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THE SPATIAL REPRESENTATION OF TIME

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Ai miei nonni,

che mi hanno insegnato il significato di

semplicità, dedizione ed equità.

“….il tempo e lo spazio svaniscono come ombre

quando sono considerati entità a se stanti,

e solo l’unione tra i due ha un’esistenza oggettiva.”

Hermann Minkowski, 1908

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INTRODUCTION

Time is a dimension which permeates the whole human existence. We cannot avoid to perceive its passage, to count and measure it. The struggling question “What is time”, was born together with the fundamental human questions “who are we”, “where are we from”, “where are we going”, but its eternal trait has not provided an answer yet. Indeed, the nature of time slips out of our hands, we don’t know exactly what it is so, as the philosopher Saint Augustine taught, we cannot formulate a right definition of time.

Before Science coming, the complex nature of time have been one of the main topics of religions. Religions have different points of view regarding the birth of universe, the meaning of human existence and god countenances. However, they all conceptualize time as a dimension created by god in order to beat and define the passage of every singular human life on earth, underling that time is an inner component of human being. This concept of time as a fundamental property of human essence has been inherited by philosophers, who discussed for centuries about the nature and the meaning of time. Heraclitus, who in the VI century a.C. stated that “everything flows”, and the milestone Aristotle (IV century a.C.) who defined time “the measure of movement depending on before and after”, introduced that time function is to order in one direction our soul stream. In a similar vein, Hobbes in the 1655 identified time with “succession” and Kant, in his “Critique of Practical Reason” (1788), specified that the succession forced by time is the only empirical criterion for the effect of causality. Of course this is not the right place for an expansive discussion on the philosophical concepts of time. However, it is worth noting that Philosophy, during its evolution has renounced to the question “what is time”, trying to answer which are the main features of time. As evident in the citation above, there is one relevant feature of time conceptualizations which crosses throughout story of Philosophy: the linearity of time.

Mechanical Physics has been the first science which tried to dominate time, treating it as a simple parameter to apply to the study of physical phenomena. For three centuries after Galileo, Physics had followed the schema of reversibility of time: if we have a system in which the parameter of time assumes increasing values for the unfolding of a phenomenon, applying decreasing values to the time parameter, the system must retrace the same backwards step and return to the initial state. But in the 1868, Carnot shocked classical Physics demonstrating that time is not reversible. For example, in the reverse passage from kinetic to thermal energy, even if we had a perfect machine that does not disperse energy, we cannot reach the initial state. Physics has been revolutionized by the concept of time: time is not reversible, but is linear and follows only one direction, from before to after. Moreover, time is not that simple parameter and its study deserves more attention. Only in the XX century the time dimension became the most important topic of study for the physicians. Also Physics, similarly to Philosophy, did not pretend to answer the question “what is time”, but to discover and describe the features of time. Thank to Albert Einstein and his precursory Minkowski, today we know that physical time is represented as a linear arrow with one direction and that time is deeply related to space, rather, they are almost the same dimension. To Einstein the Universe itself, and everything existing in the Universe is made up of a spatial-temporal tissue.

The study of time perception in Neuroscience domain is relatively young and started the last century. Neuroscientists did not wonder about the metaphysical nature of time, but they focus on how the brain perceives the passage of time, which are the cortical systems implicated in this process and which factors influence it. There is a very large number of studies that addressed those questions, providing several paradigms, results and models that will be discusses later in the present dissertation. However, following a similar ontogenetic evolution to that of Physics, Neuroscience in the recent two decades focused on discovering and describing the features of time and particularly how the passage of time is represented in the brain. Not surprisingly, we discovered that time is represented in the brain with spatial features, such as a linear arrow having one direction and that for the brain time and space are very deeply related as in the Physical Universe.

The present work, would like to be a depth dissertation on the spatial characteristics of the cognitive representation of time and on the tight link between the temporal and spatial cognition in the brain. The exposition will start with a comprehensive description of the principal cognitive models of time processing and cortical networks implicated. Then, it will keep on with the current knowledge on the relationship between time and space cognition. Moreover, the present work provides an outline of nine experiments describing the mechanisms and neural correlates implicated in the spatial representation of time. Finally, with a neuropsychological approach, we will present evidence for the pathological and rehabilitative expressions of the spatial representation of time.

CHAPTER 1. THE PROCESSING OF TIME

1.1 Cognitive models of time processing

In the 1985 Michon and Jackson defined psychological time as "...the conscious experiential product of the processes which allows the (human) organism to organize itself so that its behaviour remains tuned to the sequential (order) relations in its environment". In other words, this definition means that psychological time is related to cognitive and physiological processes which are adaptively synchronized to the linear passage of time. Before this late definition of subjective time perception, François (1927) and Hoagland (1933) had found a relation between the ability to subjectively perceive the passage of time and physiologic variables, like body temperature. This suggested the existence of an internal mechanism for time processing, which regulates cognitive and physiological time, similar to an internal clock. The idea of an internal clock subtending mental time, allowed Triesman (1963) to formulate the first cognitive model of time processing. To Triesman it was formed by a "pacemaker", which sends pulses to an "accumulator", where pulses are collected. Furthermore, a "Reference Memory" stores experienced time durations as sample time values, and a "Comparator" compares accumulated pulses with stored durations in reference memory.

The Triesman's model has been resumed more recently by Gibbon and colleagues (Gibbon et al., 1984), who added many experimental evidences and cognitive implications. This model, called Scalar Expectancy Theory (SET theory), framed in the Human Information Processing theory, is the most accredited one for time cognition. According to SET theory, time perception follows the general rules of perception of other dimensions. Particularly, for classical Subjective Psychophysics, perception of any dimensions such as brightness, loudness, motion detection and time also, follows the Weber’s law stating that the discrimination between two stimuli increases linearly with their intensity. A property that derives from this law is the scalar property that gives SET its name: as the interval “t” to be judged varies, the variability of judgements around “t” varies. This implies that the standard deviation of judgements is a constant fraction of the mean. In other words, the coefficient of variation (SD/mean) remains constant as “t” varies. The fact that time perception is a function that can be studied based on psychophysics of general perception, reinforced the hypothesis of an internal psycho-physiological system deputed to time.

The **principal level** of the SET system is the **clock** consisting of a pacemaker-accumulator. A pacemaker creates "ticks" or "pulses", which are gated, with a constant period, via a switch, to an accumulator which collects them. To time a stimulus of some duration, the switch is closed by stimulus onset, allowing pulses to flow to the accumulator, and at the end of stimulus period, the switch opens again, cutting the pacemaker/accumulator connection. At this point, since pulses have been sent with a constant period, the accumulator contains a number of pulses which corresponds to the duration of the stimulus, considered as the first raw representation of stimulus time, that will be cognitively processed in the next SET levels. Indeed this "raw" representation of the duration of the stimulus is transferred by the accumulator to a "short-term or working memory" for time, at the **memory level**. At the memory level there is another component, the “long term memory store” (reference memory), considered to contain "important times" such as, for example, standard durations used in temporal tasks. Finally, there is a **decision level** (called also comparator level), where the usual comparison is made between a sample drawn from the reference memory of the standards appropriate for the task, and the contents of working memory (See Figure 1).

Figure 1

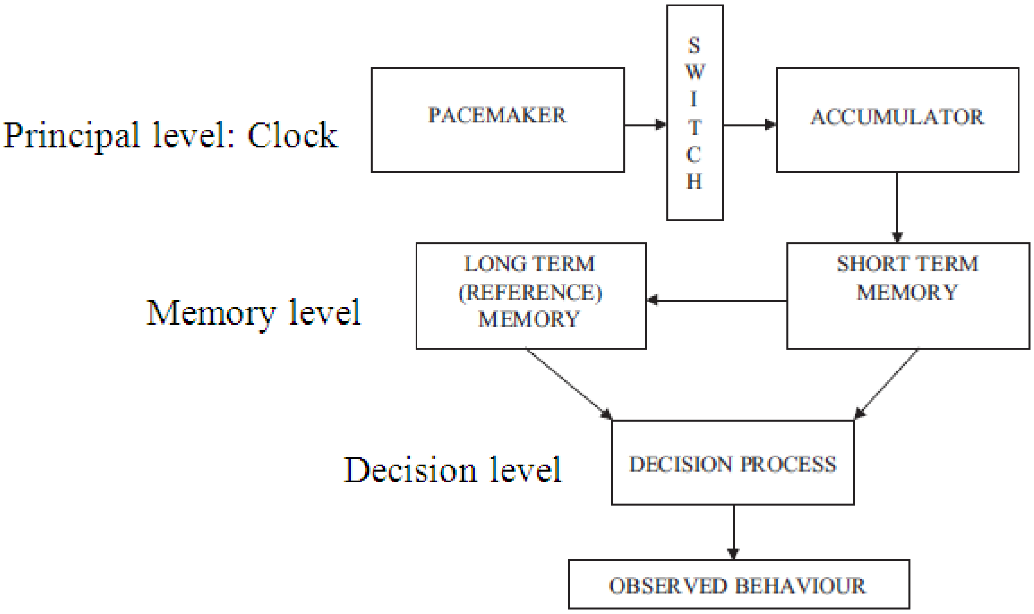

Fig. 1. Schematic representation of the Scalar Expectancy Theory (SET) system. The upper level (principal level) shows the pacemaker-accumulator clock, the middle level (memory level) the long-term reference memory and the short-term working memory, and the lowest level shows the decision level.

SET theory is supported by a very large body of evidence and it has been applied to animals (Church and Guilhardi, 2005; Church and DeLuty, 1977), human adults (Pouthas, 2005; Rammsayer, 1997) and children (Droit-Volet and Wearden, 2001; Droit-Volet and Rattat, 2006). The experimental paradigm used to prove the validity of SET is time bisection. In bisection tasks with humans, participants initially receive repeated presentations of two standard stimulus durations (identified as short and long standards) and then classify a range of probe durations (short and long, as well as intermediate stimuli) in terms of their similarity to short and long standards. This kind of paradigm assures that the probe durations presented, are compared to standard durations stored in the reference memory before the decision process occurs for a behavioural response.

The usual method of presenting data from such a task is to derive a psychophysical function consisting of the proportion of “long” responses plotted against stimulus duration. In this way, different psychophysical functions of the proportion of “long” responses derived from different experimental manipulation can be compared. For example, with this method, Droit-Volet and Wearden (2001) compared the timing performance of children aged 3, 5 and 8 years in order to study the relationship between time processing and cognitive development. They found that all children showed increasing proportions of “long” responses with increasing stimulus duration indicating that all three groups of children performed the task properly. But, the psychophysical functions were flatter in the younger children (3 and 5 years old) than in the 8-years-old children (Figure 2).

Figure 2

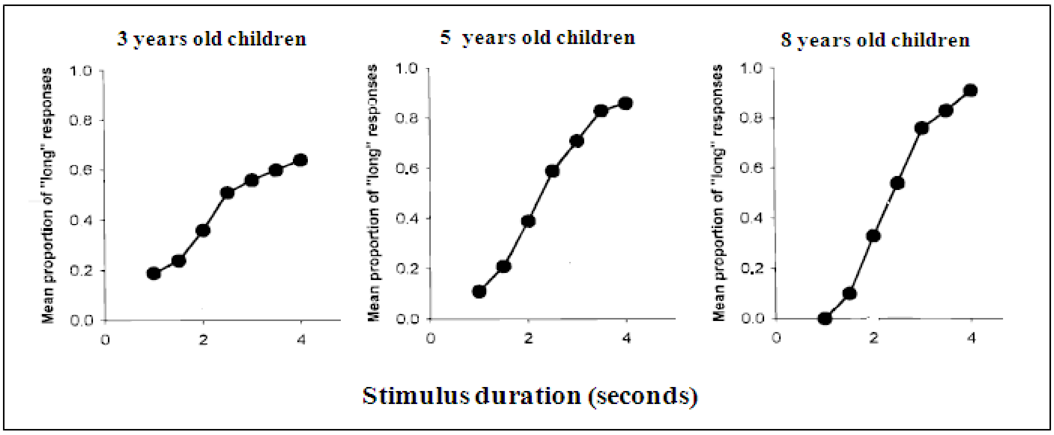

Fig. 2. Mean proportion of “long” responses plotted against stimulus duration (in seconds). Left panel: data from the 3 years old children; centre panel: data from the 5 years old children; right panel: data from the 8 years old children.

