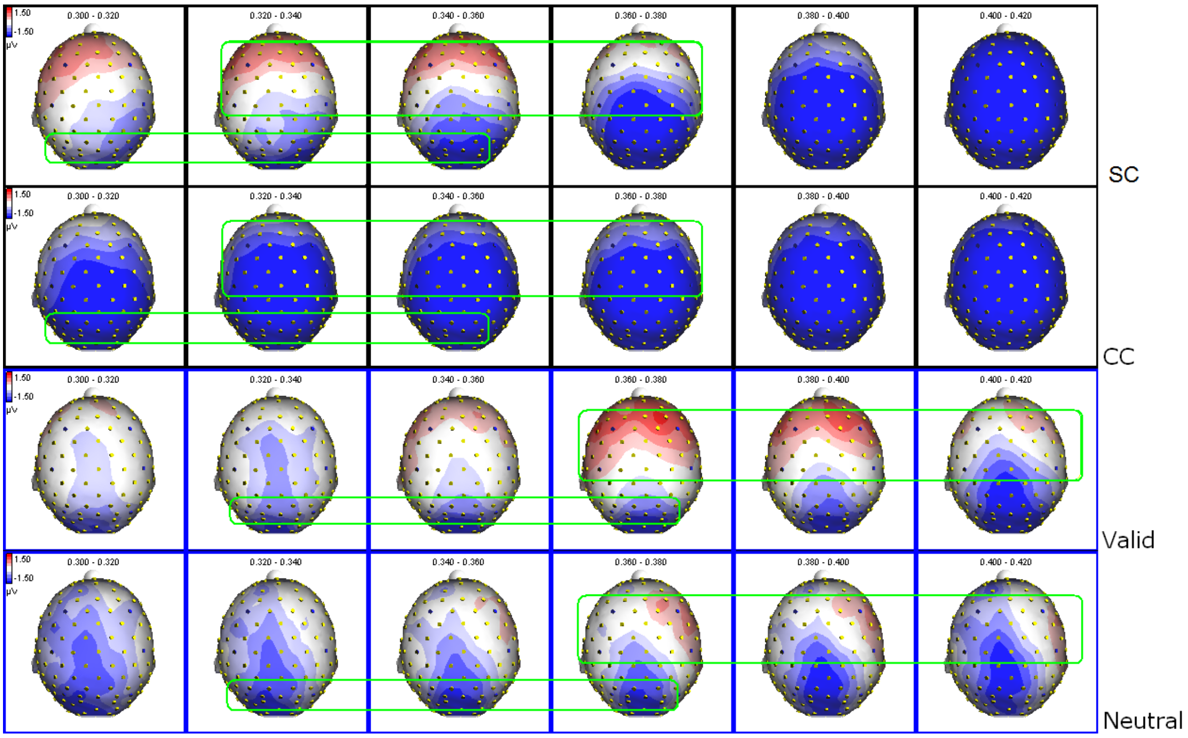


Fig. 5.7. Time series of the scalp voltage maps obtained in response to the different cueing modalities and cue types. Highlighted in green are the time windows in which the P300 component was scored. Note that the component peaks earlier for both tasks at parietal sites, and only later at central and fronto-central ones. Moreover, the P300 is generated with slightly earlier latencies for the exogenous task than for the exogenous one (i.e. between 300 and 380 ms, compared with 320-420 ms).

,P300	**Exogenous**	**paradigm**	**Endogenous**	**paradigm**	
	Left Hemisphere	***Right Hemisphere***	***Left Hemisphere***	***Right Hemisphere***	
SC	-0.25 (0.6)	-0.49 (0.5)	0.23 (0.6)	0.12 (0.6)	**VC**
CC	-1.49 (0.7)	-1.76 (0.6)	-0.45 (0.9)	0.05 (0.8)	**NC**

Table 5.3. P300 Task x Cue Type x Hemisphere interaction. Values are expressed in µV, as Mean Amplitude (S.E.). As highlighted, the difference between paradigms is significant in favor of the endogenous cueing, except for the spatially valid cues over the left hemisphere, where the two values do not differ significantly.

Contingent Negative Variation. In Figure 5.8 the responses to the different cues at central electrodes are presented, and the CNV response is present as the strong negative drift. Consistently with the pattern visible in the figure, the analysis carried out on the CNV showed highly significant main effects of Task ($F_{1,13}$ = 9.25, $p < 0.01$) and Cue Type ($F_{1,13}$ = 21.19, $p < 0.001$). The exogenous task showed a stronger CNV (-4.37 µV, S.E. 0.99 µV) than the endogenous one (-2.78 µV, S.E. 1.10 µV), and the Valid/Spatial cues elicited stronger negativities than the spatially non-informative ones (-4.38 µV, S.E. 1.04 µV, vs -2.78 µV, S.E. 1.02 µV). No interaction between the two factors was significant, nor any Lead or Hemisphere main effects or interactions.

5.3.2.2 ERPs in response to targets

Fronto-central negativity (Non-target minus target DW), peak amplitude. The ANOVA performed on the peak amplitude values of the fronto-central negativityDW in response to stimuli preceded by different categories of cues in the two tasks, showed a significant main effect of Lead ($F_{3,39}$ = 4.27, $p < 0.05$). The effect was driven by s significant decreased N2 difference at frontal leads (F1/f2: -5.46 µV, S.E. 0.8 µV) in respect to all the other leads (FC1/2: -6.78 µV, S.E. 0.9 µV;C1/2: -6.95 µV, S.E. 0.8 µV; CP1/2: -6.73 µV, S.E. 0.8 µV). Additional effects were the interaction between Cue Type and Lead ($F_{3,39}$ = 3.64, $p < 0.05$) and the more informative triple interaction Cue Type x Lead x Hemisphere ($F_{3,39}$ = 4.15, $p < 0.05$). Following the post-hoc tests performed upon the triple interaction, the analysis revealed

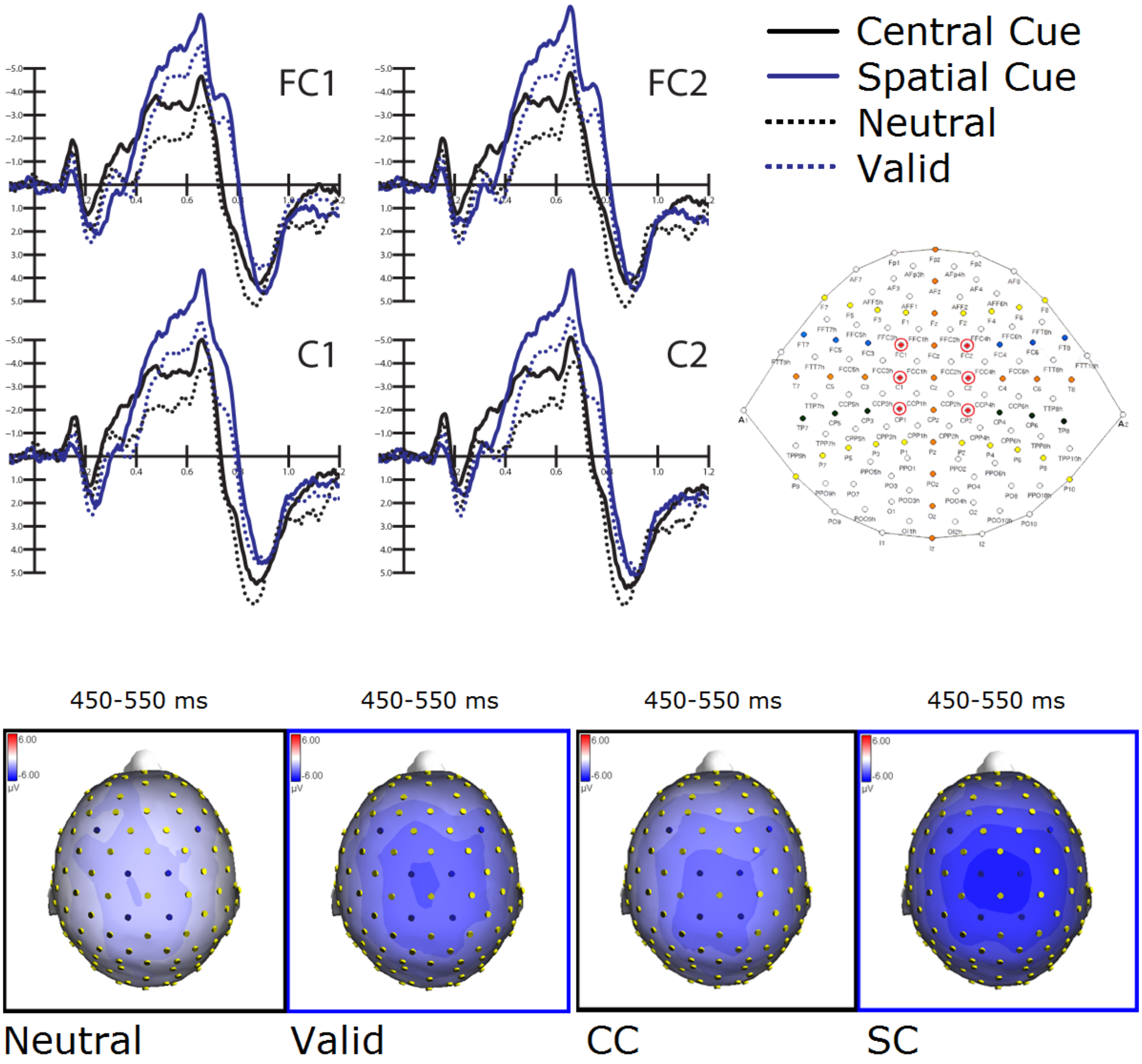


Fig. 5.8 Upper panel: electrophysiological responses elicited by the four types of cues (symbolic valid, symbolic neutral, lateralized valid, central neutral) at a selection of central electrodes. The electrodes at which the CNV was scored are highlighted in the electrode layout. In the ERP waveforms the highly significant effects of cueing modality and cue validity are evident in the strength of the negative deflection preceding target onset (between 400 and 600 ms). Lower panel: voltage maps correspondent to the CNV responses in the four cue types.

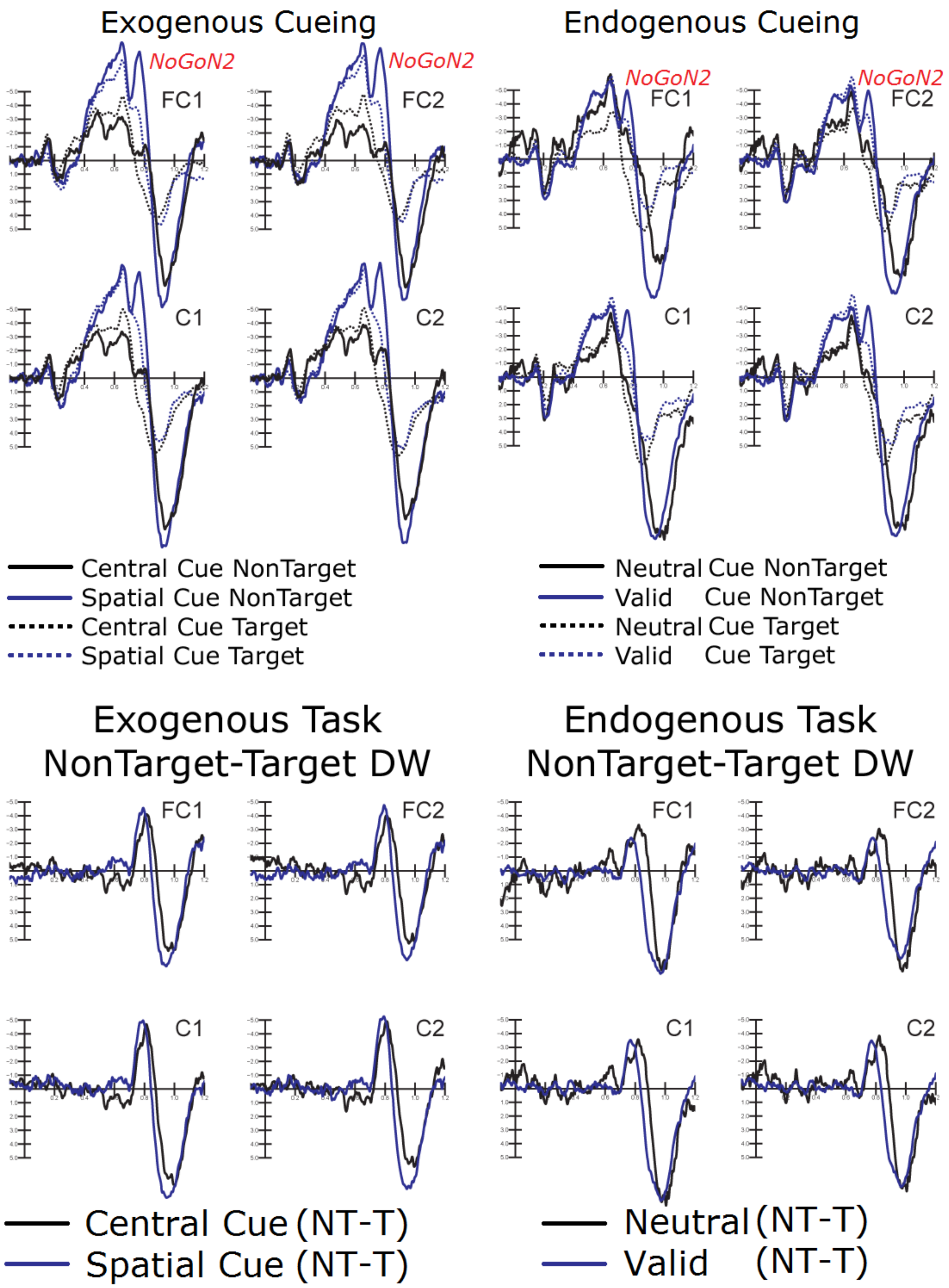


Fig. 5.9 Upper panel. ERP responses elicited by the four types of cues (central neutral, lateralized valid, symbolic neutral, symbolic valid) followed by target stimuli (dotted lines) and non-target stimuli (solid lines) at a selection of central electrodes. The fronto-central negativity specific for non-target stimuli is evident at about 800 ms latency (300 ms after target onset). It is also evident the maximal amplitude of the component for validly anticipated non-targets, as compared to neutrally anticipated ones. Lower panel: Difference waves computed between nontarget and target stimuli preceded by for the four cueing types (symbolic valid, symbolic neutral, lateralized valid, central neutral). Noteworthy, the computation of the difference wave enabled the isolation of the CNV from the fronto-central negativity selective for targetness. The negative component

present in the difference wave peaks significantly earlier for stimuli anticipated by spatially predictive cues, regardless for the attention direction modality (both exogenous and endogenous).

decreased N2 differences at the frontal electrodes only for the valid cues, and a differentiation across hemifields only for the central/neutral cues at the more posterior sites (CP2 more negative than CP1, with values of CP1: -6.04 μV, S.E. 0.8 μV;CP2: -7.36 μV, S.E. 0.7 μV).