Since the steepness of the function is an indicator of the sensitivity to time, Droit-Volet and Wearden concluded that the sensitivity to time durations growths with cognitive development. Another way to analyse data within the time bisection paradigm, is to calculate a so called bisection point. This corresponds to the subjective medium point of durations distribution, giving rise to 50% of “long” responses (Wearden & Ferrara 1995; Allan et al., 2002; Kopec & Brody, 2010). However, the objective medium point of the durations distribution (the middle duration), unlike the short and long intervals, is not repeatedly presented in the initial phase of the task so that its representation is not stored in the reference memory. Thus, the bisection point provides a measure of the subjective mental representation of that duration that can be compared to the objective one, or can be experimentally manipulated. For example, in another study, Droit-Volet and Wearden (2002), found that a train of “clicks” preceding the duration to be judged by participants, changes the bisection points relative to a condition without “clicks”. This result was interpreted as a change in the subjective time perception due to the train “clicks” manipulation.

It is clear from this exposition that SET is a rather complex multi-process model. Despite a first representation of stimulus duration is already formed in the first level (in the accumulator), it needs more cognitive processes for the observation of a timing behaviour. Moreover, when we submit a participant to a timing task, according to SET, we must consider the observed behaviour as reflecting underlying clock processes only indirectly. Different conditions and different participant groups may produce different behaviours not because their "raw" timing (i.e., clock) processes differ, but because of differences in memory and decision mechanisms (Wearden, 2004). This importance of cognitive components integrity (memory and decision) in the processing of time has been recently supported by the identification of cortical mechanisms specialized for the encoding of stimulus duration, that will be described in the next paragraph (Gibbon, Malapani, Dale andGallistel, 1997; Leon and Shadlen, 2003; Lewis and Miall, 2003a, 2003b; Pouthas, 2005; Rammsayer, 1997; Rao, Mayer and Harrington, 2001). For this reason today, time processing, is recognized as a fundamental topic for Cognitive Neuroscience.

This recent interest in cognitive time processing gave raise to alternative models which agree with SET theory for the involvement of processes such as memory, but that differ from the principal model challenging the idea of a clock level. For example, one model, called *state-dependent networks model* (SDNs) assumes specific neuronal system properties for encoding time not related to a pacemaker. Especially, it proposes that neural circuits are inherently capable of temporal encoding as a result of the natural complexity of cortical networks coupled with the presence of time-dependent neuronal properties (Karmakar and Buonomano, 2007; Buonomano and Merzenich, 1995; Buonomano, 2000; Maass et al, 2002). Another model, the *multiple time-scale theory*(MTS) proposes that the memory decay processes are the central mechanisms for time perception (Staddon et al., 1999). A similar recent attempt was that of Eagleman and Pariyadath (2009), postulating that the amount of energy spent during cognitive processing defines the subjective experience of duration.

Though numerous theoretical systems formulated to explain time processing function, the model which received the major consensus and empirical evidence is SET theory and in the study of time proposed here, we will refer to that frame.

1.2 Neural correlates of time processing

Over the past decade, numerous studies (Gooch et al., 2010; Ivry and Spencer, 2004; Bueti et al., 2008; Smith et al., 2003; Harrington et al., 1998; Rao et al., 2001; Hinton and Meck, 2004; Jech et al., 2005; Koch et al., 2005; Koch et al., 2008), have been implemented to understand neural basis of time perception according to SET model. A wide circuit comprehensive of different cortical and subcortical areas has been implicated as key parts of the neural timekeeping mechanism, where every area would undergo a specific component of the model. Indeed, the identification of a brain circuit and not of a specific area for time, is an indicator of the complexity of this function and reflects the complexity of the subtended cognitive model. Following SET schema (Figure 1, para 1.1), neural basis will be exposed starting from the clock level to the decision level.

Because of their structure similar to an oscillator, **basal ganglia,** and specifically the dopaminergic system, have been identified as the locus of the pacemaker function: the **clock**. The results of recent experiments have demonstrated that the activity of striatum and its afferent projections from the substantia nigra pars compacta (SNPC) is necessary for several temporal tasks such as temporal production and temporal estimation (Clarke et al., 1997; Dallal and Meck, 1993; Matell et al., 2000). In these studies, rats with lesions of the striatum, or selective dopaminergic lesions of the SNPC, are impaired in regulating their responses relative to the amount of time elapsed. Pharmacological data also suggest strong basal ganglia involvement in timing processes. Administration of dopaminergic drugs administered systemically (Matell and King, 1997; Matell et al., 2004; Meck, 1983, 1996), or directly into the anterior portion of the striatum (Neil et al., 1978) alters the speed of interval timing processes. Indeed, all these researches show that dopaminergic agonist (e.g., methamphetamine or cocaine) make subjects responding earlier in time (intended as a speeding up of time velocity) than under control conditions (Matell and King, 1997). An opposite pattern (responding later in time than controls intended as a slowing down of time velocity) occurs following dopaminergic antagonist administration (e.g., haloperidol) (Neil and Herndon, 1978). These results of a predictable effect of dopaminergic activity on time processing, are compatible with the idea that this system regulates the functionality of the internal clock. Indeed an increase of dopaminergic activity makes the clock to run faster than normal, whereas a decrease causes the clock speed to slow down. Further evidence comes from the study of patients with Parkinson's desease (PD). Alterations in temporal estimation have been observed in PD patients and have been associated with basal ganglia and dopaminergic dysfunction in these patients. Pastor et al., (1992) found, for example, that patients with PD underestimated the duration of an interval relative to aged-matched healthy controls. Moreover, the administration of dopaminergic medication (levodopa) significantly reduced absolute errors in time estimation and reproduction, suggesting that dopaminergic system is crucial for time perception. In line, Koch and colleagues (2004), demonstrated that by a sub-thalamic electrode implantation that stimulates the striatal system, the alteration of time perception is attenuated in these patients similarly to what happens with dopaminergic agonist administration. So far, Parkinson patients have been studied to confirm that basal ganglia support the function of the clock level of SET, that is known as the physiological low-level component of such a cognitive model.

However recent studies reported that PD patients are impaired in time not only for an altered velocity of the clock system but also because of cognitive alteration in the processing of time. In their study, Koch and colleagues (2008) demonstrated that PD patients are not impaired in time tasks when intervals are in the millisecond range, but only when time intervals are in the second range, considered as the range of cognitively controlled time (Lewis and Miall, 2003). Moreover, the deficits in time estimation were found only when the different time intervals were tested in separate sessions and patients have to recall the duration of a given interval previously learned. This suggests that PD patients are impaired in time tasks requiring cognitive processes such as memory and attention. This cognitive impairment of time processing in PD patients, is not in contrast with a role of basal ganglia in the clock function, but suggests that clock mechanism is tightly related with the other cognitive components of the model. Basal ganglia, may support the low level function to count time, but for a correct time behaviour they needs to interact with cortical areas. In support, in one recent fMRI study, Coull et al. (2004) asked participants to modulate their attention to time or color while measuring blood flow. When attention was directed to color, activity increased in visual areas of the occipital cortex, but when attention was directed to time, activity increases in the *supplementary motor* areas, *dorsolateral prefrontal cortex* and *temporal* and *parietal cortices*. This work suggests a wide **cortico-striatal network** for time, where striatum would be the clock that beats and counts time passage, while its projections to cortical structures support the cognitive component of SET model. The following presentation of several studies showing the different roles of cortical areas in the cognitive time perception, support this suggestion.

It could be surprising that **supplementary motor area** (SMA), which is a key area for the motor system, is also involved in cognitive processing of time. However, there is a large piece of evidence that this is the case. This area receives important inputs from the basal ganglia through thalamic relays. In line with motor implication of this area, it has been shown that the SMA is activated in musicians while they tap different rhythms with each hand (Lang et al. 1990), suggesting that SMA is important for motor timing. There is now an open debate on the role of SMA on cognitive time. Two recent reviews of brain imaging in the context of time processing provided different conclusions concerning the motor and/or cognitive role of the SMA in time. On one hand, Lewis and Miall (2003a) proposed that the SMA is involved mainly in motor timing in the sub-second range, whereas ‘‘cognitively controlled’’ timing involving supra-second intervals mainly relies upon prefrontal and parietal areas. On the contrary, Macar et al. (2002) pointed out that the SMA and its striatal connections, are involved in cognitive as well as motor time. Indeed, as Macar and colleagues state, SMA activations have been found in relatively complex temporal tasks requiring controlled attention and in any temporal range. This discrepancy between the two reviews, largely comes from the method that the two sets of authors used to analyse the relevant studies. However here we will try to find a point of agreement between these two perspectives. Beyond its involvement in motor tasks, activation of the SMA is typically found in tasks requiring to exert a defined level of force, pressing a key, with a right index finger flexion (Dettmers et al., 1995; Kuhtz-Bushbeck et al., 2001). Similarly activation of the SMA is typically found in tasks requiring to produce a defined duration (Brunia et al., 2000; Rubia et al., 1998). Since, both force and time are two dimensions that extend along a continuum, one can postulate that SMA is essential to encode any continuous dimension. In the time processing SMA may subtend the role of accumulating in a continuous way, temporal pulses sent by the pacemaker. Recently, Wencil et al. (2010) addressed this question. Authors implemented an fMRI study in order to separate the different components of SET model by using a temporal discrimination task in which intervals durations varied parametrically. The assumptions were that: 1) activations linearly related to duration being timed support the clock/accumulator component, 2) activations related to the quality of performance (i.e., % correct) support the comparator/decision making components, and 3) activations related to the presentation of duration to be timed are tied to attention to time. SMA activity was found linearly related to the duration being timed suggesting that this may be the locus of **accumulator** function. This finding reconciles the two opposite positions on the SMA involvement in motor and/or cognitive time described above (Macar et al., 2002; Lewis and Miall, 2003a). Indeed, since this area would be responsible of the accumulating function of the clock, it is probably engaged for any sort of duration to be timed regardless its range (milliseconds, seconds, etc) and regardless task demands (motor or cognitive). Basically, our purpose is that the SMA involvement in time, would be a central step between the physiological pacemaker and higher time processing levels, whatever motor or cognitive. Its function is that of accumulating discrete pulses and probably that of shaping the first “raw” representation of a continuous time interval.

Differently from SMA, the role of the **dorsolateral prefrontal cortex** (DLPFC) in time, is well established. The DLPFC, especially in the right hemisphere (r-DLPFC), is associated with the **memory level** of SET model and, peculiarly, with **working memory** functions. In humans the r-DLPFC is located in the middle portion of middle and superior frontal gyri (Brodmann areas 9, 46) (Rushworth and Owen, 1998). This part is strongly associated with working memory per se as widely demonstrated by neuroimaging data (for a review see Wager and Smith, 2003). Moreover, it has been shown that the r-DLPFC is activated in cognitive time tasks more frequently than any other brain area (Lewis and Miall, 2003a,b; 2006a,b). Behavioural evidence that working memory and time measurement might draw upon the same cognitive resources, comes from dual-task studies showing interference between these two types of processing. Fortin and Breton (1995) demonstrated that both visuospatial and phonological working memory tasks disrupt timing, and the extent of such disruption is correlated with the extent of working memory load. Additional evidence linking time perception to working memory derives from the observation that both are modulated by dopamine (Matell and King, 1997; Pastor et al., 1992; Marieand Defer, 2003), implying that timing might be mediated via the same dopamine-sensitive processors as working memory. Lesions studies also support the central role of r-DLPFC to working memory in time. A case-report study (Koch et al., 2002) examined the role of the r-DLPFC in time perception. The patient, after a lesion in the r-DLPFC, spontaneously reported to have difficulties in estimating durations of events, judging them shorter than they really were. Moreover, patient showed difficulties to esteem how much time had elapsed since the beginning of some events. Koch and colleagues (2002) then submitted the patient and eight healthy control subjects to a verbal estimation task in which they had to report the duration of trials, indicated by visual markers (see Mimura et al., 2000). Patient showed underestimation for the longest interval (90 sec) respect to controls suggesting that r-DLPFC plays a role in monitoring the accumulation of pulses in the central internal clock, during the interval presentation. Indeed, if the work of accumulating pulses fails, some pulses are lost, the amount of pulses is inferior than normal and the interval is underestimated. Supporting this suggestion, in a study on healthy subjects, repetitive transcranical magnetic stimulation (rTMS) on r-DLPFC induces underestimation of time intervals (Koch et al., 2003). Koch and colleagues remarked that r-DLPFC plays a crucial role in perceiving and keeping, in working memory, time intervals during the encoding phase. In more simple words we can conclude that this area is the locus of the tracking of time passage.

Another area sometimes associated with time processing is the **medial temporal lobe** (MTL). Since the MTL is known to be the locus of episodic memory (Liang et al., 2012; Joutras and Buffalo, 2010; Eichenbaum et al., 2011; Race et al., 2011), we suppose that this area is situated at the **memory level** in the timing model with the role of long-term **reference memory store** of time events. In line, direct anatomical projection from MTL to dorsal striatum areas, involved in interval timing, was discovered (Matell et al., 2003; Sorensen and Witter, 1983). In this respect it is interesting the case study of H.M. patient, who underwent a bilateral medial temporal lobe (MTL) resection that resulted in a severe memory loss following surgery (Richards, 1973). When H.M. was required to reproduce time durations he demonstrated a systematic underestimation for durations longer than 20 seconds, interpreted as a failure to encode or retrieve the task demands (Eisler and Eisler, 2001). Moreover, hemispheric asymmetries in the effects of MTL resection on time processing, have been observed: right MTL resection often produces impairment in timing, associated with underestimation of retrospective time intervals, while left MTL resection determines overestimation of prospective time intervals (Drane et al., 1999; Vidalaki et al., 1999). The organization of the episodic events based on their meaning, is typical in MTL (Liang et al., 2012). These observations suggest that MTL would work as a store in which temporal events are ordered based on their temporal meanings: past events would be scheduled in the right MTL and future events would be scheduled in the left MTL. Despite this evidence, the right role of MTL in time is not well established and it needs more attention in the future studies.

Recently, a crucial role of **right parietal cortex** in time perception has been emphasized. Bueti et al. (2008) compared fMRI activations for time estimation task (P-perception task) and time reproduction task (A-action task). Authors presented subjects millisecond to second standard durations (300, 600, 900, 1200 ms), to be estimated or reproduced after a variable delay (1 or 8 sec) (see Bueti et al., 2008). The aim was to discover selective brain activation underlying differences in encoding a time interval to be estimated or to be reproduced. The most interesting result was the activation in right inferior parietal cortex (r-IPC) for time reproduction task but not for the time estimation task. Authors suggested that r-IPC plays a role in interfacing sensor and motor processes in time reproduction task. Regarding temporal processing, r-IPC could play a role in mediating between the central clock and peripheral motor effectors. This finding supports the suggestion that r-IPC is crucial for the representation of time intervals, useful for action. At a behavioural level, we need to perform an action at the right place in the right moment in the environment; therefore space and time have to be in some way related and integrated in our brain to lead correct movements. These recent findings about right parietal cortex in time, leads us to introduce a topic that will be deeply discuss in the further chapters: the relationship between space and time representation in the brain. For the scope of the present chapter, it is sufficient to state that when the brain needs to shape the representation of a time interval to give a time response (whatever motor or perceptual as demonstrated later), it uses a code that is spatial in nature, similar to a line (Vicario et al., 2007, 2008; Oliveri et al., 2009a,b; Frassinetti et al., 2009). Moreover, this spatial representation of time is suggested to be located in the right parietal cortex (Walsh et al., 2003; Bueti and Walsh, 2009). First of all, neuropsychological studies have shown that right parietal patients are impaired in both time and space cognition (Critchley 1953; Basso et al. 1996; Danckert et al. 2007). In their study Lewis and Miall (2006), searching for neural correlates of time processing, indicate a right hemispheric fronto-parietal network for cognitively controlled time. Parietal cortex activation had been attributed by authors to the encoding of the metric to measure time intervals. Similarly, Rao and colleagues (2001), in an fMRI study, found an activation of right dorsolateral prefrontal cortex and r-IPC in a time discrimination task. According with literature, authors explained that right DLPFC has a role in working memory, maintaining active the representation of time intervals during processing. More interestingly, Rao et al. attributed the role of r-IPC to the formulation of the representation of the time interval length. Accordingly, Maquet et al., (1996), in an fMRI study using a time discrimination task, found an activation of right IPC associated with the comparison between the length of two time stimuli. Again, Lewis and Miall (2003a) found that the activation of r-IPC was related to the temporal stimulus length. Together, these results, support the suggestion that right parietal cortex is the key area encoding the metric, known as spatially organized, of the length of time intervals. The interest to the role of right parietal cortex in the spatial representation of time is really recent, it needs more studies and it is one of the aims of the present dissertation. However, if we want to allocate right parietal cortex functions in the SET timing model we could suppose a role of r-PC at the **comparator level**, where spatial representations of time intervals are measured and compared to produce a time response.

A last brain structure that has recently received attention in time cognition, is **insular cortex**. Even though its allocation in the dominant time model is not clear yet, this area has been implicated in several time studies (Wittmann et al, 2010a,b; Lewis and Miall, 2006a, 2003b). Particularly, insular cortex would be related to the *subjective experience of time passage* (Wittmann and van Wassenhove, 2009, for a review), that is not a component included in a “cognitive” model of time. Starting from the theory by James and Lange (Ellsworth, 1994), it has been suggested that affective states as well as experienced emotions are inseparable from physiological responses (for example, cardiovascular activity and breathing patterns; Saper, 2002; Pollatos et al. 2005). Interoceptive awareness of physiological responses, tested with heart rate detection tasks, activates right anterior insula (Critchley et al. 2004; Pollatos et al.

2007). Moreover, the insular cortex of primates is considered as the primary receptive area for physiological states of the body (Craig, 2002; Saper, 2002). Moreover, a posterior-to-anterior activation of the human insular cortex is considered the anatomical basis for the sequential integration of body states and internal autonomic responses with cognitive and motivational conditions (Craig, 2003). Therefore, Craig (2008), proposed a direct link between the perception of time and physiological processes, and claimed that our experience of time relates to emotional and visceral processes because they shared a common underlying neural system: the insular cortex and the interoceptive system. He suggested that, through the temporal integration of signals from within the body, the insula provides a series of ‘emotion moments’ in time. The perception of duration would be defined by the integration of these successive moments, formed by information originating within the body (see also Craig, 2009).

In conclusion the present chapter has illustrated the current state of the art on cognitive models and neural correlates of time perception in human brain. The evidence described so far, states the existence of a model for time processing made up of several components from a more physiological internal clock beating and counting the passage of time, to a series of more cognitive components such as memory and decision/comparator processes that are normally involved also in other cognitive tasks. Indeed, studies on neural basis of time perception put in light a wide bilateral cortical-subcortical network for time processing. A fronto-striatal circuit is associated with clock functions. A fronto-temporo-parietal network, with a bias toward the right hemisphere, has a role in cognitive (memory and decision) functions in time processing.

CHAPTER 2. TIME AND SPACE RELATIONSHIP IN THE BRAIN

2.1 Behavioral evidence

It has been proposed that the processing of time and space dimension share common resources. A good way to demonstrate that time and space share common properties, is to look at behavioral interactions between them. Stavy and Tirosh (2000) studied the ability of children to judge the velocity of running trains of different size. The trains ran at the same rate and the children were well informed that the trains had the same velocity. However, subjects stated that the larger train was faster than the smaller one. This is one demonstration that the spatial feature of a stimulus (size, in this case) affected the judgment of temporal feature of the same stimulus. Similar findings were previously pointed out by Levin. Levin (1979) asked children in kindergarten to evaluate which of two lights was presented for the longest time. The lights were different for some aspects such as size. Results showed that children consistently judged the larger stimuli to have lasted for more time than smaller stimuli, again supporting the hypothesis that the processing of the spatial aspect of the stimulus (i.e. size) interferes with the processing of the temporal aspect (i.e. duration). The same interference between the processing of spatial and temporal aspects of the same stimuli has been found not only in children but also in adults. Xuan et al. (2007), asked adults to make duration judgements on stimuli that varied in non-temporal attributes such as size. Xuan and colleagues observed that temporal estimation was affected by this spatial factor: the bigger the size, the longer was the temporal estimation. Another interesting proof that temporal judgment are affected by spatial feature of stimuli comes from the study of Zach and Brugger (2008). They required subjects to make duration estimates of clock movement imagined at two distances: one in the “near space” and the other in the “far space”. Subjects reported time to run faster for the near clock than for the far clock. Since the clock to be judge was the same shifted in two different positions in space, and since the size of the clock was not corrected for visual angle based on its position, there is the possibility that this experiment tested the relationship between size and time rather than distance and time. However, all the findings reported here, confirm that a manipulation of spatial aspects of the temporal stimulus being judged, reflects on its temporal estimation, suggesting that the mechanism to encode time is dependent on the mechanism to encode space. Indeed, in the experimental context it is possible to isolate time and space asking subjects to pay attention to one of the two dimensions. But, in the everyday life it is not so simple and time and space are frequently linked between each other: when you throw a ball, grasp a cup of tea or wait for the train to go on vacation, you need to know both the right place and the right time to perform your activities. If you go at the right station but in the wrong moment of time, probably you will miss the train and your trip. Therefore, there is reason to think that the brain has developed a common system to encode space and time.

2.2 Neurophysiological evidence

The study of the brain at a physiological level also supports the tight interaction between space and time dimensions demonstrating that they rely upon the same neural mechanisms. The **parietal cortex** is the principal brain area suggested to support the role of linking space and time. In a recent study on healthy subjects Oliveri et al., (2009a), found that the application of inhibitory transcranial magnetic stimulation (TMS) on right posterior parietal cortex (rPPC) induced a bias in setting the midpoint of a temporal interval and a similar bias in setting the midpoint of a spatial segment. With a similar intent, Alexander and colleagues (2005) used inhibitory TMS on healthy subjects while performing a temporal judgment task. They found that the disruption of the right inferior parietal cortex (rIPC), and not of the left IPC or the vertex, significantly impaired the performance in the temporal task. Alexander and colleagues, remembering that the right parietal cortex integrity is fundamental for space perception (Critchely, 1953) and that it is the main locus of multimodal integration, suggested that both time and space requires multimodal algorithms that are integrated in the right parietal cortex. The multimodality of parietal cortex and its involvement in space-time interaction, has been also underlined in animals studies. In a pioneer research, Onoe et al. (2001) submitted monkeys to a temporal discrimination task while scanning with PET. They observed duration-related activity both in the dorsolateral prefrontal cortex and in the inferior parietal cortex. Interestingly, it was suggested that temporal information in parietal regions "may be coded in neurons with multiplex properties and/or in cell assemblies with overlapping connections in the same region". In other words, this expression states that the temporal information is encoded by neurons which encode also other kinds of information. In a following study, Leon and Shadlen (2003), investigated more deeply the role of parietal neurons in encoding time and its overlapping with other parietal encoding functions. They recorded the activity of cells in the lateral intraparietal area (LIP) of rhesus monkeys during a temporal judgment task. Animals were trained to report whether the duration of a light was longer or shorter than a standard duration previously acquired. To give their response, the animals had to make an eye movement to a green target, in one of the two visual field, if the choice was short, or to a red target, in the other visual field, if the choice was long. Results showed that the representation of elapsed time in the LIP neurons approximates the fidelity of the monkey's timing behavior. This means that the timing behavior observed is based on the discharge of these neurons. The importance of parietal cortex in time perception was not new in literature (Harrington et al., 1998; Onoe et al., 2001; Rao et al.,2001; Schubotz et al., 2000). What is of particular interest in this study is that LIP is frequently associated to the allocation of spatial attention (Colbyand Goldberg, 1999) and to the planning of eye movements (Andersen, 1997; Mazzoni et al., 1996; Snyder et al., 2000). For this reason Leon and Shadlen suggest (see also Walsh, 2003a) that neurons of LIP area are both spatially selective and temporally selective. Moreover, further spatial functions, LIP area is also associated with formation of decisions (Shadlen and Newsome, 2001). The Leon and Shadlen task's was also built to verify how LIP neurons are related to temporal decision. Indeed, time has a direct influence on the importance of the visual field containing the target of the right choice (short or long). As time passes, the short-choice target becomes less important than the long-choice target. In accordance with this explanation, neurons in LIP encode and measure time information in order to allocate attention, plan a future eye movement and formulate the monkey's decision to choose one or the other target. This speculation is also in line with our assumption, expressed in the chapter 1 para. 2, on the role of parietal cortex in time processing. We allocated this area at the level of the comparator of SET model, with the function of representing time length in order to compare it for a decision in the timing behavior. A further information by Leon and Shadlen work is that, the comparator function in the parietal lobe overlaps with neural spatial mechanisms.