Fronto-central negativity (Non-target minus target DW), peak latency. The ANOVA performed on the peak latency values of the fronto-central negativity DW in response to stimuli preceded by different categories of cues in the two tasks, showed a highly significant main effect of Cue Type ($F_{1,13} = 28.52$, $p < 0.001$), as might be evident from visual inspection of the difference waves presented in Figure 5.9. The advantage provided by the spatially valid cues (both endogenous and endogenous) was sufficient for eliciting faster peaking difference waves (792 ms, S.E. 8 ms, as compared to 822 ms, S.E. 10 ms), with a gain of 30 ms in respect to the neutral ones. No differences were detected between the two cueing modalities, neither as main effect nor in interaction with lead or hemisphere. The only significant other effects were a main effect of Lead ($F_{3,39} = 3.84$, $p < 0.05$), with DWs at posterior electrodes peaking faster than at frontal ones (CP1/2: 803 ms, S.E. 9 ms; F1/2: 813 ms, S.E. 9 ms) and a main effect of Hemisphere ($F_{1,13} = 5.83$, $p < 0.05$), with the component peaking earlier over the left hemisphere (805 ms, S.E. 9 ms) than over the right one (809 ms, S.E. 8 ms).

5.3.3 Source reconstruction Results

P1 Exogenous and Endogenous tasks. Activations in the P1 latency window for the exogenous task were concentrated in occipito-parietal and frontal areas. In particular, the main difference between the spatially informative cues and the non-informative CC was that the former activated the occipital cortex bilaterally (lingual gyrus, BA 18, of both the left and the right hemispheres and the Middle Occipital Gyrus, MOG, BA 19, of the left hemisphere), and the precuneus (BA 7)
of the right hemisphere, while the latter showed only a right sided occipital activation (right lingual gyrus, BA 18) and no parietal involvement (see Figure 5.10). At more frontal regions the differences are partially reduced: the spatial cues activated the precentral gyrus (BA 4) bilaterally, the right middle and superior frontal gyri (BA 6 and 9) and the left middle and superior frontal gyri (in this case, BA 10 and 47), plus the left postcentral gyrus (BA 5); the central cues activated the postcentral gyrus bilaterally (BA 5), the right middle and superior frontal gyri (BA 8 and 9) and the left medial and middle frontal gyri (BA 10, 47 and 6).

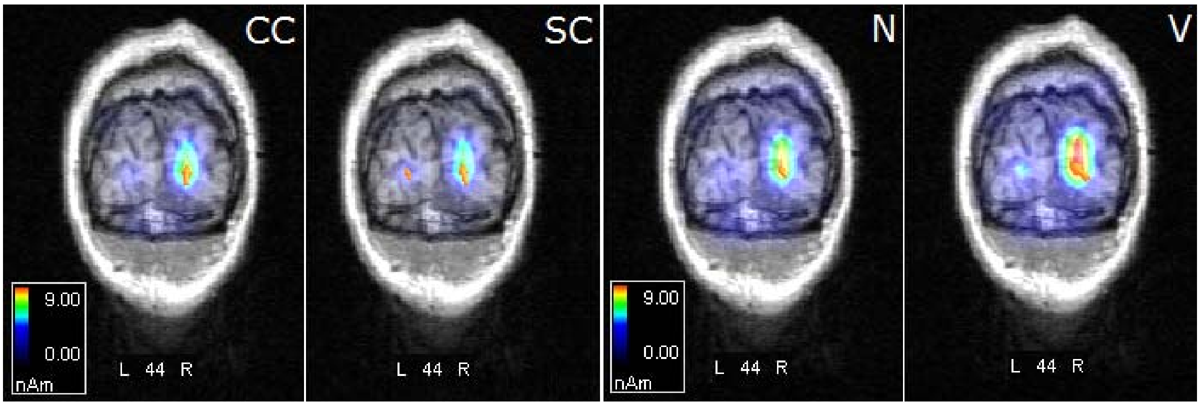


Fig. 5.10 Left panel: LORETA inverse solution for the exogenous task during the P1 interval. The bilateral occipital activation for the valid cues is evident, as well as the unilateral response for CC. Right panel: inverse solution for the exogenous task during the P1 interval. In this cueing modality, the response in occipital cortex is unilateral for both tasks, but significantly stronger for the valid cues as compared to the neutral ones.

For the endogenous paradigm, in line with the significant differences between cue conditions in the ERP component statistical analyses, the occipital activations at P1 are mainly consistent for Valid and Neutral cues, but stronger for the valid cues: consistent with the foveal presentation of the stimuli, both cue types elicited responses in the right BA 18 and 19 (cuneus, precuneus and lingual gyrus), but the strongest activations were elicited by the valid cues. At parietal level, both valid and neutral cues elicited the activation of the left superior parietal lobule (BA 7). The complete list of dipoles for the two cueing validity levels in interaction with cueing modality are presented in Table 5.4.

Anterior N1, Exogenous and Endogenous tasks. The activation pattern for the anterior N1, for coherence with the statistical analyses, was computed separately for cues in the left and in the right hemispheres. Since the anterior N1 was detected mainly at fronto-polar and fronto-lateral electrodes, the discussion will concern mainly the frontal inverse solution pattern. For the exogenous cueing, in frontal areas all directions and cue types activated the left middle frontal gyrus (BA 47), consistent with experiment 1, and the right superior frontal gyrus (BA 9). Interestingly, the middle frontal gyrus (BA 6) was active in the right hemisphere for the valid cues (both directions), while only the left hemisphere responded to the central asterisks. Also the left superior frontal gyrus (BA 10) responded selectively to the attention-directing cues (in both directions).

Concerning the endogenous paradigm, at anterior regions both the upward arrows and the spatially informative ones activated the superior, middle and precentral gyri (BA 6) bilaterally, the right superior frontal gyrus (BA 9) and the left middle frontal gyrus (BA 8 and 47). As shown by the statistics, and consistent with the source reconstruction results, no strong differences were elicited by the different cue types in the endogenous modality, at this latency.

Posterior N1 Exogenous and Endogenous tasks. At occipital regions, the main response for the central neutral cues was the activation of the right BA 18, while the responses were strongly contralateral for the presentation of the peripheral valid cues (right MOG

SC	Hemisphere	Lobe	Gyrus	BA	T-x	T-y	T-z	Magnitude
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	9 651
	Left	Frontal	Superior Frontal Gyrus	10	-29	55	22	7 561
	Left	Frontal	Precentral Gyrus	4	-43	-15	44	3 966
	Left	Parietal	Postcentral Gyrus	5	-29	-43	62	4 820
	Left	Occipital	Middle Occipital Gyrus	19	-29	-79	21	4 535
	Right	Frontal	Middle Frontal Gyrus	6	14	-2	57	3 632
	Right	Frontal	Superior Frontal Gyrus	9	14	56	37	8 594
	Right	Frontal	Precentral Gyrus	4	43	-15	44	3 899
	Right	Parietal	Precuneus	7	14	-60	49	6 677
	Left	Cereb	Anterior Lobe		-29	-54	-28	2 698
	Left	Occipital	Lingual Gyrus	18	-14	-97	-5	5 354
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	6 018
	Right	Occipital	Lingual	18	14	-97	-5	7 779

CC	Hemisphere	Lobe	Gyrus	BA	T-x	T-y	T-z	Magnitude
	Left	Frontal	Middle Frontal gyrus	6	-29	12	56	5 929
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	8 698
	M	Frontal	Medial Frontal Gyrus	10	0	52	-5	3 611
	Left	Parietal	Postcentral Gyrus	5	-29	-43	62	10 653
	Right	Frontal	Middle frontal gyrus	8	43	26	40	6 092
	Right	Frontal	Superior Frontal Gyrus	9	14	56	37	6 002
	Right	Parietal	Postcentral gyrus	5	29	-43	62	9 011
	Right	Temporal	Sub-Gyral	21	43	-8	-11	2 993
	Left	Cereb	Anterior Lobe, Culmen		-43	-52	-18	7 657
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	7 752
	Right	Cereb	Posterior Lobe, Uvula		14	-85	-26	8 736
	Right	Occipital	Lingual	18	14	-97	-5	8 435

Valid	Hemisphere	Lobe	Gyrus	BA	T-x	T-y	T-z	Magnitude
	Left	Frontal	Middle Frontal Gyrus	8	-43	11	41	5 082
	Left	Frontal	Superior Frontal Gyrus	6	-14	27	54	4 892
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	6 567
	Left	Frontal	Superior Frontal Gyrus	10	-29	55	22	7 277
	Left	Parietal	Superior Parietal Lobule	7	-29	-60	49	5 234
	Right	Frontal	Precentral Gyrus	6	58	-5	28	5 510
	Right	Frontal	Superior Frontal Gyrus	9	14	56	37	7 221
	Right	Parietal	Postcentral gyrus	5	29	-43	62	8 475
	Right	Occipital	Precuneus	19	29	-77	36	7 768
	Right	Temporal	Middle Temporal Gyrus	21	58	4	-12	2 853
	Left	Cereb	Anterior Lobe, Culmen		-43	-52	-18	6 993
	Left	Cereb	Posterior lobe, Uvula		-14	-85	-26	8 192
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	7 508
	Right	Occipital	Lingual Gyrus	18	14	-97	-5	11 322

Neutral	Hemisphere	Lobe	Gyrus	BA	T-x	T-y	T-z	Magnitude
	Left	Frontal	Middle Frontal Gyrus	8	-43	11	41	9 538
	Left	Frontal	Superior Frontal Gyrus	8	-29	41	38	16 094
	Left	Frontal	Middle frontal gyrus	47	-43	36	-4	10 981
	Left	Parietal	Superior Parietal Lobule	7	-29	-60	49	5 721
	Right	Frontal	Precentral Gyrus	6	58	-5	28	4 835
	Right	Frontal	Middle frontal gyrus	6	29	12	56	7 899
	Right	Sub-lobar	Insula	13	43	6	-2	4 895
	Right	Frontal	Superior Frontal Gyrus	9	14	56	37	17 669
	Right	Sub-lobar	Caudate,Caudate Body		14	-17	30	4 715
	Right	Parietal	Postcentral gyrus	5	29	-43	62	6 284
	Right	Occipital	Precuneus	19	29	-77	36	6 459
	Left	Cereb	Anterior Lobe, Culmen		-43	-52	-18	7 940

	Left	Cereb	Posterior lobe, Uvula		-14	-85	-26	8 641
	Right	Cereb	Posterior Lobe, Tuber		43	-69	-27	5 140
	Right	Occipital	Lingual Gyrus	18	14	-97	-5	8 955

Table 5.4. Complete list of dipoles for the P1 interval in the two tasks, separate for cueing validity.

BA 19 for the left asterisks, and left lingual gyrus, BA 18, for the right ones). At parietal sites, bilateral responses of the superior parietal lobules were elicited by the central cues, while a strong inter-hemispheric asymmetry (in line with the statistics performed on the mean amplitudes of the waveforms) was evident in case of lateralized presentation of the attention-directing cues: the right hemisphere showed strong responses regardless of the location of the cue, while the left BA 7 selectively responded only to the right-presented cues. The same pattern of activation was observed for the middle frontal gyrus (BA 46), suggesting the activation of an asymmetrical fronto-parietal network. At posterior temporal sites, the common activation of the right BA 37 was evident for both cue types and for all locations. Same happened to the right superior frontal gyrus (BA 9), showing a non-selective activation.

As for the anterior N1, also at a later stage of processing the differences between informative and non-informative cues in the endogenous paradigm were less strong than in the exogenous one. The common activations ranged from the occipital BA 18 and the superior parietal lobules (BA 7), bilaterally, till the right superior frontal gyrus (BA 9). The activations in area 6 were bilateral for the neutral cues and only right-sided for the valid cues, which showed also responses in the left BA 47 and 21 for both cued directions, and a very specific contralateral activation of the frontal BA 8 (not active for the neutral cues).