2.3 Neuropsychological evidence

Before the study of behavioral and neural interactions between space and time developed, classical Neuropsychology had pointed out that brain damaged patients after a lesion of the **right parietal cortex** often reported the association between spatial and temporal deficits. About spatial deficits, after a lesion of this area neglect syndrome is frequently described. Neglect patients show a deficit in orienting spatial attention toward the controlesional space (i.e. the left hemispace) and a severe attentional bias toward the ipsilesional space (i.e. the right hemispace) (Husain and Rorden, 2003; Mesulam, 1999; Driver and Mattingley, 1998). Early in the 1953, in his famous book on the parietal lobes, Critchley underlined the importance of this area not only in space cognition, but also in linking space and time. Particularly, Critchley noted that parietal lobes were fundamental in the understanding of the chronological order of time events. In other words, this brain region has the function to shape to time information. Further neuropsychological studies have confirmed that the right parietal lobe, plays an important role in discriminating events that are displaced in time. Rorden et al. (1997), examined two patients with left-sided visual extinction after right parietal damage. Patients were submitted to two different tasks. In the first task two bars were presented, one in each visual field, and patients were required to judge which appeared sooner than the other one. In the second task one continuous line moving was presented in the same spatial portion, and patients were required to judge which direction the line moved in. The patients performed wrong only in the first task underlining that right parietal lesions impaired the ability to temporally order separate events but not motion perception. Another single case study by Dove et al., (2007), reported an abnormal temporal order judgment in a patient with right parietal lesion and unilateral spatial neglect. This evidence support the role of right parietal lobe in ordering temporal events as suggested by Critchley (1953). Temporal order judgment is a task frequently used to investigate the integrity of the spatial attention system. Indeed, perceptual temporal order judgments require an individual to determine the relative timing of two spatially separate events (Davis et al., 2009) and a correct performance is, to some extent, dependent on the ability to allocate spatial attention to detect the targets. For this reason one could claim that patients with neglect described so far, have not a real temporal deficit but a mere spatial attention deficit. However, a large body of data have provided evidence of temporal deficits in neglect patients, by using different paradigms . Basso and colleagues in the 1996, moved the first step toward a comprehension of pure time processing deficits in a patient with neglect, trying to understand the patient's timing performance in terms of SET model (Gibbon et al., 1984, see chapter 1, para. 1). Basso et al.'s patients showed a tendency to overestimate time intervals when stimuli were presented in the neglected space (the left hemispace). In the frame of SET theory, authors interpreted this time overestimation as a consequence of reduced attentional resources for the affected space. In this way resources available to the clock processes in the neglected space are increased resulting in a greater number of pulses in the time units reflecting in a overestimation of time. In a more recent study, Danckert and colleagues (2007) reinforced the idea that spatial neglect syndrome has an impact on time processing. They examined a group of neglect patients compared with a group of right brain damaged patients (RBD) without neglect and a group of healthy controls (HC). All subjects had to estimate the time of an illusionary motion stimulus presented on the center of the computer screen. Neglect patients showed greater underestimation of time intervals compared to both RBD patients and HC. Authors interpreted their result, suggesting that time impairment is an epiphenomenon of the neglect syndrome.

In the present chapter a wide body of evidence has been presented, supporting that space and time cognition interacts in the brain and that this interaction primarily engages right parietal region. This exposition leads us to introduce the main topic deeply discussed in the next chapter. All those findings have been collected and unified under a theory which assumes that the brain has developed a common system to encode space and time and that this system is cortically located in the parietal lobe

(Walsh, 2003; Bueti and Walsh, 2009). For this theory, time and other quantities (such as brightness and numerosity) are encoded with a spatial code, the same used to encode the mere space. This theory can explain the interferences between spatial and temporal tasks and the overlapping of spatial and temporal selective neurons in the parietal lobe. Moreover, this theory, suggesting that the brain encodes time as spatial information, also explain why time processing is affected in patients with spatial cognition impairments.

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CHAPTER 3. THE SPATIAL METRICAL SYSTEM FOR TIME REPRESENTATION

3.1 A theoretical view

In the previous chapter it has been mentioned a theory which unifies all evidence about the interaction between space and time in the brain. This theory is called “A Theory Of Magnitude – ATOM theory” and it was formulated by Walsh (2003) and revised later by Bueti and Walsh (2009). The theory assumes that space, time and also any other kinds of quantity, such as numbers, are part of a generalized magnitude system, located in the parietal cortex. In other words, the parietal cortex would work as a metrical map whenever a quantity needs to be measured, regardless quantity domain (temporal, spatial, numerical). The same metrical map used to measure all quantities would have a spatial nature, with the aim to give a spatial shape and a spatial order to the dimension being measured, to allow the quantification process. Bueti and Walsh focused on the representations of space and time, to explain why the brain has developed such an economical system of map representation in the parietal lobe. Temporal and spatial information needs to interact in everyday life and particularly for action: if you throw, point, reach or attempt to grasp a moving target, you need to estimate space and time accurately. “In other words, space and time are coupled metrics for action and it would be very surprising if they were not in close proximity in the brain and close to the areas required for performing sensory-motor transformations for action, i.e. in the parietal lobes” (Bueti and Walsh, 2009). They then conclude that the parietal cortex would be equipped with an analogue system that computes the process “less than - more than”, “slower – faster”, “nearer – farther”, “smaller – bigger” useful for action. However, even if the brain develops this unique map for quantities by and for action, there is not any reason to develop another map system for other brain functions.

3.2 The spatial representation of time and spatial processing

The theory exposed gave rise, in the last decade, to a number of researches addressed to the study of the spatial code to represent time dimension. All the studies provide results suggesting that time intervals are represented via a spatial line, called Mental Time Line (MTL), with ascending order from left to right, that is, that shorter intervals are represented to left of longer intervals.

Vallesi et al. (2008), trained healthy subjects to look at a central cross fixation lasting for a “short” period of 1 sec or a “long” period of 3 sec. Then, under several conditions, subjects have to press a left or right key if they have seen the “short” or “long” period. Subjects were significantly faster and more accurate in responding to the short period pressing the left key. By contrast, subjects were also faster and more accurate in responding to the long period pressing the right key. This pattern of results supported that elapsing time is internally mapped onto a spatial representation and associated with spatial properties of motor response, with a short-left long-right order. A similar representation of time has been demonstrated not only for durations in the second range, but also for temporal metaphor concepts. In a recent study by Ouellet et al. (2010), the results showed that the mere activation of the past or future concepts, by visually projected words, primed motor responses to left or right space, respectively. Similarly, Torralbo et al. (2006), showed that when participants are asked to give a left-right manual response, they activate a left-past right-future representation of time. In another study, Santiago et al. (2007), found a facilitation effect when subjects had to respond past words with the left hand, whereas the opposite was true for future words.

Again, more recently, Santiago et al. (2010), extended their analysis on this left-right space-time congruency effect to meaningful event sequences presented by means of movie clips or picture sequences. Order judgments between two events were faster when subjects responded “before” with the left and “after” with the right hand. All the experiments described, have used visual stimuli to prove evidence for a directional representation of time that primes spatial motor responses. There is also evidence that this is the case for auditory stimuli. In the study of Ishihara et al. (2008), young healthy subjects listened sequences of auditory clicks, separated each other by an “inter-onset-interval” (IOI). After that, they had to judge if the last click (probe click) was earlier o later than the expected critical IOI, pressing a left or right key. Results showed that reaction times (RTs) for early onset timing were shorter than those for late onset timing in left-side responses, and vice versa in right-side responses. This proved that “early” auditory events were associated with response in left space, whereas “late” auditory events were associated with response in right space. In a very recent work, similar data have been obtained with past and future words auditory presented (Kong and You, 2011).

In sum the studies presented, indicating a tight relationship between the left-right representation of time and motor response in space, support the thesis of Bueti and Walsh, of a coupled spatial-temporal metric for **action**. However there is evidence supporting that this metrical interaction between time and space occurs also in the absence of action and at other levels of spatial cognition. For instance, Vicario and colleagues (2008) found that the duration of visual stimulus is underestimated when it is presented in the left space and overestimated when it is presented in the right space, proving that **encoding the spatial location** of visual stimuli interferes with the duration processing. In another study, Vicario et al. (2007) showed that a directional optokinetic stimulation biased time perception in a left-to-right manner: rightward optokinetic stimulation induced an overestimation of time perception compared with baseline and leftward optokinetic stimulation. Since optokinetic stimulation is known to induce a shift of **spatial attention**, this finding suggests that also this spatial function is related to the spatial representation of time.

Despite a huge literature describing the spatial representation of time and its relationship with spatial cognition, a lot of aspects of this intriguing interaction remain unknown. The present thesis is addressed to the study of such interaction, as exposed in details in the “Open questions and thesis overview” chapter (5). Especially the mechanisms, the neural correlate and pathological expressions of the relationship between time representation and spatial attention will be investigated. To address our questions we implemented a series of experiments in which we investigated the effects of spatial attention plasticity on time representation with different paradigms and approaches. To induce changing in spatial attention plasticity we had taken advantage of a well known technique called Prismatic Adaptation that will be described in detail in the next chapter.

CHAPTER 4. PRISMATIC ADAPTATION AND SPATIAL ATTENTION PLASTICITY

4.1 Prismatic Adaptation procedure

Prisms are particular lenses mounted on goggles that induce a shift of the visual field (Figure 3).

Figure 3

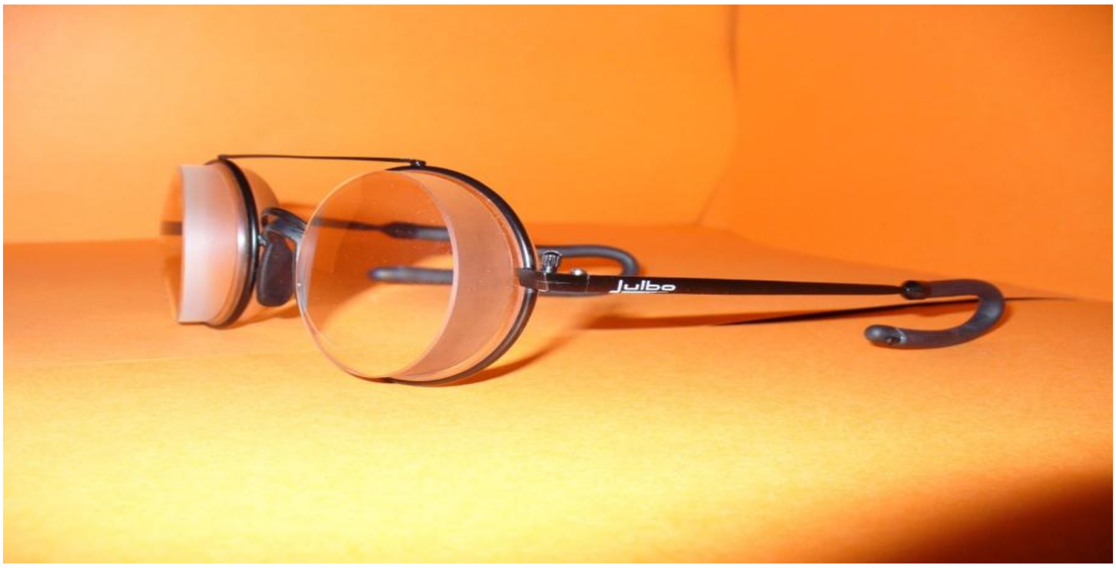

Fig. 3. Picture representing an example of prismatic goggles which induce a shift of the visual field toward the right.

During **prismatic adaptation** (PA), subjects are required to perform a manual pointing task, while wearing prismatic lenses: they have to point, extending the superior arm, as accurately and faster as possible, towards a visual target stimulus, presented by the experimenter in different spatial positions. In the first trials of PA, pointing deviation towards the side of the visual shift, induced by prisms, is visible. After few trials, this displacement is gradually reduced (error reduction, ER), until subjects point exactly towards the stimulus: this means that subjects “are adapted” to the displacement of visual field induced by prisms. This pointing deviation, in first trials, constitutes the direct effect of PA. The reduction of this error in pointing deviation is due to a short-latency process activated by the discrepancy between the real position of the target stimulus and the position of the pointing movement (error feedback, Redding and Wallace, 1985). At the end of PA procedure, prismatic lenses are removed, and subjects show a pointing deviation of the adapted limb, towards the opposite side of the prismatic shift. This visuomotor bias reflects the displacement of visual and proprioceptive spatial coordinates and is called After-Effect (AE). Several studies (Serino et al., 2006; Pisella et al., 2006; Angeli et al., 2004) suggested that the AE displacement concerns not only the visuo-motor level directly involved in PA procedure, but also the spatial representational and spatial attentional level.

4.2 Prismatic Adaptation and spatial processing

Prisms effects on visuo-motor and attentional space have been revealed at a **behavioural level** in healthy subjects. In the study of Colent et al. (2000), healthy subjects were required to perform a line bisection task in manual version (they had to mark the middle of a line) and perception version (they had to judge whether a line is pre-transected to the left or to the right of its real centre). Tasks were performed before and after PA with lenses inducing leftward or rightward shift of the visual field. Results showed that adaptation to left-deviating prisms induced a strong rightward bias for the perception task but not for the manual task. Furthermore, no significant effect was found after adaptation to the opposite right-deviating prisms. Results suggested that prisms adaptation can induce an asymmetrical perceptual cognitive bias in normal individuals, only to the right, due to leftward PA. This bias is in the same direction as the bias observed in unilateral neglect. No effects on manual task were found. These evidences suggested that PA induces a shift at the level of spatial representation, and not at the primary visual-motor level. For this reason, Colent et al., suggested that PA can provide a valid simulation of unilateral neglect in normal individuals. However, the effect of the distortion of spatial representation is weaker than that shown in neglect patients, probably since an intact brain should be more resistant to manipulation than injured brain. Moreover, these asymmetrical results may reflect the inherent bias of the brain's structural organization, and provides an empirical explanation for the left-side predominance of unilateral neglect. More recently, another study provided by the same research group (Michel et al., 2003) submitted healthy subjects to the same tasks described above (Colent et al., 2000), before and after PA. Michel and colleagues wanted to establish whether the amount of the spatial bias, after PA, varied with the relative spatial location of the lines (position effect), and relative to lines' length (length effect). The aim of that study was similar to that of Colent et al., (2000): to understand whether the spatial bias, induced by PA, relies upon sensori-motor or higher cognitive mechanisms. The "Position effect" and "Length effect" are present in neglect patients (Monaghan and Shillcock, 1998; Halligan and Marshall, 1995). When lines are presented to the damaged left side of space, neglect patients show a more severe bias in bisecting lines toward the right, than for lines presented in the unaffected right side of space (position effect). Furthermore, neglect patients bisect longer lines more to the right respect to shorter lines (length effect). The presence of these effects in neglect patients suggest that neglect syndrome is not a visual-perceptive disorder, but it is a higher cognitive disorder. Indeed, if the deficit of neglect patients in line bisection would be explained by sensori-motor mechanisms, the same amplitude of deviation in line bisection tasks would be observed for line in any spatial location of lines and any line length. Based on these assumptions, Michel et al.'s group implemented a research in two experiments to investigate in normals the efficacy of PA in inducing this two "neglect-like-effects". They used the same manual and perceptual line bisection task of Colent et al. (2000). However, in experiment 1 lines were presented in 3 possible positions (on the left, middle and right side). In experiment 2, the length of a single line, presented straight-ahead, was varied. The hypothesis were that, if the bias, due to PA, was explained by sensori-motor mechanisms, it would be observed the same amplitude of deviation in line bisection tasks, regardless of spatial location of lines and line length. Moreover, the same amplitude of deviation in line bisection task would be observed both in manual and in perceptual bisection task. By contrast, if the bias, due to prismatic adaptation, was explained by higher level mechanisms, the amplitude of the deviation in line bisection task should be influenced by spatial location of the line to be bisected (position effect), and by line length (length effect). Finally, the deviation in line bisection would be observed mainly in the perceptual task respect to the manual task. In Experiment 1 results, after PA, a significant rightward shift, in the line bisection, was observed both in manual and perceptual tasks for left and middle lines, but not for right lines. Experiment 2 results showed that rightward shift in the line bisection increased as a function of the length of the lines for the perceptual task; a similar, but weaker trend was found in the manual task. Authors suggested that PA effects depend on spatial location (position effect) and on line length (length effect), more in perceptual than in manual task.

Taken together, these studies (Michel et al., 2003; Colent et al., 2000) allowed us to conclude that left PA, providing a rightward after-effect, can produce neglect-like symptoms in healthy subjects. More interestingly, results also permitted to understand that spatial bisection bias, following a simple visual-motor adaptation such as PA, directly affects not only sensori-motor spatial mechanisms but also higher levels of spatial cognition.

Given the interpretation of neglect syndrome as a disorder in spatial attention and representation (Kisbourne, 1970; Halligan et al., 2003) and given the proved effects of PA on high levels of spatial cognition, it not surprising that this procedure has been revealed as useful in the recovery of neglect symptoms. Indeed, several studies have demonstrated that a single session of *PA, inducing an after-effect toward the left*, contrasts the classical rightward bias of spatial attention and spatial representation presented by neglect patients.

Rossetti et al. (1998) required neglect patients to perform classical neuropsychological tests based upon visual-spatial tasks (cancellation, copying, bisection) before and after a session of PA. The procedure consisted of 50 pointing movements for an exposure period of 2-5 min. The main result was that patients showed amelioration in all tasks for at least 2 hours after PA. Rode et al. (1998) also found an amelioration of neglect symptoms, after PA, in drawing from memory task and naming from a mental map task. Particularly, neglect patients showed an amelioration lasting at least 24 hours for the drawing from memory task. Other single-case study (Jacquin-Courtois et al., 2008; McIntosh et al., 2002) demonstrated that PA can improve spatial cognition as measured over a wide range of spatial task (e.g. wheel-chair driving), or involving different modalities (e.g. haptic exploration). Other investigations (Tilikete et al., 2001; Rode et al., 2001, 1998) reported that also posture and mental imagery can be improved after PA. Interestingly, Farnè et al. (2002) found that in neglect patients, PA, not only provides amelioration in visual-motor tasks (cancellation and line bisection tasks), but also in visual verbal tasks (object recognition, object naming and naming of word and non-words tasks). Improvement was maintained after 1-day delay from PA, and decayed after 1-week interval. Since beneficial effects of PA were seen in different kind of tasks, requiring different solving strategies, but whose common feature can be identified in the basic visual-spatial nature, authors could confirm that PA can directly influence high-order level of visual-spatial representations. PA effects may trigger or improving active processes involved in brain plasticity related to multisensory integration and space representation.

The success of PA in reducing neglect symptoms after a session was a significant finding for clinical rehabilitation of neglect syndrome. In the Frassinetti et al.'s study (2002), neglect patients were administered with a battery included classical clinical measures (Conventional BIT) and ecological visuo-spatial tests (Behavioural BIT), before, immediately after, 2 days, 1 and 5 weeks after PA. Authors also investigated effects of PA on different spatial domains, using room description task for far space, object reaching task for near space, and fluff test for personal space. Results showed a consistent improvement of neglect symptoms, equally in all tasks after PA training, lasting at least 5 weeks. Moreover, some preliminary data suggested that amelioration can last 17 weeks after the end of treatment. Significant improvements were also found in far space and near space (less evident was the amelioration for personal space). This study confirmed and extended previous findings (Rossetti et al., 1998) indicating that the process of PA is not only involved in the recalibration of visuomotor coordination (pointing task), but is also able to affect the organization of higher-level of spatial representation, such as those impaired in neglect patients. Furthermore, in accordance to previous findings (Farne` et al., 2002), PA effects extend to tests requiring visuo-motor coordination (cancellation and object reaching test), as well as tests that do not require motor response (e.g. reading test, room description test). Another interesting result was that, while neglect amelioration was fully maintained for at least 5 weeks after PA, AE lasted only 12 hours in mean. Frassinetti et al., suggested that once the mechanism responsible for neglect recovery is implemented, it continues to exert its effect after the treatment procedure is completed. Authors also could conclude that the improvement was not due to a low-order factor such a leftward visuo-motor bias (AE); indeed, PA effects on low-order functions (AE) were short-lasting (12h), while effects on high-order functions, like neglect symptoms improvement on spatial representation, were long-lasting.

Other recent studies (Serino et al., 2006; Angeli et al., 2004) set out to better understand the mechanism to account for the improvement in neglect patients, after PA. One of the most accredited theories suggests that PA improve neglect symptoms modulating eye-movements .

It is well known that neglect patients show a failure to make eye movements toward stimuli presented in contralesional side of space (Walker et al., 1996; Girotti et al., 1983; Chedru et al., 1973), and deviation of eyes towards ipsilesional side (Hornak, 1992). Moreover, the irrepressible gaze deviation towards right side of space is associated with increased time for leftward eye movements (Chedru et al., 1973). Doricchi et al. (1993-1991) discovered that, during REMs sleep, characterized by rapid eye movements, neglect patients did not show eye movements toward left. Authors suggested that neglect causes impairment in automatic gaze orienting towards the controlesional visual field, while voluntary eye movements are preserved (Niemeier and Karnath, 2000). Other authors supposed that unilateral neglect may be due to an ocular disorder that prevents from exploring controlesional side of space (Gainotti, 1993; Scott et al., 1966). In line, in another study, Meador et al. (1987) found that, in a representative task, in which neglect patients were asked to imagine the street leading to their house and to name the building on the street, recall of item lying in the left hemispace improved when patients rotated eyes on the left. Thus, this finding led to the hypothesis that the direction of eye movement can influence spatial representation.

On the basis of this hypothesis of relationships between neglect symptoms and eye movement deficit, Angeli et al. (2004) studied the amelioration of neglect patients after PA and disturbance of eye movements' behaviour (Walker et al., 1996; Hornak, 1992; Girotti et al., 1983; Chedru et al., 1973). Authors asked neglect patients and healthy control subjects to perform a reading task before and after PA. Results showed that, before PA, neglect patients had the tendency to explore more the right side of the stimulus, compared with healthy control subjects. After PA, subjects significantly improved in reading task. They showed an increased time of left side eye movements' exploration and a decreased time of exploration on the right side. Furthermore, authors found a tendency of the first saccade to land nearer the beginning of the letter string. Authors concluded that, in neglect patients, there is an asymmetrical distribution of eye movement exploration which disappears after PA, determining also an amelioration in reading task. It is assumed that the saccade's direction, which defines the direction of the fovea (site of maximum visual stimuli processing), is linked to the direction of spatial attention. The functional state of the oculor-motor system can determine specific effect on visuo-spatial attention allocation (i.e. the ability to report letters located on the left side of the string): PA can reduce the chronic oculo-motor orienting bias towards right in neglect patients, compensating this asymmetrical distribution of spatial attention. Again, Serino et al. (2006) focused their study to identify the relationship between visuo-motor effects of PA and the amelioration in a wide range of visuo-spatial attention tasks in neglect patients after PA. The aim of the study was to find out how the low-order effects provided by PA (error-reduction - ER, aftereffect - AE) can provide and predict high-order modifications on visuo-spatial-representation. Visual-spatial abilities in neglect patients before and immediately after, 1 week after, 1 and 3 months after, 10 PA daily sessions, were explored. Moreover, neglect patients were required to perform a reading task, in order to measure oculo-motor response, before and after PA. Results showed no correlation between ER and AE, suggesting that these measures reflect different processes during PA procedure. Furthermore, Serino et al. found, after PA, an increase in the first saccade amplitude towards left and in the time of exploration of the left side of the word to be read. In addition, PA effects on eye movements and neglect symptoms amelioration were correlated: patients with greater leftward first saccade deviation after PA obtained also the greater improvement in visuo-spatial tasks. Authors suggested that the increase in first saccade amplitudes towards left, after PA, produces also a shift in visual attention towards left, thus mediating neglect recovery.

In sum, the studies presented above provide evidence for an effective influence of PA on spatial representations and spatial cognition. In the present dissertation, this procedure will be used to study the spatial representation of time in a very new fashion never used before.

CHAPTER 5. OPEN QUESTIONS AND THESIS OVERVIEW

Despite the evidence on the spatial representation of time and its links with spatial cognition, a lot of questions are still open. The goal of the present thesis is to explore the interaction between the spatial representation of time and the spatial attention plasticity, adopting prismatic adaptation (PA) technique.

The first experimental part goes into the **mechanisms** underlying the interaction time-spatial attention, at a behavioural level. In chapters 6 and 7, three experiments on healthy subjects are presented to answer the question how the modulation of spatial attention affects the representation of time in normal cognition and in different sensory systems. First of all, we asked whether directing spatial attention toward a side of space by PA, time representation of visual stimuli is affected in the left-short right-long manner, suggested by literature (Vicario et al., 2007, 2008; Oliveri et al., 2009a,b). Subsequently, we investigated whether time representation of auditory stimuli are affected by spatial attention modulation as visual ones.