P300 Exogenous and Endogenous tasks. The source reconstruction on the P300 time window showed a pattern of strong similarity across tasks and cue types. The exogenous paradigm was characterized by activations of the left middle frontal gyrus (BA 6 and 47), of the bilateral postcentral gyri (BA 5) and of the right middle temporal gyrus (BA 21 and 37), together with the right lingual gyrus (BA 18). Main differences between CC and SC were selective activations of the left superior frontal gyrus (BA 10), the left superior and inferior parietal lobules (SPL, BA 7 and IPL, BA 40) and of the right middle and inferior frontal gyri (BA 6, 9 and 46) for the SC, versus activations of the left FEF (BA 8), the left middle temporal gyrus (BA 21) and the bilateral MOG (BA 19) for the central cues. In the endogenous task the common pattern includes activations of the middle and superior frontal gyri (BA 8, 47 and 10), SPL (BA 7) and of the MOG (BA 19) on the left hemisphere, of the right precentral and superior frontal gyri (BA 6 and 9), of the middle temporal gyrus (BA 37) and of the right lingual gyrus (BA 18). tThe left BA 40 and right postcentral gyrus (BA 5) selectively responded to the valid cues, whereas the activations sensitive to the neutral cues were the left superior frontal gyrus (BA 6) and the right temporal BA 21 and precuneus (BA 7).

CNV Exogenous and Endogenous tasks. The source reconstruction pattern of the CNV latency in the exogenous task (showing the strongest CNV) included bilateral activations of the precentral and middle frontal gyri (BA 6), of the superior and medial frontal gyri (BA 10) and of the postcentral gyus (BA 5), together with responses of the left middle frontal gyrus (BA 47). Selective activations for the spatially informative cues were the right inferior frontal gyrus (BA 9), of the right middle temporal gyrus (BA 37), of the right MOG (BA 19) and left lingual gyrus (BA 18). Selective for CC were only activations in the left superior frontal gyrus (BA 8) and of the left middle temporal gyrus (BA 21). The cerebral response pattern for the endogenous task showed bilateral activations of the superior, middle and precentral gyri (BA 6), of the left superior and middle frontal gyri (BA 10 and 47, respectively) and of the left SPL (BA 7), together with the right lingual gyrus (BA 18). The valid cue elicited specific activations in the left precentral gyrus (BA 4) and in the right superior frontal and postcentral gyri (BAs 10 and 5, respectively). The neutral arrowheads, on the other hand, activated the left FEF (BA 8) and MOG (BA 19), and the right superior frontal gyrus (BA 9), right superior temporal gyrus (BA 22) and precuneus (BA 7).

5.4 Discussion

The present study was designed capitalizing on the results of study 1, which indicated early effects of validity manipulations in the ERP responses to visual cues, and later interactions between attentional and control mechanisms: in Experiment 2 the combination of two spatial cueing tasks with a go/no-go task was utilized in order to address the questions which were still unanswered after Study 1. The behavioral results, showing a significant benefit for valid cues in both modalities, and a non significant effect of cueing modality (central symbolic vs peripheral) indicated that spatial attentional shifts were correctly elicited by the informative cues in both modalities, and that no inhibition of return patterns were elicited by the peripheral cueing (in line with Study 1), due to the high predictive value of the warning signals in the valid condition. This study was primarily designed in order to clarify a series of questions which were not fully addressed in the electrophysiological literature so far. First, the comparison between cues that are assumed to elicit reallocation of spatial attention because of their high predictive value with cues that don’t provide any spatial information about the target position, thus are not assumed to elicit attentional shifts, has been seldom utilized in the ERP literature. Furthermore, the few studies addressing the ERP reflections of attentional control mechanisms following this approach reported contrasting results. The earliest attentional effects in the ERP responses haves been proposed to take place around 400 ms as sustained negativities in response to attention-orienting cues (Grent-‘t-Jong & Woldorff, 2007), spreading from frontal areas towards more posterior sites, and from lateral sources to more medial structures; in this study, the comparison was carried out between orienting letters, which coded the position of the coupled target, and neutral letters, which coded catch trials (thus, did not require any attentional deployment). On the other hand, an independent study (McDonald & Green, 2008) addressed the same question with the use of complex colored pointers which may or may not contain the color which was related to the spatial information (thus, which could be either informative or neutral). The results of this study, which used a relatively long cue-target SOA, indicated the earliest attentional effects at posterior scalp sites at about 250-300 ms, in accordance with previous reports (Slagter *et al.*, 2005): these early effects were interpreted in terms of attentional processing of the cue itself, in line with findings showing enhanced sensory processing of stimuli containing features that matched the participants' attentional set, as compared to stimuli lacking the task-relevant feature (Arnott *et al.*, 2001; Green & McDonald, 2008). Subsequent to these early effects, which were distributed as a positive difference in favor of orienting cues at central leads and as a negative shift over contralateral occipital scalp sites, a second frontal negativity (and posterior contralateral positivity) was recorded between 450 and 500 ms post-cues, increasing at frontal and central scalp locations in later intervals. Based on this pattern, the authors suggested an approximately contemporary involvement of frontal and parietal cortices in the mechanisms of attentional control, which subsequently modulated the activities of the sensory cortices deputed to the processing of the upcoming target stimuli. Within this theoretical and empirical framework, the early enhanced positivities for valid cues (in both endogenous and exogenous tasks) reported in the present study, can be interpreted as indications of an early engagement of the attentional system in case certain key properties are present in the warning stimuli. Since the informative cues shared some attended features (such as the orientation, in case of the endogenous arrowheads, or the peripheral position, in case of the exogenous asterisks), the reported early effects (110-150 ms) may plausible be attributed to the activation of selective attention mechanisms, repeatedly reported to influence early ERP components, as the P1 and even earlier responses, in case of non-spatial features (Zani & Proverbio, 1995, 1997 & 2005; Proverbio & Zani, 2005). Cueing tasks activate in the participants specific selective attention sets, which modulate the sensory filters as early as in the striate (Somers *et al.*, 1999; Kastner *et al.*, 1999) or extrastriate cortices (e.g., Scerif *et al.*, 2006; Clark & Hillyard, 1996; Zani *et al.*, 2005 for a review on this issue); in order to rapidly detect task-relevant objects or features (in our case, the direction or position of the informative cues), the attentional set magnifies the sensory responses to the key features, as reflected in enhanced P1s to valid cue stimuli, which trigger the activation of the fronto-parietal attentional network deputed to the spatial selection, through occipito-parietal pathways. Consistent with this view, early orienting responses to the informative cues (in particular in case of peripheral cues, see also Chapter 4) were also observed at contralateral frontal leads as enhanced orienting N1s in response to the spatially valid cues, in a time range comprised between 130 and 170 ms. An alternative explanation of the magnified occipital responses to the spatially predictive cues could involve their differential position in respect to the neutral ones; nevertheless, this explanation can be challenged in different ways: first, the effect was observed also in case of endogenous cues, which were all presented at fixation and symmetrically centered in respect to the vertical and horizontal meridians; second, the fact that no magnification factor was used in case of peripherally presented cues (i.e., exogenous valid cues) would, conversely, suggest the expectation of significantly smaller visual components in response to these cues, as compared to foveally presented neutral asterisks (as in Experiment 1). Moreover, the increased sensory processing driven by the presence of task-relevant features in the valid cues is also consistent with previous indications of enhanced occipital negativities for shifting cues as compared to neutral ones, which were differentiated by the presence of a task-relevant color (McDonald & Green, 2008); methodological differences, as the complexity of the cueing stimuli or the cue-target SOA, might account for the inconsistencies (mainly concerning the latency of the earliest effects) across different studies. For the same reason, the absence of early validity effects in Grent-'t-Jong & Woldorff (2007) might be due to methodological factors, such as the nature of the cueing stimuli (letters), which might have required specific neurocognitive operations for their interpretation (Green & McDonald, 2008a), or to the duration of the cue-target interval, which was very long and randomly varied.

Differently from the P1 response, the occipito-parietal N1 showed an interesting inter-hemispheric asymmetry in response to the spatially informative peripheral cues in the exogenous task, as compared to a bilateral (and stronger) response for all the stimuli presented at fixation. In detail, the N1 was stronger for cues delivered in the left hemifield only over the right hemisphere, while the same deflection was observed with comparable intensities over both hemispheres in response to cues directing attention towards the right hemispace; moreover, confirming these results, the amplitude of the N1 response recorded at right-hemisphere leads didn't differentiate between cues delivered in the two hemifields, while at left-hemisphere electrodes the response was significantly enhanced for cues appearing contralaterally (replicating Brignani *et al.*, 2009, which found an asymmetry in the N1 in response to cues, interpreting this pattern as an EDAN-like effect). The innovative aspect of the present study is that the results of the ERP analysis can be better interpreted in light of the highly consistent distributed inverse solution results: the source reconstruction showed the involvement of the superior parietal lobules in concomitance with enhanced ERP responses, thus asymmetrically engaged in response to left- or rightward attentional shifts. The spatial selectivity of the superior parietal lobules and their involvement in spatial attention mechanisms has been repeatedly reported in functional hemodynamic-based literature and in patients studies (Corbetta *et al.*, 1993; Nobre *et al.*, 1997; Gitelman *et al.*, 1999; Mesulam, 1999 for a review; Corbetta & Shulman, 2002). Therefore, the fact that the asymmetry in the N1 responses was plausibly generated in the

SPL, which is consistently associated in functional literature with the control of spatial attention (Kastner *et al.*, 1999; Gitelman *et al.*, 1999; Corbetta & shulman, 2002 for a review) can be taken as an indication of the attentional nature of the phenomenon. However, the observation of a bilateral activation of the SPL in response to medially presented spatially informative symbolic cues might challenge the attentional deployment explanation for the N1 effect in the endogenous task. Conversely, the dorsal fronto-parietal network (thus, also the SPL) has been proposed to be engaged in consequence to activations in the ipsilateral ventral network, in response to the need to re-orient the attentional focus after peripheral stimulation (Corbetta & Shulman, 2002), which is required in case of exogenous cues. At the same time, foveal stimulation might engage the activation of the SPL independently of the requirement for attentional shifts, and generate bilateral foci. However, some indications of a lateralized involvement of the SPL in attention *direction* can be found in the observation of stronger contralateral than ipsilateral sources in the SPL for informative cues in the endogenous paradigm, in the context of bilateral SPL activations for both valid and neutral cues. A possible way to address the question of the spatial attention (or position) specificity of the SPL asymmetrical activations might be the use of contralateral informative cues (i.e., right-sided peripheral stimuli which indicate left-sided targets), in order to tease apart the contributions of *cue position* and *attentional shift direction*. Unfortunately, the interaction between stimulus position and its predictive value was not systematically manipulated in our exogenous paradigm (i.e., no right-sided cues ever predicted left-sided targets): therefore, we cannot directly attribute the activation of the SPL to *purely* attentional mechanisms.

At longer latencies, the previously reported observation of enhanced positivities starting around 300 ms after cue onset for shift trials (McDonald & Green, 2008) was replicated: stronger P300s, previously associated with context updating and stimulus relevance or importance (Johnson, 1998), were elicited by the spatially valid cues in both paradigms, in particular over the left hemisphere. This unexpected lateralization pattern can be explained taking into account the fact that the P300 was nested in a strong negative drift (CNV, Walter *et al.*, 1964, Eimer, 1993a, see Chapter 4), which was also more prominent for valid than for neutral cues and might have modulated the scalp distribution of the positive component. The differential amplitudes of the CNV as a factor of validity, not observed in Study 1, can be partially explained on the basis of the motor preparation elicited by the cues (Loveless and Sanford, 1973; Perchet and Garcia-Larrea, 2005). In fact, since the hand of response was coded at the beginning of each block, the predictive cues also primed the manual response, which should be withheld in case of non-targets. The observation of enhanced anterior and central negativities in response to shift cues strongly resembles the sustained negativities reported by previous works with onset around 400 ms (Grent-‛t-Jong & Woldorff, 2007) or 450 ms post-cue (McDonald & Green, 2008).

The last scope of the study was the investigation of possible interactions between spatial orienting and executive control systems. The interaction between cue validity and conflict-monitoring and resolution has been addressed by means of the calculation of a difference wave, computed subtracting the ERP responses to targets for those elicited by Non-targets. This dERP is characterized by a strong *NoGoN2*, which has previously been reported in case of situations involving the need for motor inhibition (Jodo & Kayama, 1992; Kopp *et al.*, 1996; Falkenstein *et al*., 1999; van Boxtel *et al.*, 2001; Nieuwenhuis, Yeoung and Cohen, 2004) or response conflict (Donkers & van Boxtel, 2004; Nieuwenhuis *et al*., 2003, Bekker, Kenemans & Verbaten, 2005; Bruin and Wijers, 2002). The results of the present study showed an anticipation of the peak of the difference wave in case of non-targets preceded by spatially informative trials, as compared to neutrally cued ones. This effect might be taken as an indication of the influence of the spatial attention system upon the monitoring system, which is embedded in the ACC (Bush *et al.*, 2000; Botvinick *et al.*, 2001 & 2004), and in dorsolateral prefrontal cortices (Van Veen & Carter, 2002, Fan *et al.*, 2003). Modulations of the posterior N2 latency have been reported as a function of cueing validity (i.e., earlier N2s for validly cued trials as compared to invalidly cued ones, Fu *et al.*, 2001), but, to our knowledge, no previous reports of integration between go/no-go tasks and spatial cueing tasks have been presented, therefore our latency displacement of the NogoN2 in case of neutral trials (i.e., when the no-go stimuli fell outside the focus of attention) cannot be compared with previous literature. However, this negative ERP component has been previously showed to be sensitive to the amount of conflict elicited by the task, expressed as the proportion of go/no-go trials (Nieuwenhuis *et al*., 2003, Bekker, Kenemans & Verbaten, 2005; Donkers & Van Boxtel, 2004), or as the amount of perceptual overlap between go and no-go stimuli (Nieuwenhuis, Yeoung and Cohen, 2004). The fact that, in the present experiment, the N2 was anticipated for validly cued trials can be interpreted in terms of a decreased level of response conflict in case of targets and non-targets anticipated by predictive cues; in other words, the reported modulation of conflict-related ERP effects might be taken as a facilitatory effect of the attentional control system upon the executive control system, in line with the results obtained in Experiment 1.