After the understanding of the cognitive dynamics connecting time representation and spatial attention, we focused, for the first time in literature, on the **neural basis** subtended. Chapter 8 will start with a neuropsychological study on unilateral brain damaged patients, searching for the role of left and right hemisphere in mediating PA effects on time. The chapter will keep on, with a neurophysiological study exploring the peculiar role of parietal cortices in this interactive process. The chapter will end with a neuroimaging study to best indentify which brain areas mediates the effects of PA on time.

The third experimental part also addresses an issue never explored before: the **pathology** of the spatial representation of time. In the chapter 9, first of all we asked whether a spatial attention deficit following a right hemispheric stroke impairs the function to spatially represent time. Given the wide evidence of the effects of PA in the recovery of spatial attention deficits, we asked whether PA would be a useful technique also for the recovery of time impairments. Finally, but intriguingly, we explored for the first time, the impact of temporal deficits on daily functionality and the possible effects of PA on time at an ecological level.

CHAPTER 6. THE ROLE OF SPATIAL ATTENTION IN THE SPATIAL REPRESENTATION OF TIME

6.1 Prismatic Lenses shift time perception

6.1.1 Introduction

After the demonstration of a spatial code left-to-right oriented for time representation (Vicario et al., 2007, 2008), we investigated whether spatial attention may work as a cognitive link between space and time dimensions. Neuropsychological studies in patients (Basso et al., 1996; Danckert et al., 2007) and psychophysical studies in healthy subjects (Chen and O’Neill, 2001; Mattes and Ulrich, 1998) have found a link between attention and time perception. However, other studies cast doubts on the role of attention in spatially dependent temporal illusions (Johnston et al.,2006; Morrone et al., 2005). We tested on young healthy subjects whether spatial-attention shifts, created through prismatic adaptation (PA), induce relative compression and expansion of experiential time. More specifically, our hypothesis was that PA inducing a rightward orientation of spatial attention would produce an overestimation of time intervals, whereas PA inducing a leftward shift of spatial attention would produce an underestimation of time intervals.

6.1.2 Experiment 1

6.1.2.1 Methods

Participants and Tasks

Twelve right-handed, healthy subjects (6 men, 6 women; age range: 19–34 years) who were totally naive as to the purpose of the study participated. They had no history of neurological diseases. All subjects gave their informed consent for participation in the study. Subjects sat facing a Macintosh computer, at a distance of 60 cm, with their right hand on the space bar of the keyboard. The visual stimuli were little squares (1 cm x 1 cm) presented at the center of the computer screen. A blue square was presented for a variable time interval: 1600, 1800, 2000, 2200, or 2400 milliseconds (ms). Next, a red square appeared on the screen and remained visible for as long as subjects pressed the space bar on the keyboard. The task was to reproduce the entire duration of the preceding blue square (time-reproduction task) or half the duration of that square (time-bisection task; see Figure 5). No accuracy feedback was given. All subjects used their right index finger to respond. For each task, 50 trials (10 for each time interval) were presented in random order. Subjects performed each task twice in a single session, once before and once after PA. The task order was counterbalanced across subjects. Before starting the experimental session, subjects were allowed to practice (100 trials) both tasks.

Figure 4

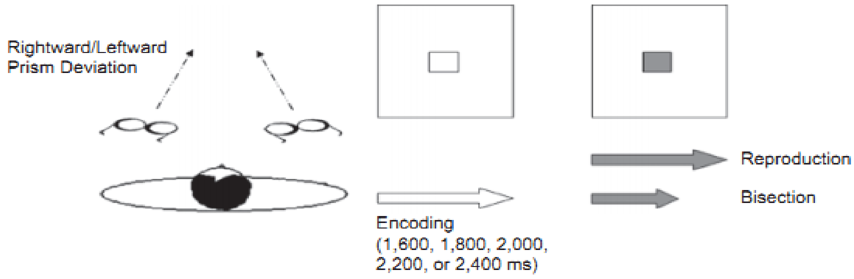

Fig. 4. Experimental procedure. Subjects performed a time-reproduction task and a time-bisection task (represented on the right), before and after leftward and rightward prismatic adaptation (PA; represented on the left). During PA, subjects performed a pointing task while wearing prismatic lenses that induced a shift of the visual field to the right or to the left. The time task was articulated in two steps: In the first step (encoding), subjects were asked to study the duration of a visual stimulus (shown here as a white square), presented for a variable time interval; in the second step, a new stimulus was presented (shown here as a gray square), and

subjects were required to reproduce the entire duration (time reproduction task) or half the duration (time-bisection task) of the previous stimulus.

Prismatic Adaptation procedure

During PA, participants sat at a table in front of a box (height = 30 cm, depth = 34 cm at the center and 18 cm at the periphery, width = 72 cm), open on the side facing the participant as well as the opposite side facing the experimenter. The experimenter placed a visual target (a pen) at the distal edge of the top surface of the box, in one of three possible positions (randomly determined on each trial): a central position (0°), 21° to the left of center (-21°), and 21° to the right of center (+21°). Participants were asked to keep their right hand at the level of the sternum, to point to the pen using the index finger of the right hand, and then return the hand to the chest. The experimenter recorded the end position of the participant's pointing direction, by writing down the number of degrees of visual angle between the index finger and the pen position. The pointing task was performed in three experimental conditions: pre-exposure, exposure, and post-exposure. In the pre-exposure condition, participants performed two types of trials. On half of the trials, their pointing was visible to them, (30 trials) and on the other half, they could not see their pointing (30 trials). Note that these two conditions were comparable to the exposure and the post-exposure conditions described later, respectively. In the exposure condition, participants performed the task (30 trials for each spatial position: -21°, 0°, +21°), while wearing prismatic lenses inducing a 20° shift of the visual field to the right or to the left. In this condition, they always saw the trajectory of their arm (i.e., visible pointing).In the post-exposure condition, run immediately after removal of the prisms, participants were required to make their pointing movements underneath the top surface of the box so that the index finger was never visible at any stage (i.e., invisible pointing; 30 trials). In this phase, all participants were expected to show pointing movements in the opposite direction of the visual shift induced by lenses, called after-effect. In the present experiment 1, half subjects were submitted to lenses inducing a leftward aftereffect, while the other half were submitted to lenses inducing a rightward aftereffect (see figure 5 for graphical representation)

Figure 5

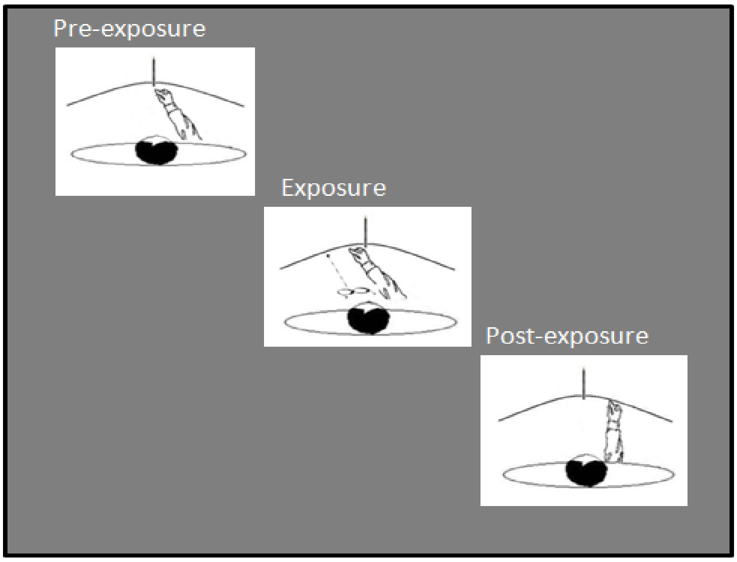

Fig. 5. Graphical representation of the pointing task under the three conditions of PA procedure. In the Pre-exposure condition, the pointing is precise to the target. In the Exposure condition, the pointing is toward the lenses direction (left in this case). In the Post-exposure, the pointing is the opposite direction of lenses (right in this case) .

6.1.2.2 Results

For each subject, we subtracted the reproduced time intervals before PA from the reproduced time intervals after PA. Thus, this difference was positive when reproduced time was longer after than before PA (underestimation of time duration) and negative when reproduced time was shorter after than before PA (overestimation of time duration). Subjects were divided into two groups depending on the direction of the prism-induced aftereffect (i.e., leftward aftereffect induced by rightward PA, rightward aftereffect induced by leftward PA). A separate analysis of variance (ANOVA) on the difference between pre-PA and post-PA reproduced time was conducted for each task (time bisection and time reproduction), with group as a between-subjects variable and time interval as a within-subjects variable. Post hoc comparisons were conducted using the Newman-Keuls test.

A significant effect of prism-induced directional shift was found in the time-bisection task, in which subjects were required to reproduce half the duration of a previously presented visual stimulus. The underestimation of time duration induced by the leftward aftereffect (M = 79 ms) was significantly different from the overestimation of time duration induced by the rightward aftereffect (M = -59 ms), [F (1,10) = 7.11; p = 0.03; η_p^2 = .416] (Figure 6). In addition, in the group with the leftward induced aftereffect, underestimation of time duration was greater for medium time intervals (900–1100 ms) than for shorter (800 ms) and longer (1200ms) time intervals ($p > 0.22$) (see Fig. 6a). This effect likely reflects a range of higher sensitivity to prism-induced shifts[F(4, 40) = 3.5; p = 0.02; η_p^2 = .261]. The prismatic manipulation of spatial attention also affected performance on the time-reproduction task, in which subjects were required to reproduce the entire duration of a previously presented visual stimulus.

The underestimation of time duration induced by the leftward aftereffect (M = 113 ms) was significantly different from the overestimation of time duration induced by the rightward aftereffect (M = -131 ms), [F (1,10) = 7.96; p = 0.02; η_p^2 = .444] (see Fig. 6b).

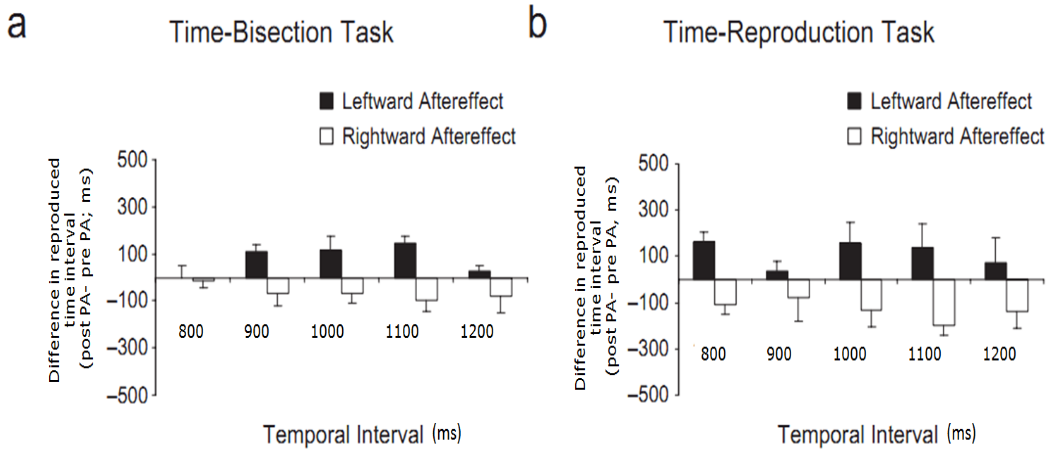

Fig. 6. Effect of prismatic adaptation (PA) on time perception in Experiment 1. The graphs show the mean difference between reproduced time intervals after PA and reproduced time intervals before PA as a function of time interval and direction of the induced aftereffect (right or left). Positive values indicate underestimation of time intervals, and negative values indicate overestimation. Error bars represent standard errors of the means. Results are shown separately for the (a) time-bisection and (b) time reproduction tasks.

We then, ensured that the pre-PA/post-PA differences in time processing were due to the PA procedure by assessing the presence of both error reduction and aftereffect. To verify whether subjects showed an error reduction as they adapted to the prisms, we conducted an ANOVA on the mean displacement (expressed as degrees of visual angle) of subjects' visible pointing, with group (leftward aftereffect, rightward aftereffect) as a between-subjects variable and condition (pre-exposure condition, first three trials of the exposure condition, last three trials of the exposure condition) as a within-subjects variable (more details on this procedure can be found in Frassinetti et al., 2002). The interaction between group and condition was significant, [$F(2,20) = 11.1$; $p < 0.01$; $\eta_p^2 = .526$]. Pointing displacement was significantly greater in the first three trials of the exposure condition than in the pre-exposure condition (leftward aftereffect: $p < 0.05$; rightward aftereffect: $p < 0.02$), but was not significantly different between the last three trials of the exposure condition and the pre-exposure condition (i.e., subjects exhibited error reduction; leftward aftereffect: $p > 0.7$; rightward aftereffect: $p > 0.6$; Figure 7a).To verify the presence of an aftereffect, we compared subjects' displacement during invisible pointing in the pre-exposure and post-exposure conditions. An ANOVA on the mean displacement of invisible pointing responses was carried out with group (leftward aftereffect, rightward aftereffect) as a between-subjects variable and condition (pre-exposure, post-exposure) as a within-subjects variable. The interaction between group and condition was significant[$F(1,10) = 163.9$; $p < 0.01$; $\eta_p^2 = .393$]. As expected, the leftward-aftereffect and rightward-aftereffect groups showed significant leftward and rightward deviations, respectively, in the post-exposure condition relative to the pre-exposure condition ($p < 0.01$; Fig. 7b).

Figure 7

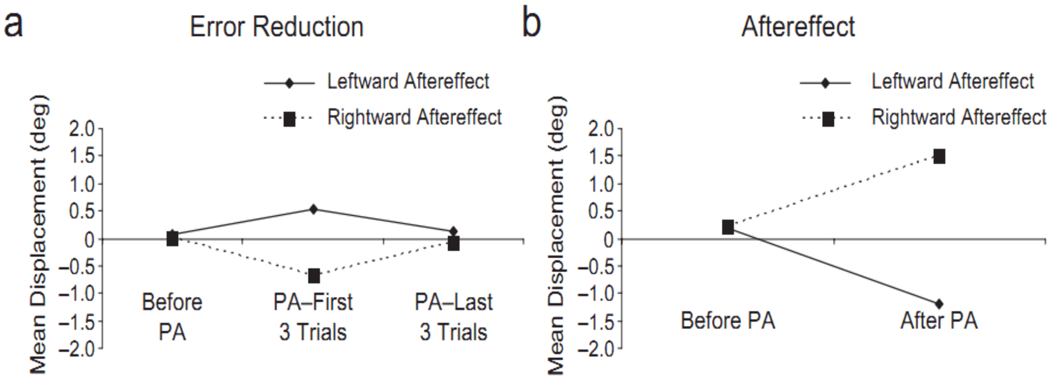

Fig. 7. Mean displacement (in degrees of visual angle) of pointing responses in subjects with a leftward aftereffect and subjects with a rightward aftereffect (induced by rightward and leftward prism adaptation, respectively). Results demonstrating error reduction are shown in (a), which presents mean displacement of subjects' visible pointing before prismatic adaptation (PA) and in the first three and last three trials during PA. Results demonstrating aftereffects of PA are shown in (b), which presents mean displacement of subjects' invisible pointing before and after PA. Negative values indicate a leftward pointing displacement with respect to the target's actual location, and positive values indicate a rightward pointing displacement.

Finally, to assess whether the prism-dependent error reduction or aftereffect affected time perception, we conducted a separate Pearson correlation analysis for each task[1]. Significant negative correlations were found between error reduction in pointing and the effect of PA on subjects' performance in the time-bisection task ($r = 0.67$, $p < 0.03$) and the time-reproduction task ($r = 0.76$, $p < 0.02$). This means that as the pointing displacement in the last three trials of the exposure condition decreased, the magnitude of the effect of PA on performance in both temporal tasks increased. Similarly, positive correlations were found between aftereffect and the PA effect on subjects' performance in the time-bisection task ($r = 0.59$, $p < 0.05$) and the time-reproduction task ($r =0.54$, $p < 0.05$). This means that larger pointing displacements in the post-exposure condition (i.e., bigger aftereffect) were accompanied by larger effects of PA on time perception, in both tasks.

6.1.3 Experiment 2

6.1.3.1 Methods

Six right-handed, healthy subjects (3 men, 3 women; age range: 18–35 years) who did not take part in the previous experiment performed the time-reproduction and time-bisection tasks before and after both rightward and leftward PA. Order of the tasks and order of the direction of prismatic deviation were counter-balanced across subjects. Subjects were examined in two sessions. In the first session, they performed the tasks before PA (baseline), underwent the PA procedure, and then performed thetasks again. After 1 week, in the second session, subjects underwent the same procedure, but with prisms inducing the deviation opposite to that induced in the first session.

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[1] Error reduction was measured using pointing displacement in the last three trials in the exposure condition, and the aftereffect was calculated from pointing displacement in the postexposure condition. The effect of PA on time perception was measured for each task as the difference between performance after PA and performance before PA; the bigger the difference, the stronger the effect of prism exposure on time perception.

6.1.3.2 Results

Similarly to the experiment 1, for each task, we analyzed the differences in reproduced time (post-PA minus pre-PA) in an ANOVA with direction of aftereffect (left, right) and time interval as within-subjects variables. In the time-bisection task, direction of aftereffect had a significant main effect[F (1,5) = 9.63; $p < 0.01$; $\eta_p^2 = .659$] leftward aftereffect induced an underestimation (M = 153ms) of time duration that was significantly different from the overestimation (M = 71 ms) of time duration induced by rightward aftereffect (all subjects showed the effect; see Fig. 8a). In the time-reproduction task, direction of aftereffect also had a significant effect [F (1,5) = 25.5; $p < 0.02$; $\eta_p^2 = .837$]: leftward aftereffect induced an underestimation (M = 141 ms) of time duration that was significantly different from the overestimation (M = 144 ms) of time duration induced by rightward aftereffect (all subjects showed the effect; see Fig. 8b). The effect of time interval and its interaction with the direction of aftereffect were not significant for either task. To verify that subjects showed an error reduction, we conducted an ANOVA with direction of aftereffect (left, right) and condition (pre-exposure condition, first three trials of the exposure condition, last three trials of the exposure condition) as a within-subjects variables. This analysis revealed a significant pointing deviation [F (2,10) = 17.92; $p < 0.01$; $\eta_p^2 = .782$], relative to the pre-exposure condition, in the first three trials of the exposure condition ($p <0.05$, for both leftward and rightward aftereffect), but not in the last three trials of the exposure condition ($p > 0.81$ for both leftward and rightward effect). Thus, subjects exhibited error reduction. To verify the presence of an aftereffect, we conducted an ANOVA on displacement in invisible pointing in the pre-exposure and post-exposure conditions. This analysis showed significant [F (1,5) = 198.6; $p < 0.01$; $\eta_p^2 = .975$] leftward deviation (in the leftward-aftereffect condition)and rightward deviation (in the rightward-aftereffect condition)in the post-exposure condition, relative to the pre-exposure condition (p<0.01).

Figure 8

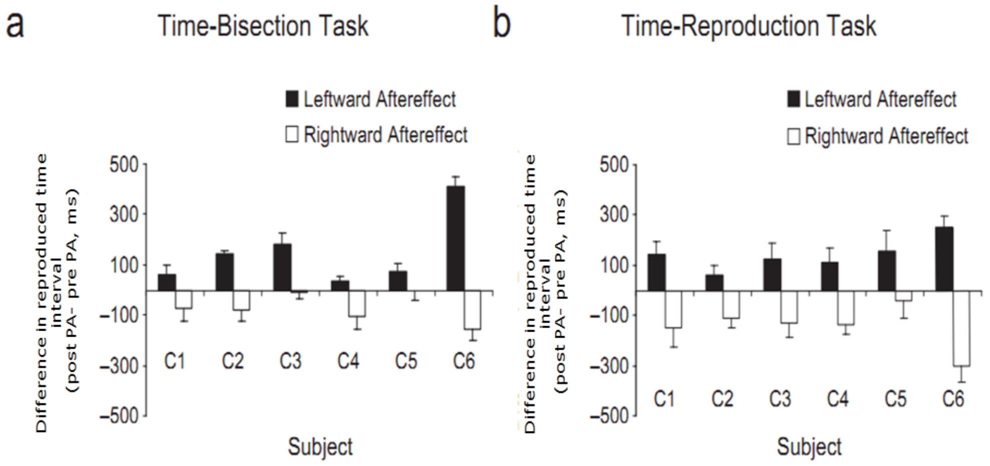


Fig. 8. Effect of prismatic adaptation (PA) on time perception in Experiment 2. The graphs show the mean difference between reproduced time intervals before PA and reproduced time intervals after PA for each subject (C1–C6) after induction of a leftward aftereffect and induction of a rightward aftereffect. Positive values indicate underestimation of time intervals, and negative values indicate overestimation. Error bars represent standard errors of the means. Results are shown separately for the (a) time-bisection and (b) time-reproduction tasks.

Finally, a positive correlation was found between aftereffect and the effect of PA on subjects' performance in the time-bisection task ($r = 0.65$, $p < 0.02$) and the time-reproduction task ($r = 0.75$, $p < 0.01$).

6.1.4 General Discussion

The main finding of this study is to investigate if altering spatial attention via PA induces a modification of time processing. Subjects' time processing before PA differed from their time processing after PA, and the directional bias observed after PA depended on the direction of the prismatic deviation. Indeed, leftward and rightward prism deviation induced opposite effects on both time-processing tasks: After rightward optical deviation (inducing a leftward aftereffect), subjects showed a significant underestimation of time duration (relative to before PA), whereas after leftward optical deviation (inducing a rightward aftereffect), they showed a significant overestimation of time duration.

Also supporting the notion of a link between PA and temporal processing are the significant correlations between the effect of PA on subjects’ performance on the time-reproduction and time-bisection tasks and the parameters indexing the effectiveness of the PA (error reduction and aftereffect). The effect of PA on time perception correlated negatively with error reduction during PA and positively with aftereffect. These results were highly consistent across the two experiments, one following a between-subjects experimental design (Experiment 1) and the other using a within-subjects experimental design (Experiment 2). Moreover, the effects of PA were generally the same for all time intervals. These results do not contradict the hypothesis that short durations are represented toward the left and long durations toward the right, but simply indicate that sensitivity to prism-induced (left or right) shifts was similar for all time intervals considered in this study. The consistency of this result further supports the conclusion that attention shifts are linked to changes in the durations of experiential time. Evidence for a link between spatial attention and time perception comes from studies of both patients and healthy subjects. Recent investigations have demonstrated that patients who exhibit a deficit in orienting attention in space (i.e., neglect patients) may also be impaired in orienting attention in time (Berberovic et al., 2004; Basso et al., 1996; Baylis et al., 2002; Husain et al., 1997). For example, Basso et al. (1996) found that visual spatial neglect can cause overestimation of stimulus duration at a neglected location. Also, in healthy participants, a modification of temporal processing is obtained following manipulation of spatial attention (Mattes and Ulrich, 1998). Mattes and Ulrich found that subjects reproduced longer duration in an attended than in an unattended location (see also Chen and O'Neill, 2001; Enns et al., 1999). Vicario, Caltagirone and Oliveri (2007) reported opposing biases of temporal estimation following rightward and leftward optokinetic stimulation. Here we have shown that time processing can be directly affected by altering spatial-attention processing via PA, thus demonstrating that PA induces a shift of spatial attention that can modify the processing of the time duration of visual stimuli according to the attentional shift in a left-short right-long manner.

A last point deserving discussion concerns the link between PA and spatial attention. Although numerous clinical studies have found that PA induces an amelioration of a visual spatial deficit (i.e., neglect; Farnè et al,2002; Frassinetti et al., 2002, see also chapter 4), few experiments have explicitly addressed the question of whether adaptation affects the bias in spatial attention that is at the core of neglect (Striemer and Danckert, 2007). Previous investigations have examined the effects of PA on spatial attention in patients, with partially conflicting outcomes. Maravita et al. (2003) showed that visual and tactile extinction were reduced following adaptation to rightward prisms, whereas Morris et al. (2004) found no effect of adaptation on the pathological spatial gradient of visual search times in right-brain-damaged patients. The present results add to this previous evidence, providing convergent support for the notion that PA induces shifts of spatial attention.