5.5 Conclusions and open questions

By means of the combination among electrophysiological recording, source reconstruction methods and the combined spatial cueing-go/nogo tasks, multiple crucial findings were achieved: first, the early effects observed in extrastriate cortices might be attributed to a selective attention mechanism, which was engaged in order to rapidly detect the relevant features in the cues (i.e., the arrowhead-direction or the asterisks position). Second, it has been possible to identify the long latency positivities and negativities, reported by previous works in response to lateralized shift cues as compared to neutral ones, with enhanced P300s and CNVs. Third, the interaction between spatial orienting and executive control has been detected in yet another executive task, requiring inhibitory control instead of interference monitoring (as in Experiment 1). This latter conclusion stimulated further questions: since the inhibitory component of the go/no-go task involves mainly the response selection stages, it would be crucial to demonstrate whether the cognitive systems for attention and control also interact in tasks which require the inhibition of a prepotent response, as the stop-signal task. Moreover, the first two studies indicated facilitations of the activity of the executive control system by means of activations in the attentional domain: it might be highly informative to test the hypothesis by which the interaction is bidirectional (i.e., the activation of the executive control system exerts an effect upon the attentional allocation) instead of unidirectional. These questions have been addressed in Experiment 3.

Chapter 6.
Study 3: ERP indexes of the interactions between attention, response selection and response inhibition processes

6.1 Introduction

Flexible and adaptive behavior is crucial in daily-life: in order to select and pursuit relevant goals, fast and effective analysis of salient stimuli is mandatory, coupled with the ability to suppress deep processing and prepotent responses to non-relevant stimuli. However, interindividual differences in the effectiveness of decision making are striking: at the two extremes of a virtual continuum, studies performed with different populations of healthy participants provided evidence for strong variability in the processing of task-related and distracting information (Costa *et al.*, 2008; Emmorey *et al*., 2008; Li *et al*., 2006, Stahl & Gibbons, 2007, Boehler *et al*., 2008 and Forstmann *et al.*, 2008), while on the other hand a body of converging evidences from frontal, schizophrenic or AD/HD (Attention Deficit/Hyperactivity Disorder) patients indicated how the goodness and speed of decision making and motor inhibition are supported by a cerebral frontal network whose damage results in disrupted performance in monitoring and inhibition tasks (di Pellegrino *et al*., 2007; Neuhaus *et al.*, 2007; Enticott *et al.*, 2008; Di Michele *et al*., 2005; Doyle, 2006). In the last twenty years, this body of experimental findings alimented an extraordinarily rich theoretical debate concerning the functional and cerebral architecture of the executive functions, including the processes of conflict monitoring, interference control and response selection and inhibition (Paus *et al.*, 1993; Posner & Dehaene, 1994; Bush *et al.*, 2000; Botvinick *et al.*, 2001 & 2004; Miyake *et al*., 2000, updated in Friedman & Miyake, 2004; Fan *et al.*, 2003; Carter & van Veen, 2007). Experimental psychology, in particular, has provided numerous models and paradigms which supported, in turn, different perspectives concerning the control systems. In the inhibitory functions domain numerous experiments have been conducted using the well-known ‘Stop-Signal Paradigm’ in order to clarify the processes involved in motor inhibition (Lappin & Eriksen, 1966, Logan & Cowan, 1984; Verbruggen & Logan, 2009 for a review). In the Stop-Signal Paradigm an imperative go-stimulus is presented, requiring a motor response (usually a simple or a choice reaction time); briefly after the appearance of a minority of go-stimuli, a stop-signal (usually a short tone, or a different visual stimulus) is delivered, instructing the participant to withhold any motor response during that trial. The manipulation of the temporal distance between go-stimuli and countermanding stop-stimuli (called *Stop-Signal-Delay*, SSD), allows the experimenter to balance the proportion of correct and failed inhibitions around 50%, permitting a more reliable estimation of the reaction time to the stop tone (*Stop signal Reaction Time*, SSRT). This construct is routinely used as a measure for behavioral inhibition in healthy subjects and patient studies (Bekker *et al*., 2005; Lansbergen *et al.*, 2007; Overtoom *et al*., 2009); on the other hand, the *interference effect* (i.e. the behavioral cost in reaction times due to the presence of incongruency in the target stimuli, as opposite to congruency, which leads to behavioral benefits) is used as an efficiency measure for the conflict monitoring/interference control systems (Fan *et al*., 2003; Milham & Banich, 2005; Lansbergen & Kenemans, 2008; Verbruggen *et al.*, 2006; see also Chapter 4). Very few studies, however, tackled the integration of those processes combining in the same task distracting information, which requires conflict monitoring and resolution, and a stop-signal, which requires the inhibition of a prepotent motor response (Kramer *et al*., 1994; Ridderinkhof *et al*., 1999; Verbrugen *et al*., 2004, 2005 and 2006; Chambers *et al*., 2007). These studies reported behavioral costs for the presentation of distracting information of various types: crucially, these costs were evident not only on go reaction times, but also on response inhibition indexes, as showed in an increased stop-signal reaction times (SSRTs) for target stimuli accompanied by incongruent flankers. Although results obtained using different paradigms and stimuli are mainly consistent, the interpretations of the phenomena underlying this interaction partly differed, mainly because of the intrinsic constraints of the experimental designs. Kramer *et al.* (1994) and Ridderinkhof *et al.* (1999) using an Eriksen task (Eriksen & Eriksen, 1974) suggested an explanation of their interference effect at the response-suppression level. Verbruggen and colleagues (Verbrugen *et al*., 2004, 2005 & 2006) carried out a series of studies addressing the problem of stimulus incompatibility, introducing flankers which were stimulus-incompatible (SI), but not response-incompatible (RI): they found that also flankers out of the response set affected the inhibition process. The authors therefore concluded that the interference takes place at an earlier stage than response selection/inhibition. Recently Chambers *et al*. (2007), conducting a repetitive Transcranial Magnetic Stimulation (rTMS) study, concluded that the right inferior frontal gyrus (rIFG) is crucial for aspecific response inhibition (stopping) in case of incongruency, while the right dorsal premotor cortex (rDPM) accounts for speed of response selection. This rTMS study, suggesting a selective involvement of the right hemisphere (in particular the IFG) in stopping (specifically in case of incongruency), is in line with functional and structural models of the inhibitory functions based on neuropsychological and neuroimaging data (Aron *et al.*, 2003; Zheng *et al.*, 2008; Li *et al*., 2008). The poor temporal resolution of rTMS and fMRI techniques, however, does not allow an integration of the anatomical models with the notion that each stop-signal is analyzed on-line, in a multiple-stage processing characterized by a clear temporal structure. Thus, to our knowledge, the temporal features of the interactions between response selection and inhibition have not been fully addressed yet.

On the other hand, the first two studies presented in this work strongly pointed towards an integration between attentional systems and both response selection and response inhibition mechanisms; however, the direction of the interaction was to some extent *a priori* determined by the spatial cueing designs, which postulated attentional activation prior target delivery, thus enabling only unidirectional influences of one system upon the other. The results presented in Chapter 4 and 5 confirmed the presence of a multifaceted link between attentional phenomena and executive control operations; nonetheless, it is plausible to hypothesize a bidirectional effect linking the two cognitive systems. Therefore, the use of an integrated task, which requires the engagement of conflict resolution and response selection mechanisms, together with the need to on-line reallocate attention from a visual stimulation to task-relevant auditory stimuli (but doesn’t allow the pre-activation of the attentional control system, as in the spatial cueing tasks previously reported) might be a useful tool in order to test the hypothesized bidirectional integration among systems.

This study was therefore designed to test the bidirectional integrative hypothesis for the attention deployment and control systems, and to clarify what stages of processing are modulated by information that interferes upon go and stop processes. The dependent variables were the ERP responses to the stop-signal, presented in a mixed stop-signal/flanker paradigm. The electrophysiological responses to the stop-tone are composed by at least two phases (the stop-N1 and the stop-P3, Bekker *et al.*, 2005), each involved in different stages of processing and resolution of the motor inhibition required by the stop-signal task: we reasoned that these responses, which are known to differentiate between successful and failed inhibition trials already at the auditory stages of processing (Bekker *et al.*, 2005), would be modulated by compatibility manipulations. The incongruency effect could take place at an early, attentional stage (N1), therefore confirming the hypothesis of a bidirectional attention/control modulation, or at a later, more inhibition-related stage (P3). This temporal distinction could disentangle two possible explanations of the behavioral effect: if the N1 effect were modulated, this would be in line with accounts claiming that the conflict monitoring system (embodied in the medial frontal cortex, Botvinick *et al.*, 2001 & 2004) is responsible for the engagement of the more dorsolateral control system for resolving the response-incongruency caused by RI flankers, and, at the same time, for the attentional reallocation of attention towards the task-relevant auditory stimuli: the need for control in the response-conflict resolution would therefore prevent the system from acting as an attentional buffer which should guide a fast attentional switch from the visual go-stimulus towards the auditory stop-stimulus. If, on the other hand, the N1 effect were not affected, while the Stop-P3 effect resulted sensitive to flanker category, then it would be possible to attribute the go-stop interference to a stage which involves both the outcome of the motor choice and the outcome of the stopping process itself, rather than to an attentional switch deficit, ruling out the hypothesis of bidirectional attention/control influences.

6.2 Methods

6.2.1 Participants

20 healthy dutch students were paid or received university credits for their participation in the study (age range 18-30 years, mean age 23.12 years, S.D. 3.0 years, 15 males). All participants had normal or corrected-to-normal vision, no history of neurological or psychological diseases and were unaware of the purpose of the study. One participant was excluded from ERP analyses because of an excessive percentage of artifacts, resulting in a sample of 24 participants (14 males).

6.2.2 Task

The study design included an auditory-visual stop-signal paradigm (modified after Verbruggen *et al.*, 2006). Participants were presented with a small white fixation cross (0.5 ^{o} of visual angle), in the center of the screen on black background. After a randomized interval (200-500 ms) the cross was substituted by the go-stimulus, a pattern of three colored parallel lines subtending 1^{o} x 1^{o} of visual angle, presented at fixation for 1 sec (see Figure 6.1 for a graphic illustration of the trial structure). Participants were required to detect the color of the middle line, ignoring the flankers, and to press a button with their right or left index fingers as fast and as accurately as possible. The target could be either red (RGB: 255, 0, 0), orange (RGB: 255, 153, 0), yellow (RGB: 255, 255, 153) or green (RGB: 153, 204, 0). The four colors were mapped on the two response hands (eg., green and yellow on the left hand, orange and red on the right hand, counterbalanced across subjects, see figure 6.2). The possible combinations of target and flankers colors gave rise to three categories of trials: fully compatible (C: target and distractors were identical), stimulus incompatible (SI: target and flankers were physically dissimilar, i.e. different in color, but mapped on the same hand), and response incompatible (RI: target and flankers were physically different and mapped on opposite hands). Stimuli belonging to the three categories were equally represented in each block, and pseudorandomized (i.e., not more than three stimuli of the same type or requiring the same motor response were presented in a row). In order to avoid focusing strategies, stimuli were rotated in different randomized directions (Cohen & Shoup, 1997), and they were separated by an ISI comprised between 1000 and 1250 ms. Randomly, on 30% o f the trials a stop tone was binaurally presented shortly after the visual go-stimulus (frequency: 1000 Hz, intensity: 83 Db; duration: 400 ms).

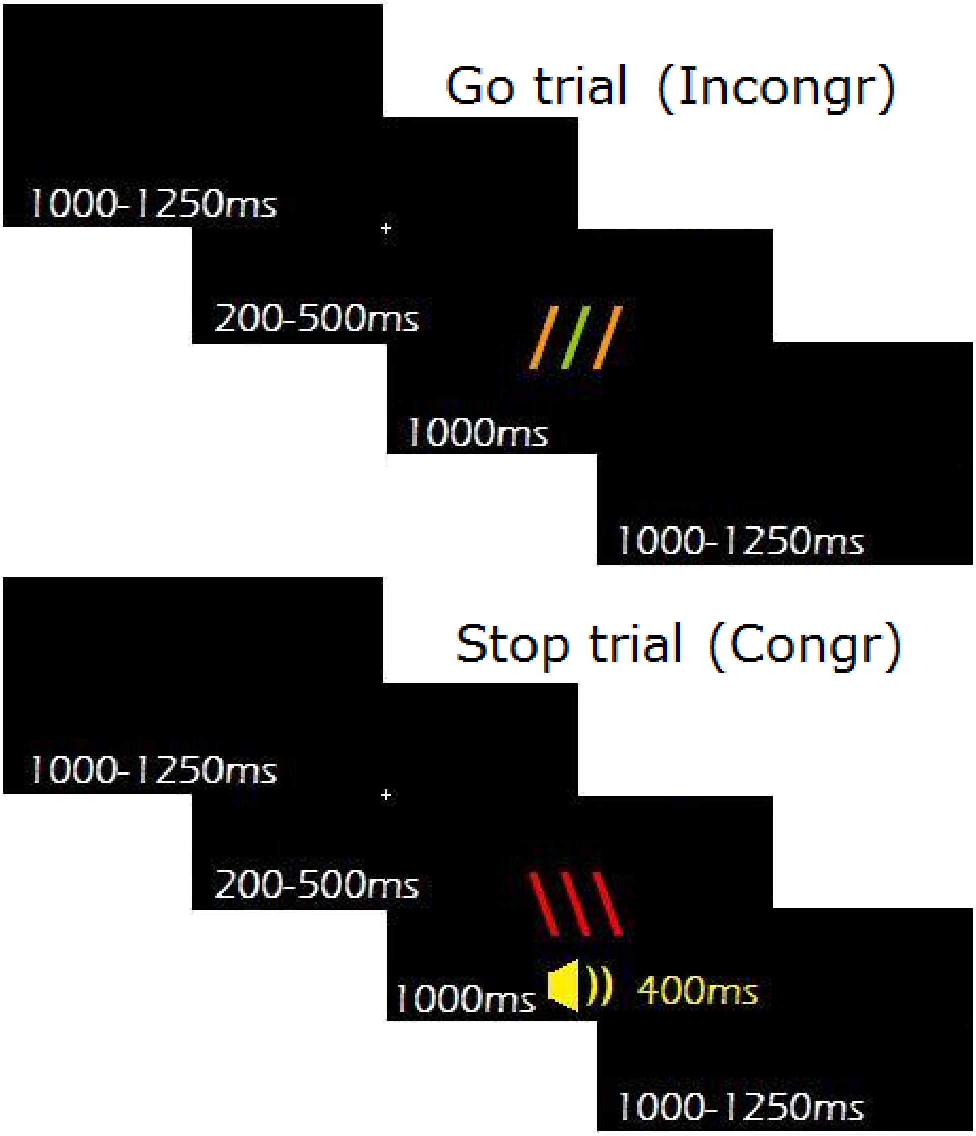


Figure 6.1 Graphic ilustration of the trial structure for a Go incongruent trial and for a Stop congruent Trial in the combined flankers/stop-signal paradigm

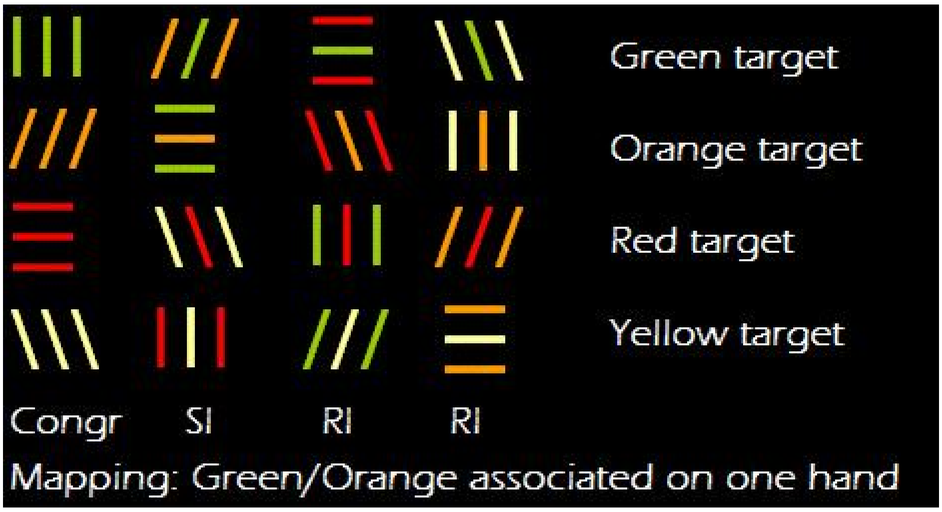


Figure 6.2 Graphic illustration of all the possible go-stimulus combinations, presented in an exemplificative mapping (Green/Orange right hand, Red/Yellow left hand).

Participants were instructed to withhold any motor response to trials in which the tone was presented. The timing of the stop-signal in respect to go stimulus (SSD) was determined on the basis of a staircase tracking system, which delayed the next stop tone if the previous stop-trial was correctly inhibited, while anticipated it, if during the previous stop-trial the inhibition failed (independently for the three categories, steps of 50 ms). The aim of the staircase algorithm was to keep the proportion of correct and failed inhibitions around 50%, distribution that maximizes the reliability of the SSRT estimation (Logan & Cowan, 1984). In order to perform a correction for overlapping upon the stimulus-locked waveforms (ADJAR method, Woldorff, 1993), the SSD was additionally jittered around the value calculated by the staircase system, within a range of ±125 ms.

6.2.3 Procedure

Participants were required to sign a consent form, prepared for the EEG recording and then presented with the task, each block preceded by instructions. They performed a go-only practice block of 48 stimuli (16 for each congruency category), and, subsequently, 10 blocks with intermixed go and stop trials (120 stimuli per block, 40 per category, with a total amount of 120 stop trials per category).

6.2.3 EEG recording and processing

EEG signals were continuously recorded at 2048 Hz (ActiView-5.37-Lores, BioSemi, Amsterdam) from Ag-AgCl electrodes distributed on 64 scalp sites according to the 10.10 International System (see Figure 6.3). On-line reference was CMS (Common Mode Sense, BioSemi). Eye movements were monitored through 4 additional bipolar electrodes positioned on the outer canthi of both eyes, and above and below the left eye. CMS and DRL (Driven Right Leg, Bio-Semi) served as ground, and 2 extra electrodes were placed on the mastoids. Offsets were kept below 25 µV. Data were analyzed using Brain VisionAnalyzer (Vers. 1.05.005): EEG signals were off-line referenced to the average of all electrodes (Lansbergen *et al.*, 2007), band-passed at 0.05-30 Hz and down-sampled at 250 Hz (Bekker *et al.*, 2005). For each subject, ERPs were computed from – 100 to 1552 ms relative to the onset of the visual go-stimuli and the auditory stop-stimuli, and referred to the 100 ms interval prior to stimulus onset. A first artifact rejection was performed with a differential criterion based on scalp distribution; eye movements artifacts were removed by means of the Gratton *et al.* (1983) ocular correction algorithm, and an additional artifact rejection step was performed (absolute amplitude criterion: ±80 µV; difference criterion: 100 µV; maximal allowed voltage step: 50 µV).

ADJAR level 2 (Woldorff, 1993) was performed to remove any residual overlap between go and stop stimuli. Averages were calculated for each subject for visual stimuli and for

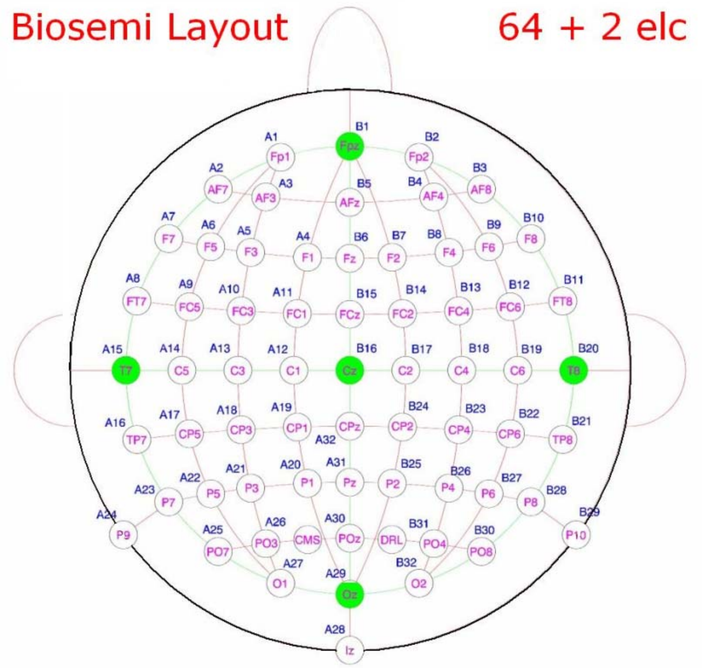


Figure 6.3 Recording layout with 64 channels distributed over the scalp surface following the 10.10 I.S.

auditory stop-stimuli, separately for different congruency levels and for successful and failed inhibitions. Difference waves (DW) were computed subtracting the responses to tones followed by a failed inhibition from the responses to tones that elicited a successful motor inhibition.

5.2.6 Behavioral and electrophysiological analyses

Mean reaction times (MRT), the Percentage of Omissions (Pom) and the Percentage of Errors (Per) were calculated in response to the go-stimuli, while the Percentage of successful Inhibitions corrected for the amount of omissions (Pic, Tannock *et al.*, 1989) was computed for stop trials. SSRTs were estimated on the bases of go RTs distribution and Pic, following Logan (1994).

All the behavioral results were analyzed with repeated measures ANOVAs with Congruency (C, SI, RI) as a factor.

Concerning the electrophysiological responses, after visual inspection of the grand average ERPs across subjects, the N1 effect was defined as the first negative peak in the DW, scored between 80 and 150 ms after the onset of the auditory stimulus; the stop-P3 effect was scored as the most positive peak present in the DW between 150 and 300 ms. For both the components, a pool of 9 central, fronto-central and frontal electrodes was chosen for scoring (F1, Fz, F2; FC1, FCz, FC2; C1, Cz, C2), following previous literature and the visual inspection of the scalp distribution of the components. The ERP scores were analyzed with 3-ways repeated measures ANOVAs with Congruency (C, SI, RI), Lead (F, FC, C) and Lateralization (Left, Midline, Right) as factors.

All results were corrected with Greenhouse-Geisser procedure when necessary, and only the corrected *p* values are reported. All the interactive significant effects were interpreted in light of post-hoc (Tuckey) tests.

6.3 Results

6.3.1 Behavioral Results

Go trials. Mean Reaction Times (MRT), omission and error data are presented in Table 6.1. Analyses performed on MRTs and error percentages showed a main effect of Congruency: $F_{2,46} = 69.08$, $p < 0.001$ and $F_{2,46} = 14.93$, $p < 0.001$, respectively. Comparing the three congruency levels with post-hoc tests, a significant difference between the Response Incongruent condition and the Congruent and Stimulus Incongruent conditions was found for both MRTs and errors ($p <.001$ for RTs and $p <.01$ for error rates), indicating the absence of a behavioral cost for stimulus incongruency, and a robust cost for response conflict. Additional paired *t* tests on MRTs showed a trend towards significance for the comparison between C and SI: $t_{23} =-2.03$, $p= 0.054$. Analyses performed on the omission rate did not result in any congruency effect : $F_{2,46} = 2.18$, $p >.1$. For a graphic illustration of the behavioral results, see Chart 6.1.

Stop trials. Stop-Signal Delays (SSDs), Stop-Signal Reaction Times (SSRTs) and Percentage of correct inhibitions (Pic) were calculated for the stop-signal trials, and are reported in Table 6.1. Repeated measures ANOVAs showed a marginally significant congruency effect for SSRTs: $F_{2,46} = 3.53$, $p < 0.05$, and post-hoc tests revealed a small difference between SSRTs for congruent flankers and stimulus-incongruent flankers, while no differences were present between response-incongruent flankers and either congruent or SI stimuli. SSDs and Pic showed a highly significant effect of stimulus type: $F_{2,46} =40.36$, $p < 0.001$, and $F_{2,46} = 12.70$, $p < 0.001$, respectively. Even though Pics were situated very close to the aimed value of 50% (showing that the staircase procedure worked succesfully in this experiment), the post-hoc tests indicated that stimuli with congruent flankers are inhibited slightly less efficiently than stimuli accompanied by incongruent distracters (both SI and RI), as pointed out by significantly lower Pics and shorter SSDs for C stimuli in respect of SI and RI stimuli. SSD differentiated also between SI and RI stimuli, as indicated by the post-hoc comparison ($p <0.001$).

Although the expected congruency effect on SSRTs was not observed, we acknowledged the expected variability in the incongruency effect on SSRTs, expressed by the comparisons $SSRT_{RI}> SSRT_{C}$; $SSRT_{RI} > SSRT_{SI}$; $SSRT_{SI} > SSRT_{C}$ (values ranged between 20 and -73 ms, 41 and -54 ms and 32 to -46 ms, respectively). These

	Overall (n=24)			**Group NoSSRTEffect (n=12) vs Group SSRTEffect (n=12)**		
	C	**SI**	**RI**	**C**	**SI**	**RI**
MRT	554 (17)	560 (16)	584 (16)	$t_{22}=0.15$,p=0.9	$t_{22}=0.39$,p=0.7	$t_{22}=0.44$,p=0.7
Per	5.3 (0.9)	4.7 (0.8)	7.0 (0.9)	$t_{22}=0.00$,p=1.0	$t_{22}=-0.28$,p=0.8	$t_{22}=-0.57$,p=0.6
Pom	0.5 (0.2)	0.6 (0.3)	0.7 (0.3)	$t_{22}=0.85$,p=0.4	$t_{22}=0.67$,p=0.5	$t_{22}=0.82$,p=0.4
SSD	334 (18)	347 (18)	368 (17)	$t_{22}=0.00$,p=1.0	$t_{22}=-0.17$,p=0.9	$t_{22}=-0.48$,p=0.6
SSRT	200 (7)	189 (6)	192 (8)	$t_{22}=0.48$,p=0.6	$t_{22}=1.48$,p=0.2	$t_{22}=2.87$,p<0.01
Pic	49.6(0.5)	50.3(0.3)	50.9(0.3)	$t_{22}=-0.17$,p=0.9	$t_{22}=-0.45$,p=0.7	$t_{22}=-1.96$,p=0.06

Table 6.1. Left panel: Mean Reaction Times (MRTs, in ms), Error and Omission rates (Per, Pom, in %) in response to the visual go stimuli; Stop-Signal Reaction Time (SSRTs, in ms) estimated for the stop-trials; Stop-Signal Delays (SSDs, in ms) and Percentage of Correct inhibitions (Pic) calculated for the stop-trials. Values are expressed as: Mean (S.E.)
Right panel: t tests performed on the average values of the two groups defined by a split half on the RI-C SSRT effect ($t_{22}=4.996$,p <0.001), for MRTs, Per, Pom, SSD, SSRTs and Pic. Note that the two groups are completely similar, except for their SSRT to RI stop-trials.
C = Congruent; SI = Stimulus Incongruent; RI = Response Incongruent

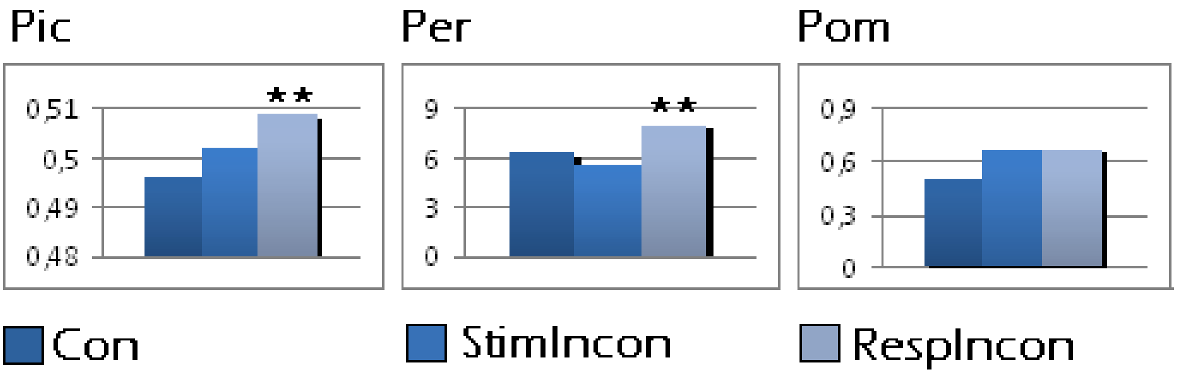


Chart 6.1 Behavioral results effects for the percentage of inhibition (corrected for the amount of omissions, the percentage of errors and for the percentage of omissions)

distributions confirmed the existence of strong interindividual differences in the effect that congruency manipulation has on aselective stopping performance (especially for the RI>C contrast). Based on previous literature (Ridderinkhof *et al.*, 1999), we expected the MRTs and SSRTs to show no or weak correlations, in line with the idea that overall speed in go response is not necessarily coupled with speed in stopping performance; conversely, we expected to be able to predict the size of incongruency effects on SSRTs on the basis of the same effect on go MRTs, in line with the idea that monitoring is involved in both go and stop processes, causing comparable costs in the two separate dimensions of the combined task. As expected, correlations between MRTs and SSRTs were weak or null (C $r = -.09$, $p > .6$; SI $r = -.19$, $p > .3$; RI $r = -.09$, $p > .6$). On the other hand, the finding of strong correlations between go and stop *effects* (RI-C $r = .52$, $p < 0.01$; RI-SI $r = 0.48$, $p < .05$; SI-C $r = .68$, $p < 0.001$) supports the idea of a common ground shared by selective and non-selective inhibition, or the alternative idea of an interference exerted on the process of activating the attention reallocation system (in stop-trials), when the control system is already engaged in the process of selecting the correct motor response in case of incongruency. The observed interindividual variability on the response-incompatibility effect allowed us the partition of the sample with a *median-split* procedure, based on the $SSRT_{RI} > SSRT_C$ effect: the two subgroups did not differ in any dimensions (see *t* tests in Table 1, right panel) except for the $SSRT_{RI} > SSRT_C$ effect (7.3 ms for the group $SSRT_{RI} > SSRT_C$, vs -24.3 ms for the group $SSRT_{RI} < SSRT_C$); this difference was driven by the $SSRT_{RI}$ and not by the $SSRT_C$, as can be seen in Table 1 ($SSRT_{RI}$ 211 vs 173 for the two groups). Since the subgroups were divided on the basis of behavioral differences in the impact of *response incompatibility* on their SSRTs, in the ERP analyses interactions of *stimulus incompatibility* with group level will be reported when present, but not discussed further.

6.3.2 Electrophysiological Results

6.3.2.1 Group analysis

N1 effect. No effect of congruency was observed, neither as main effect nor in interaction with lead or lateralization (all Fs <0.95, all $p > 0.47$); the significant main effects of Lead, $F_{2,46} = 19.70$, $p < 0.001$ and Lateralization, $F_{2,46} = 17.38$, p 0<0.001 were better explained by a Lead x Lateralization interaction, $F_{4,92} = 4.03$, $p < 0.01$, following which the N1 component peaked at fronto-central and central sites, especially at midline and right electrodes, whereas it did not differentiate across hemispheres within the frontal electrodes.

Stop-P3 effect. Besides the main effects of Lead, $F_{2,46} = 35.44$,p <0.001) and Lateralization $F_{2,46} = 26.73$,p <0.001, again conjunct in a Lead x Lateralization interaction, $F_{4,92} = 6.99$, $p < 0.001$, also the Congruency main effect became significant $F_{2,46} = 3.73$, p <0.05. Post-hoc tests resulted in a significant difference between C and RI conditions (4.1 μV for RI vs 3.1 μV for the C condition, $p < 0.05$), while the P3 elicited in the SI condition (3.3 μV) was not different from any of the other two ($p > 0.1$ and $p > 0.8$). The Lead x Lateralization interaction indicated that the component peaked at Central (4.4 μV) and Fronto-Central sites (4.1 μV), which showed significantly more positive P3s than the Frontal electrodes (1.9 μV), and that both the peaking areas had their maximum at midline electrodes (5.3 and 4.8 μV, respectively); on the other hand, at frontal electrodes no differences were present among midline or lateralized sites. Note that the strongest Stop-P3 effect was elicited under the RI condition, not in line with the SSRT values (not significantly different, at a group level, between C and RI stimuli), but mirroring the Pic values, significantly higher for the RI condition than for the C condition.

6.3.2.2 Between-Subjects analysis

All the analyses performed on the two groups deriving from the median-split procedure based on the SSRT effect were 4-ways repeated measure ANOVAs with Congruency (C, SI, RI), Lead (F, FC, C) and Lateralization (Left, Midline, Right) as within-subjects factors, and Group ($SSRT_{RI} > SSRT_{C}$; $SSRT_{RI} < SSRT_{C}$) as between-subjects factor.

N1 effect. Inserting the between subjects Group factor in the analyses on the N1 peak values resulted in an additional interaction among Congruency, Lateralization and Group, $F_{4,88} = 3.39$, $p < 0.05$. On the basis of follow-up analyses, it became clear that the two groups did not differ in the N1 amplitude at any of the leads, but the interaction was driven by the fact that only the group which suffered a cost for the incongruency in the behavioral index ($SSRT_{RI} > SSRT_{C}$) showed a diminished N1 effect for the RI condition, in respect to the C condition, at midline and right-sided electrodes. The interaction is shown in Figure 6.4 (waveforms and voltage distribution maps) and in Chart 6.2. The complete overview of the values is presented in Table 6.2 (mean values of the peak amplitude as a factor of group, congruency level and electrode side). No differences whatsoever were significant under the SI condition.

P3 effect. Inserting the between subjects Group factor in the ANOVA on the stop-P3 resulted in an additional triple interaction Congruency x Lateralization x Group, $F_{4,88} = 2.93$, $p < 0.05$. Post-hoc analyses showed that the interaction was driven by the fact that the group characterized by costs for response incongruency on SSRTs showed significantly different RI and C P3 effects on both hemispheres, while the group showing the reverse effect showed the differentiation only at left and midline sites. Despite the interaction, the direction of the difference is, for both groups, of a stronger P3 effect for RI stimuli than for CI stimuli, as in the group analyses (see Chart 6.3).

Behavioral cost (SSTR RI-SSRT C >0)			
	CON	RI	p
Left	-2.40 (0.4)	-1.96 (0.3)	p >0.3
Midline	-3.02 (0.5)	-2.22 (0.3)	p <0.01 **
Right	-2.87 (0.4)	-2.03 (0.3)	p <0.01 **
Behavioral benefit (SSTR RI-SSRT C <0)			
	CON	RI	p
Left	-2.06 (0.4)	-1.88 (0.3)	p > 0.9
Midline	-2.57 (0.5)	-2.66 (0.3)	p =1.0
Right	-2.11 (0.4)	-2.52 (0.3)	p >0.4

Table 6.2. N1 peak values (S.E.) for the two groups at midline (average of Fz, FCz, Cz), on the left hemisphere (average of F1, FC1, C1) and on the right hemisphere (average of F2, FC2, C2). C = Congruent; SI = Stimulus Incongruent; RI = Response Incongruent

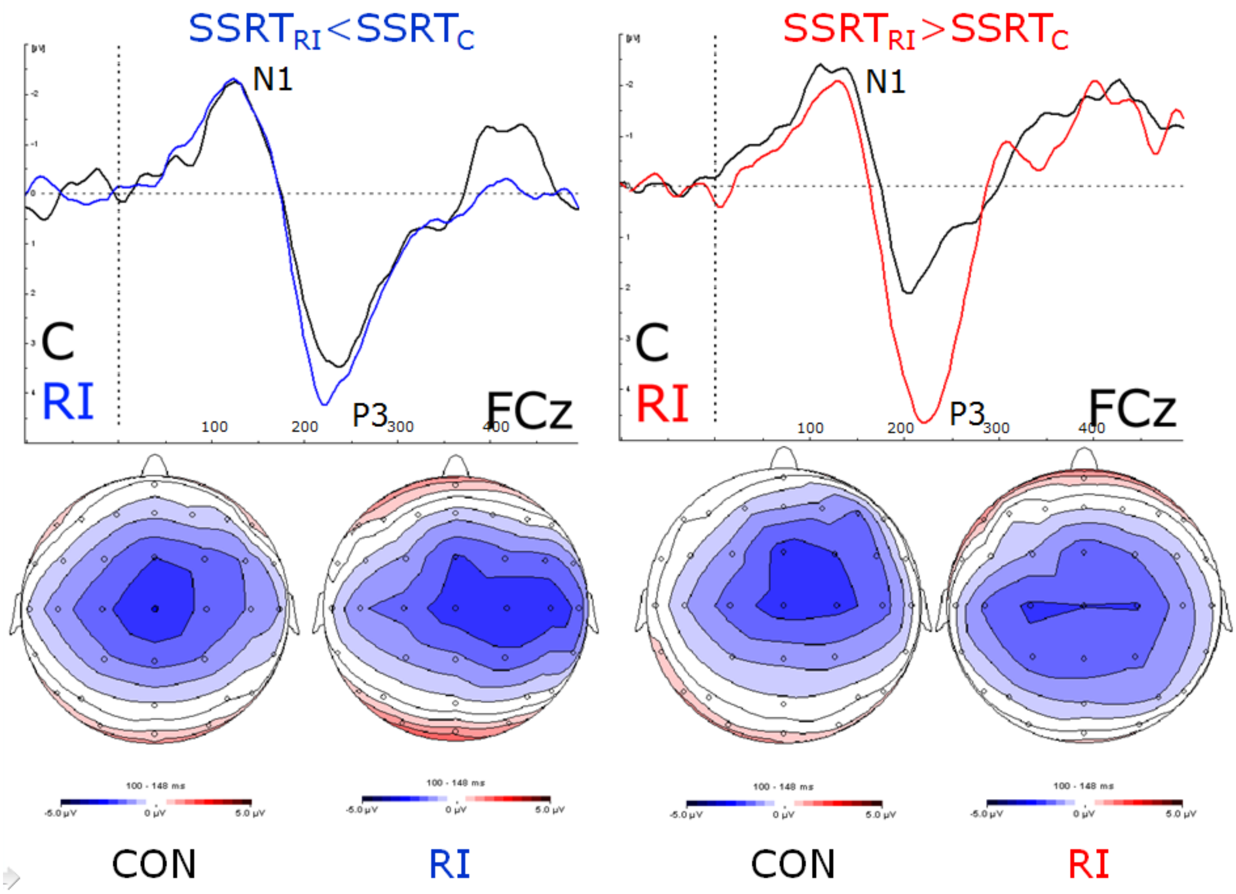


Figure 6.4 Upper panel. Illustration of the ERP responses at the Cz sensor for the two groups of participants, in response to auditory stop-signals in case of primary stimuli accompanied by congruent and incongruent flankers.
Lower panel: voltage maps of the N1 response distribution over the scalp, for the two separate groups of participants, as a function of flanker category.

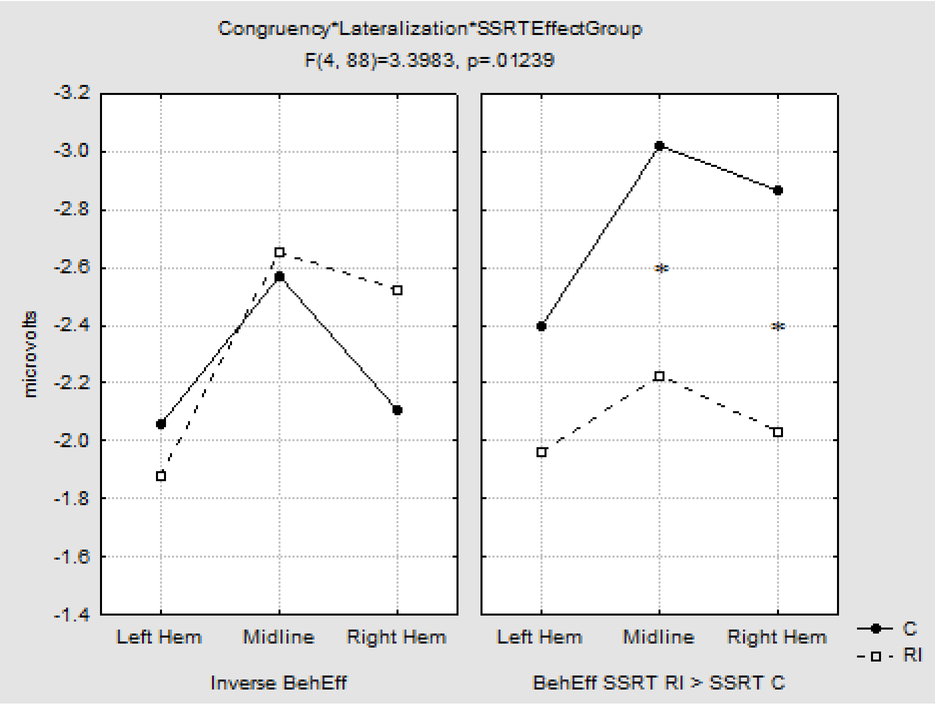


Chart 6.2 Interaction between Group, Congruency level and lateralization of the electrodes for the N1 effect in response to the stop-tones.

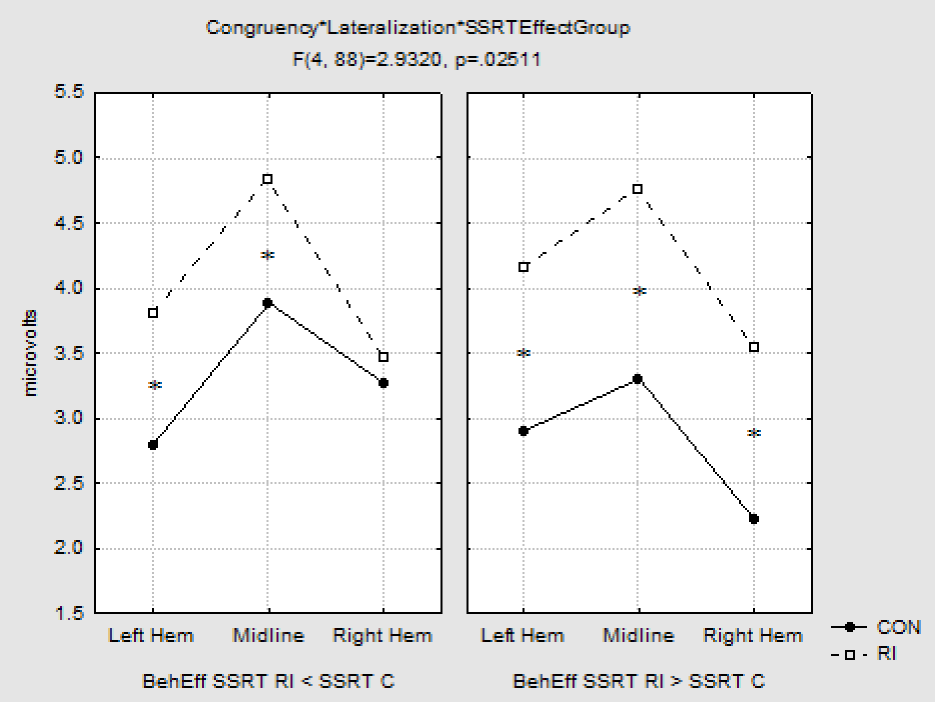


Chart 6.3 Interaction between Group, Congruency level and lateralization of the electrodes for the P3 effect in response to the stop-tones.

6.4 Discussion

This study was designed to investigate, by means of an ERP experiment, at what stage of processing the behavioral interaction between response selection and inhibition, previously observed (Kramer *et al*., 1994; Ridderinkhof *et al*., 1999; Verbrugen *et al*., 2004, 2005 and 2006), was situated, and to test the hypothesis of a bidirectional interaction between attentional and control mechanisms. The SSRT effect had been previously observed in populations showing strong incongruency effects on the go RTs, which were replicated in this study, especially for the response incompatible stimuli. The effect of stimulus incongruency, however, was not observed in this sample, neither on the go RTs, or on SSRTs. This lack of replication might be due to several factors: the age of the participants in this study was rather lower than the mean age of samples taking part to the aforementioned studies (age range: 18-33, against 18-48 for the direct comparison, experiment 2 in Verbruggen *et al.*, 2006). Moreover, a subsequent behavioral study of the same group (Verbruggen *et al.*, 2006a) also failed to replicate the stimulus-incongruency effect on RTs, indicating that external factors might influence this intermediate category. Besides the SI effects, also our SSRT analysis failed to replicate a strong effect for incongruency, reported by Verbruggen and colleagues (2006). In this case, the strong connection between SSRT estimation and go-RTs distribution, which in this sample displays a highly significant but not wide (30 ms) incongruency effect, might be the cause for this null-finding. However, within a 24 participants' population, half of the sample showed a cost for response incongruency, while the other half didn't (they showed, reversely, an advantage for stop-trials accompanied by RI flankers). Even more interestingly, mirroring the difference in behavioral performance, the ERP analyses showed that the group in which incongruent trials were more costly (as indirectly indicated also by the significant correlation between incongruency cost in go and stop measures)showed dimmed early cerebral responses to the stop-tones in response-incongruent trials, on the fronto-central surface of the scalp and with a right-sided asymmetry. It was hypothesized that the activation of the conflict monitoring system in response to the go stimulus incongruency would recruit dorsolateral frontal areas in order to resolve the conflict itself (Botvinick *et al.*, 2001 and 2004; Van Veen *et al.*, 2001; Fan *et al.*, 2003; Van Veen & Carter, 2002); we reasoned that this process would interfere with the recruitment of the same medial-to-dorsolateral frontal circuit involved in the attentional switch from the analysis of the visual stimulus towards the analysis of the auditory stop-tone (Bekker *et al.*, 2005), resulting in an affected N1 (attentional-sensitive) effect. The fact that the expected pattern was observed only for those people who, at the same time, showed the behavioral effect of this interference, is in line with MEG data recorded in a visual version of the stop-task (Boehler *et al.*, 2008), which showed how an impoverished analysis of the stop-signal leads to less efficient stopping performance. The involvement of fronto-medial structures (especially the dorsal anterior cingulate cortex) in processes of conflict monitoring, response conflict in particular, has been suggested by several computational, ERP and fMRI studies (Botvinick *et al.*, 2001; van Veen & Carter, 2002; Fan *et al.*, 2003); moreover, strong connections of the monitoring system with primary and secondary sensory areas, as well as dorsolateral frontal cortices, is sustained by ERP and fMRI studies (Scerif *et al.*, 2006; Crottaz-Herbette & Menon, 2006). Our results indicate that the detection and resolution of response conflict involves a common frontal circuit for both conflict resolution and attentional switch, resulting, in some individuals, in a dimmed attentional response to incompatible trials, which ends up in delays in the analysis of the inhibitory signals, in turn causing a delayed recruitment of the inhibitory system (as reflected in slower stop-signal reaction times).

At a later stage of processing, the successful-stop P3 has been previously hypothesized to reflect the success of the stopping process (Dimoska *et al.*, 2006), and has been shown to display smaller amplitudes for populations that showed decreased inhibition percentages (Overtoom *et al.*, 2002 with AD/HD children) or slower stopping performance (van der Schoot *et al.*, 2002, with dyslexic children). Our P300 effect was robustly influenced by compatibility manipulations, at a group level as well as in the two subgroups, showing a clear dissociation with the behavioral SSRT effect. It resembled, in line with Overtoom *et al.* (2002), the pattern of the percentage of correct inhibitions (Pic), which was significantly higher for RI than C stimuli. The fact that the P300 effect so strongly mirrored the ‘goodness’ (as opposite to the speed) of stopping, sheds some light on the theoretical implications of the Stop-P3, which was never, to our knowledge, tested before in a context in which a manipulation of the go stimuli created a significantly different distribution of the

Pics across stimulus types. Additional correlation analyses performed on the Pic and the P300 effect showed how the P300 effect amplitude is linearly related to the overall Pic of the participants ($r = .42$, $p < .05$ at FC1; $r = .53$, $p < .01$ at FCz; $r = .51$, $p < .05$ at FC2), further confirming the interpretation that relation linking P3 effect and stopping performance should be searched in the effectiveness, rather than the speed of the stopping process. The stop-P3 may therefore be interpreted as a correlate for a feedback circuit that adjusts the performance of the individual on a trial-by-trial basis, leading to a balance trading accuracy of the inhibitory performance off speed in the primary task.

6.5 Conclusions and further directions

All in all, our findings shed light on the temporal dynamics of the complex interplay between conflict resolution, inhibitory processes, and attentional mechanisms, providing evidences for an early locus of interaction. The attentional switch necessary in order to analyze and utilize the stop-signal in the demanding and effortful process of overriding a prepotent response is the cognitive step which is affected in case of response selection conflict, as indexed by affected auditory N1 amplitudes in response to stop-signals delivered during conflicting situations and to particularly sensitive subjects. These conclusions further clarify the integrative approach among cognitive systems in the frontal and parietal lobes, attempted in the previous chapters.

The fact that the interactive effect, at least in the interference dimension, shows high interindividual variability suggests that complex mechanisms are at play in case of overload of one system by external stimulation. The observation of the reported integrative phenomena, obtained by the use of combined designs and neuroscientific techniques, in different populations (e.g., clinical or sub-clinical populations previously linked to attentional/inhibitory/monitoring deficits, as obsessive-compulsive, schizophrenic patients or inattentive patients), or the combination of such techniques with genetic mapping (which could account for the observed phenotypic differences) is desirable in order to further clarify these integrative aspects of the cognitive systems.

Chapter 7.
General discussion and conclusions

Several unresolved issues, derived from the analysis of the theoretical and empirical state of the art in neuroscientific research investigating the attentional and control systems, contributed to stimulate the questions which drove this research project. Consequently, the results of the empirical part of this work have been separately discussed in the research chapters, and will be inserted in a broader perspective in the context of this integrated discussion.

All in all, the results of the present work are in line with previous literature in indicating the role of frontal and parietal structures, integrated with reciprocal connections in a network, in the attentional control mechanisms (Corbetta & Shulman, 2002; Mesulam, 1981 & 1999; Gitelman *et al.*, 1999), the involvement of left and right portions of the frontal and parietal cortices in the alertness function (Sturm *et al.*, 1999; Sturm & Willmes, 2001; Coull *et al.*, 2001), and the engagement of fronto-medial and dorsolateral/ ventrolateral prefrontal cortices in the executive functions as conflict monitoring, response selection and inhibition (Bush, Luu & Posner, 2000; Botvinick *et al.*, 2001; Van Veen & Carter, 2002; Fan *et al.*, 2003; Carter & Van Veen, 2007).

A host of studies, capitalizing on the functional properties of diverse neuroscientific techniques (ERP, MEG, fMRI, TMS) demonstrated how the attentional control system, which includes two partially segregated streams (Corbetta & Shulman, 2002) is able to modulate brain activity at sensory cortical levels, prior to stimulation (Kastner *et al.*, 1999; Brefczynsky & De Yoe, 1999; Hopfinger, Buonocore & Mangun, 2000; Giesbrecht *et al.*, 2006; Bestmann *et al.*, 2007), and to enhance the sensory responses to attended stimuli (Zani & Proverbio, 1997 & 2006; Hopfinger, Buonocore & Mangun, 2000; Natale *et al.*, 2006). The differential engagement of dorsal or ventral modules of this system has been sustained by behavioral, neuropsychological and physiological evidences, integrated in a functional model (Corbetta & Shulman, 2002): the more dorsal component, embedded in the superior posterior parietal and dorsolateral prefrontal cortices, together with structures within the medial frontal wall, is mainly involved in endogenous attention, intended as the top-down selection of sensory information and responses (goal-directed activity); the ventral reorienting and expectation system, more lateralized and involving the temporo-parietal junction and the inferior frontal cortices of the right hemisphere, subserves the stimulus-driven, bottom-up reallocation of attention, functional in case of abrupt onset of behaviorally relevant stimuli (i.e., the exogenous orienting, Shulman *et al.*, 2009). However, most of the functional studies implicating endogenous and exogenous cueing tasks, assumed to tackle and compare both systems, in fact encountered some methodological issues when contrasting peripheral and central cueing. In other words, in blocked-designs in which the central, endogenous, cueing validity is continuously manipulated (e.g., 80% validity), the endogenous attention system is *purely* involved only in case the cues validly anticipate the appearance of the targets (i.e., in case of valid cues); in case targets fell at the unattended location, also the bottom-up system of attention reallocation would be engaged, but the two activities, impossible to segregate, would both be attributed to the endogenous attention system (unless an event-related hemodynamic analysis is performed). Equally, during exogenous cueing paradigms, the bottom-up capture of the attentional control by the peripheral cueing is, to some extent, confused with the re-orienting effect caused by the abrupt onset of the target stimuli at the unattended location, in case of invalid trials. These methodological shortcomings might account for the inconsistent patterns of neural activations shown by the neuroimaging studies trying to directly compare endogenous and exogenous mechanisms, reporting either identical (Kim *et al.*, 1999) or highly overlapping (Corbetta *et al.*, 1993; Nobre *et al.*, 1997; Mayer *et al.*, 2004) brain networks, including bilateral premotor cortex, medial frontal areas, and bilateral posterior parietal cortex (both superior and inferior parietal lobules). The use of combined tasks, as the double cue paradigm (Natale *et al.*, 2009) or techniques characterized by a finer temporal resolution (as the event-related potentials or the transcranial magnetic stimulation) might shed some light on the issue. The results presented in Chapter 5, obtained comparing a purely endogenous task with a peripheral cueing (voluntary attention) paradigm, demonstrated highly similar activations for the two cueing types; however, our peripheral task was affected by a limitation: the valid cues were highly predictive in respect to the position of the coupled S2, introducing an aspect of voluntary attention in the 'exogenous' task. Plausibly, this aspect of the design influenced the ERP components, which showed highly similar effects at similar latencies across cueing modalities. Nevertheless, the different position of the cues in the exogenous cueing elicited strongly lateralized superior parietal activations within the first 200 ms after cue onset, with a pattern of inter-hemispheric asymmetry, absent in the purely endogenous paradigm. The same pattern of inter-task parietal disparity has been previously observed in a functional neuroimaging study (Kim *et al.*, 1999): however, the hemodynamic-based design didn't allow the authors to disentangle an explanation purely based on the spatial determinants present in their exogenous task as compared to the endogenous one, from an interpretation driven by the different percentage of invalid trials in the two paradigms. Conversely, in our study the informative value of the valid cues was absolute in both paradigms, allowing more straightforward conclusions: the superior parietal asymmetry observed only for the exogenous cues (and the bilateral pattern observed in response to the centrally presented signals) could be directly attributed to the spatial factor.

In addition to the lateralized parietal activations, in all the cueing tasks presented in this work we observed an early (100-150 ms) magnification of the sensory signals in response to the valid cues, as compared to the neutral ones. This pattern, reported in Experiment 1 and 2 (for both symbolic and peripheral cues) has been coupled, by means of source reconstruction methods (LORETA), to activations in the occipito-temporal cortices, and might be explained under multiple scenarios. Following one of these scenarios, the mechanism of spatial attention could be engaged very early after cue onset by means of a modification of the task-set, in which the participants actively orient their focus immediately after cue delivery. However, to our knowledge, no evidences have been provided sustaining this position, yet. On the other hand, feature selective mechanisms could be engaged in the early phases of visual cueing when facing highly relevant stimuli (the valid cues), which carry a significant predictive value for the detection of the following targets. Selective attention processes have been repeatedly shown to take place during the P1 window (e.g., Zani & Proverbio, 1995 & 1997), thereby our pattern of results might be interpreted as an indication of an activation of the selective (object-based) component of the attentional system in response to the cues themselves, caused by their relevance for the goal-directed activities of the cognitive system. If that holds, the differential complexity of the pointers used in previous ERP literature addressing the attention control system (Grent-'t-Jong & Woldorff, 2007; McDonald & Green, 2008) might directly explain the inconsistencies in the onset of the reported attentional effects: the selective attention system has been shown to modulate the occipito-temporal components in response to relevant stimuli either at the N1/N2 level (*selection negativity*, onset at about 250 ms, Harter & Guido, 1980; Hillyard *et al.*, 1998) or in earlier windows (Zani & Proverbio, 1995; Karayanidis & Michie, 1997; Annlo-Vento *et al.*, 1998), and to be sensitive to stimulus features, as their orientation (Proverbio *et al.*, 2002). Therefore, the differences in onset of the attentional effects, ranging from 250 to 400 ms after cue onset in different reports (McDonald & Green, 2008; Grent-'t-Jong & Woldorff, 2007) might be attributed to the nature of the utilized cues. Therefore, the present results strongly suggest that, when setting up the design for an attentional cueing paradigm, much cautiousness should be put in the choice of the spatial cues, since the stimulus selection processing is recruited in the early phases of spatial orienting and might confound the interpretation of the attentional effects latencies and scalp distributions (already hinted at by Nobre *et al.*, 2000 and by Van Velzen and Eimer, 2003), even when comparing shift and neutral cues.

A second methodological limitation of the previous studies was the impossibility to disentangle orienting effects from alertness effects, since the cue-target interval was often varied across trials (e.g., Grent-'t-Jong & Woldorff, 2007), causing rather the spreading over time than the elimination of the expectation and preparation development effects.

The expectancy has been shown, in our Experiments 1 and 2, to be related to the activation of frontal asymmetrical circuits. We showed with high consistency (during endogenous, exogenous vertical and exogenous horizontal paradigms) that the left middle frontal gyrus, with a contribution of the left premotor/prefrontal cortex is involved in the generation of the frontal orienting N1 and CNV, both recorded in the fronto-central regions of the scalp. This recruitment of left fontal regions in phasic orienting and tonic anticipatory responses, and the attribution of these components to the alertness system response, is in line with the left frontal asymmetry previously reported in fMRI studies in temporal orienting (Coull & Nobre, 1998, Coull *et al.*, 2001) and spatial orienting tasks (Hopfinger, Buonocore & Mangun, 2000; Vandenberghe *et al.*, 2000). At the same time, attributing the frontal negative effects to the *arousal* rather than the *orienting* system can explain the reasons for incongruencies reported in the spatial unfolding of the activations in different ERP studies addressing the cue-target interval: the activation of the fronto-parietal networks has been reported to develop with a frontal-to-parietal vector (Grent-‘t-Jong & Woldorff, 2007), with a parietal-to-frontal direction (Green & McDonald, 2008) or with no directionality, with a concurrent activity in both districts (McDonald & Green, 2008). Our results didn’t show a strong directional effect, since we reported frontal and superior parietal sources for the valid cues as early as at the P1 latency. However, the left frontal sources were commonly active for both spatially valid and neutral cues, while the right-sided activations were more specific for the spatially informative cues, indicating differential functional origins for the sources (orienting and alerting systems); interestingly, these results could be achieved only by means of a methodological approach which compares, rather than subtracts, the inverse solutions for the two cue types (and cueing modalities). The subtractive method, used in previous studies, most likely cancelled out the common sources and left the authors with patterns of activation that were partly due to spatial orienting operations (right foci) and others that were, to some extent, due to the differential strength of the preparatory activity (intended as motor preparation *and* cognitive expectation *and* temporal orienting) elicited by the orienting cues (in line with our CNV effects in Experiment 2). Therefore, the differential amount of preparatory activity elicited by the valid and neutral cues in studies using diverse temporal parameters (e.g., fixed or randomized SOA, different cue-target intervals etc.), combined with the subtractive method, traditionally applied prior to source reconstruction, might have been responsible for the reported differences in spatial unfold of the orienting components. On the other hand, our design and methodological approach, revealing the existence of both segregated and common (although differentiated in strength) neural activations for the orienting and neutral cues, suggested the idea that the orienting cues are never *purely* spatial, and that the simple subtraction of the ERP response between the two categories of signals might lead to spurious effects. Moreover, the use of non-lateralized stimuli (i.e., the presentation of cues and targets along the vertical meridian, see Experiment 1) also elicited highly consistent frontal and superior parietal activations, indicating that structures in the fronto-parietal network carry out the spatial deployment of attention in the three-dimensional space, regardless of the need to shift attention along the vertical rather than the horizontal meridian (Mangun *et al*., 1993; Zani & Proverbio, 1997 & 2009).

Additionally, the present series of studies provided evidences clarifying a different controversial aspect of the literature addressing the attention networks, that is the integrative aspect of the model. Previous reports of behavioral interactions between alertness, executive control and spatial orienting (Fan *et al.*, 2002; Callejas *et al.*, 2004 & 2005, Fuentes & Campoy, 2008) were replicated in our combined spatial attention/executive control tasks. The behavioral pattern of facilitated conflict detection/resolution was sustained by the observation of enhanced ACC activity in response to validly cued incongruently flanked targets. This observation sustained the theoretical assumption advanced by Fan *et al.* (2002) which proposed that the use of spatial cues, which permits participants to direct attention to the target stimulus ahead of time, reduces the influence of the surrounding flankers through a boost of the executive control system driven by the orienting system. Conversely, the reduced costs for incongruency observed in the control (uncued) condition were not replicated in our experiment. The effect, which originally surprised the authors (Fan *et al.*, 2002), was in fact in line with the modulation of the response conflict effects observed as a function of overall reaction times (Ridderinkhof, 2002 & 2002a), and therefore could be accounted for by the slower motor responses to the uncued trials. A different explanation for the effect was proposed in terms of an inhibition of the anterior network by the alerting network, which would increase the costs for incongruent trials in case of high activation, as compared to uncued and validly cued situations (Callejas, Lupianez & Tudela, 2004; Callejas *et al.*, 2005; Fuentes & Campoy, 2008). However, the hypothesis of a shutdown of the control activity by means of the alertness system (Posner, 1994) was challenged by our observation of an equal level of arousal in the neutrally and validly cued trials (Experiment 1 & 2), which could rule out the 'clearing of consciousness' hypothesis. Moreover, in our case, the uncued trials showed the highest conflict costs (not significantly different from the case of neutrally cued stimuli), thus supporting the idea that the difference between compatibility costs in neutral and valid conditions was driven by an effective integration of the fronto-parietal system with the monitoring/control one, rather than depending from a cost exerted by the engagement of the alertness system. Consequently, the behavioral effect might be attributed to the influence of the control system early activations upon the cognitive processing of the target stimuli, as early as in the sensory areas, in line with previous reports of tight connection of the ACC with sensory regions (Crottaz-Herbette & Menon, 2006). Additionally, the role of medial frontal structures in the generation of conflict-related ERP components (N2, Liotti *et al.*, 2000; Lange *et al.*, 1998; Van Veen & Carter, 2002) has been consistently reported. Our observation, in Experiment 2, of enhanced N2s in response to validly cued NoGo stimuli further confirmed our hypothesis of a tight connection between the orienting and executive control systems. Therefore, previous reports of the ACC as the source of modulation in widely distributed regions of the brain, among which the sensory cortices (Crottaz-Herbette & Menon, 2006), can be complemented with evidences sustaining that the executive control activation can be in turn modulated by the attentional system, particularly in its dorsal component. Furthermore, the ACC activation has been shown to elicit facilitation of the sensory processing of subsequent stimuli by modification of the task-set (Sherif *et al.*, 2006); in addition (and, again, complementarily), we demonstrated with Experiment 3 that the heavy engagement of the control system in response selection, especially in case of response incongruency, might, in a subset of the population, modulate the attentional set within the trial. The selective response inhibition processes, required by incompatible trials in the stop-signal task, were able to dim the sensory responses to the salient stop-tones, highly relevant for goal-related activities, thus increasing the behavioral cost for aselective response inhibition processes (Kramer *et al.*, 1994; Ridderinkhof *et al.*, 1999; Chambers *et al.*, 2007).

In conclusion, our series of studies provided evidences for an integrated model of the frontal and parietal attention networks (Posner & Petersen, 1990; Corbetta & Shulman, 2002), involving multifaceted interplays among parietal cortices, structures of the medial frontal wall, dorsolateral prefrontal areas and sensory cortices, in the auditory and visual domain.

Future directions

The methodological limitations of our studies are numerous, and the possible developments of this research line are multiple.

First, the fixed SOA has been an extremely useful tool in the investigation of the integration and dissociations between the alertness and orienting systems. However, most of the studies interested in the temporal and spatial unfolding of the orienting activations used either longer (Harter *et al.*, 1989; Hopf & Mangun, 2000; Van Velzen & Eimer, 2003; Green *et al.*, 2005; Gomez, Flores & Ledesma, 2007; Green & McDonald, 2008;), randomized (Grent-‘t-Jong & Woldorff, 2007), or systematically manipulated cue-target intervals (Yamaguchi *et al.*, 1994; Nobre *et al.*, 2000). Long-latency components, as the LDAP/BRN have been reported to build up slowly, therefore the systematic manipulation of the SOA might help a more detailed investigation of the temporal unfolding of biasing activities in sensory cortices. At the same time, our categorical manipulation of the predictive values of the cues (maximal for the valid trials, null for the neutral ones), enabled a reliable and consistent deployment of attention in the participants in our studies, during valid trials in the peripheral cueing paradigms also, thus avoiding the *inhibition of return* phenomenon even at long SOAs (500 ms). This manipulation, however, did not allow the observation of re-orienting phenomena, which has been shown to require the recruitment of the ventral attentional control system. The introduction of a small amount of invalid trials might diminish the preparatory activities in prefrontal cortex, and hamper the reliability of the attentional shifts, but it could be highly informative for the investigation of the sub-components of the attention control mechanisms, especially in combination with neutral cues and with event-related techniques, which are able to tease apart the contributions of different structures to the behavioral outcome. Furthermore, the observations reported in Chapter 7, concerning the complex interplay among response activation, selective and non-selective response inhibition and attentional switches deserve further investigation: the interpretation of the relation between electrophysiological components and behavioral indexes was straightforward, but the characteristics which drove the group differences remained unclear.

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