CHAPTER 7. MULTISENSORY SPATIAL REPRESENTATION OF TIME AND ITS RELATIONSHIP WITH SPATIAL ATTENTION

7.1 Experiment 3 – Changing auditory time with prismatic lenses

7.1.1 Introduction

Looking at the literature, the most part of the studies focused on the spatial representation of time have used *visual* stimuli (Vicario et al, 2007, 2008; Vallesi et al., 2008; Oliveri et al., 2009b), including the experiments 1 and 2 just exposed. This raised the question of whether time processing in other sensory modalities would also show a similar spatial organization. The studied we described in the chapter 3, dedicated to the spatial representation of time (Ishihara et al., 2008; Kong and You, 2011), are in favor to this purpose. For example, Ishihara and colleagues (2008) found a left-to-right correspondence between response position and auditory stimulus duration. These results were interpreted as evidence for a spatial representation of auditory time, horizontally aligned from left to right, which interacts with motor preparation in space. The hypothesis of a spatial representation of auditory time has now received further support by evidence in brain-damaged patients with hemi-spatial neglect (Calabria et al., 2011), showing that duration comparison between a standard tone and a test tone is worse in brain-damaged patients showing neglect, compared to brain-damaged patients without neglect or healthy controls.

However, the fact that interference between space and time processing can emerge in a similar fashion in the visual and the auditory modality is, in some respect, surprising. In the visual modality, space is immediately available in retinotopic coordinates on the receptor surface. By contrast, in the auditory modality information is initially encoded tonotopically, and space is not immediately available on receptor surface (Barker et al., 2011; Hall et al., 2009). The brain reconstructs the spatial location of an auditory stimulus based on interaural and monaural auditory cues (Blauert and Lindemann, 1986), and the output of this computation is typically less precise than the localization of a visual stimulus. Studies on animals (Lee and Middlebrooks, 2010; Populin and Rajala, 2010) and humans (Pavani et al., 2002) have also shown that localization of sounds is most precise when the spatial encoding of the auditory stimuli is salient for the task. In cats, Lee and Middlebrooks (2010) showed that the width of spatial receptive fields (from 180° to 360°) of neurons in the auditory primary cortex (A1) becomes sharper when the localization of sounds is requested by the task, as compared to when spatial factors are not salient for the animal's behavior. In humans, there is neuropsychological evidence that hemispatial neglect for auditory targets worsens when patients are asked to encode the spatial location of the stimuli, with respect to when they are asked to process the tonal aspect of the stimuli (Pavani et al., 2002; see also Deouell and Soroker, 2000). These considerations raise the possibility that any spatial representation of auditory time would emerge more strongly whenever a spatial encoding of the auditory stimuli is enforced.

The first goal of the present study was to verify this hypothesis. To this aim, 28 young healthy participants were submitted to two time bisection experiments with auditory stimuli. Time bisection is a classical task, frequently used in the time perception literature (Wearden, 1991; Wearden and Ferrara, 1995). It consists in verbal classification of auditory stimuli of different duration, with respect to previously acquired pair of reference durations ("short" or "long"). In the present study, each auditory stimulus was either of high or low pitch, and it was presented to the left or to the right with respect to the participant's midsagittal plane. Most important, the time bisection task was presented as a go/no-go task. This means that, in the Spatial experiment, participants were asked to classify tone durations as “short” or “long”, only when the stimulus occupied a pre-determined location in space (left or right), but regardless of its pitch. This forced spatial encoding of each auditory stimulus, regardless of its pitch. In the Tonal experiment, participants were asked to classify tone durations as before, but only when the stimulus was of a pre-determined pitch (high-frequency or low-frequency), regardless of its spatial location. This forced tonal encoding of each auditory stimulus, regardless of its location. The choice of the go/no-go paradigm was instrumental to selectively orient participants’ attention to either the spatial or the tonal feature of the stimulus, while maintaining the stimuli completely identical between the two experiments. Participants were equally exposed to spatial and tonal variations in the spatial and tonal experiments. However, by instructing participants to respond to the frequently occurring ‘Go’ stimuli (defined either on the basis of a spatial or tonal feature) and to inhibit responses to infrequent ‘NoGo’ stimuli, we ensured that our duration measures were linked selectively to the processing of either the spatial or the tonal aspect of the auditory stimulus.

Our predictions were as follows. If the spatial representation of auditory time emerges primarily (or selectively) when spatial encoding of the auditory stimuli is enforced, we expected interference of spatial location on time perception in the *Spatial* experiment more than in the *Tonal* one. More specifically, we expected duration underestimation for left sounds and duration overestimation for right sounds, in line with the hypothesis described above of a left-to-right orientation of the mental time line.

Another essential goal of the present study, was to verify whether the manipulations that proved effective in changing the spatial representation of visual time would also be effective in changing representation of auditory time. One manipulation that recently we proved useful in distorting the spatial representation of visual time is prismatic adaptation (PA). Using visual stimuli, in the previous two experiments we demonstrated that PA can induce spatial attentional biases toward the left or the right side of space, which in turn produce opposite measurable effects on time estimation (Frassinetti et al., 2009; Magnani et al., 2011). Specifically, duration underestimation emerged following leftward shift, and duration overestimation emerged following rightward attentional shift. If PA induces effects on time representation for auditory stimuli similar to those found on visual stimuli, underestimation of sounds duration should be expected after leftward attentional shift and overestimation of sounds duration should emerge after a rightward attentional shift.

7.1.2 Methods

Participants

Twenty-eight right-handed, Italian native-speaker students (5 males), aged 20 to 30 years (mean age = 24.8 years; SD = 1.9 years), were enrolled in the study. All participants were naïve as to the purpose of the study and had not history of hearing or neurological diseases. All participants gave their informed consent to participate in the study.

Apparatus and Stimuli

Participants were tested individually in a silent and dimly lit room, with the apparatus approximately 70 cm in front of them. The apparatus (see Figure 9) comprised a HP laptop computer to control stimuli and collect responses, and two Olidata G-422 loudspeakers (0.4 W, 6 Ω) to deliver the auditory stimuli. With respect to the subject's midsagittal line, one loudspeaker was positioned 25 cm to the left and the other 25 cm to the right. Loudspeakers were covered by a black cloth mounted on a wooded frame, to avoid any visual cue about sound location. The auditory stimuli consisted in pure tones that could vary in fundamental frequency (523 Hz, corresponding to the DO5 and 262 HZ, corresponding to the DO4 on the musical scale) and duration (1400, 1700, 2000, 2300, 2600 ms). Tones were presented at approximately 70 dB (SPL), as measured from the participant's head. The experimental program was written with E-Prime software (Psychology Software Tool Inc.), which assured millisecond accuracy for timing.

Figure 9

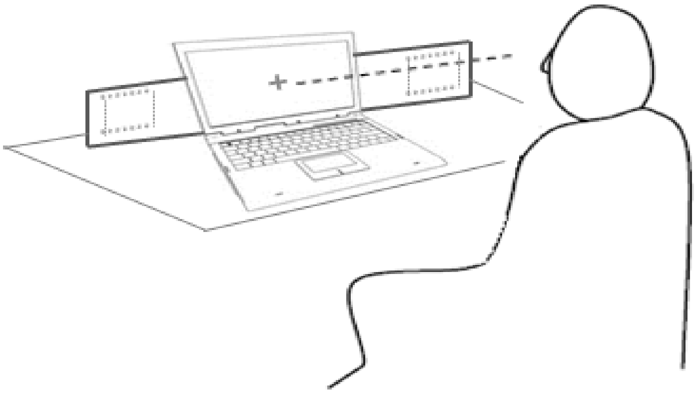


Fig. 9. Schematic view of the experimental setup. The dashed square indicate that the two loudspeakers (one on the left and one on the right) were hidden behind by black cloth mounted on a wooded frame. The dashed line indicates central fixation during the trial.

Experimental Procedure

All participants were first trained to classify two reference tone durations (1400 and 2600 ms) as short or long (practice session). Subsequently, they were presented with the full range of tone durations (1400, 1700, 2000, 2300, 2600 ms) and were again asked to classify them as short or long (time bisection task). This range of tones durations, was chosen because they proved sensitive to PA effects in visual modality

(Frassinetti et al., 2009) and because we wanted to focus on the cognitive controlled time perception. Classically, time perception is known to rely on cognitive systems when the estimated intervals are in the range of seconds-to-minutes (Meck, 2005; Gallistel and Gibbon, 2000; Lewis and Miall, 2003a,b). Given the length of the intervals employed, participants were explicitly required not to count aloud or sub-vocally in all phases of the experimental procedure, in accordance with similar paradigms used in previous studies (Oliveri et al., 2009a).

The time bisection task was always performed according to one of two go/no-go instructions. In the Spatial experiment, participants only responded when the tone was delivered from a specific location (left or right), ignoring its pitch; in the Tonal experiment, participants only responded when the tone was of a specific pitch (high-frequency or low-frequency), ignoring its location in space. After the time bisection task, participants performed a prismatic adaptation (PA) session, in which no auditory stimulus was delivered. Finally, they repeated the time bisection task (both Spatial and Tonal experiments). In the following paragraph, all phases of the experimental session are described in details.

Practice session

The practice session served to familiarize participants with two reference durations (1400 and 2600 ms). Twenty stimuli were presented in a pseudo-random order, from both loudspeakers stereophonically, giving the impression of a sound delivered straight ahead of the participant. For each duration (1400 or 2600 ms), half of the tones were high pitch and the other half was low pitch. Participants were instructed to verbally classify the stimuli as “short” or “long”, while maintaining gaze on a central fixation cross, and ignoring the tone pitch. The experimenter recorded the participant’s response by pressing one of the two mouse keys (left for “short” and right for “long”) and controlled that the participant complied with the fixation instruction during stimulus presentation. The practice session was repeated until the participant had reached at least 80% of accuracy. All participants reached such a level of accuracy with no more than two practice sessions.

Time bisection task

The experimental procedure of the time bisection task was the same of practice session, with the following exceptions. First, the full range of tone durations was presented (1400, 1700, 2000, 2300, 2600 ms); second, each tone originated either from the loudspeaker on the left or from the loudspeaker on the right; third, participants responded in a go/no-go manner, as a function of stimulus location or stimulus pitch.

When responding as a function of stimulus location (Spatial experiment), participants classified the tones as “short” or “long” with respect to the reference durations, only when the stimulus occupied a pre-specified spatial location, regardless of its pitch. In one block, the participant responded only to stimuli presented on the left, ignoring stimuli presented on the right. To maximize go trials, in this block 80% of stimuli were presented on the left and 20% were presented on the right. In the other block, instructions and proportions were reversed: participants responded only to stimuli presented on the right, ignoring stimuli presented on the left and 80% of stimuli were presented on the right and 20% of stimuli were presented on the left. The proportion of high and low pitch tones remained equiprobabile in both these spatial blocks.

When responding as a function of stimulus pitch (Tonal experiment), participants classified the tones as “short” or “long”, only when the stimulus was a pre-specified pitch, regardless of its spatial location. In one block, participants responded only to high pitch tones, ignoring low pitch ones. In this block, 80% of stimuli were high pitch and 20% of stimuli were the low pitch. In the other block, instructions and proportions were reversed: participants responded to low pitch tones, ignoring high pitch tones; 80% of stimuli were the low pitch and 20% of stimuli were high pitch. The proportion of left and right tones remained equiprobabile in both these tonal blocks.

Both the Spatial and Tonal experiment comprised 50 stimuli, resulting in 200 trials overall. The order of experiments before and after PA and of blocks within each experiment was counterbalanced across participants.

Prismatic Adaptation procedure

The procedure adopted is the same exposed in the previous chapter 6 experiment 1. Participants were randomly divided in two groups. One group, was only exposed to prisms inducing a rightward visual shift and showed a leftward after-effect, whereas the other group was only exposed to prisms inducing leftward visual shift and showed a rightward after-effect.

Data Analysis

For each participant and each condition, we computed the bisection point as the estimated temporal value (in milliseconds) for which participants would respond “long” or “short” with equal probability. To this aim, we first computed and fitted the percentage of “long” responses across different stimulus durations using a logistic regression. The bisection point corresponded to the estimated stimulus duration giving rise to 50% of “long” responses (Wearden and Ferrara 1995; Allan et al., 2002; Kopec and Brody, 2010). In our paradigm, the objective stimulus duration representing the medium point between the short and long reference duration was 2000 ms. Bisection points below 2000 ms reflects duration overestimation (i.e., durations are perceived longer than they actually are), whereas bisection points above 2000 ms reflects duration underestimation (i.e., durations are perceived shorter than they actually are).For each participant, the bisection points were separately calculated in the tonal and spatial experiment, for each stimulus position (left and right) and tone (high and low).

Then further analyses were made on the percentage of “long” responses for each interval duration (1400, 1700, 2000, 2300, 2600 ms).

7.1.3 Results

First of all we analyzed data on PA procedure to ensure that participant reached adaptation and aftereffect. Then, In order to investigate if the spatial location of the auditory stimulus interacts with auditory temporal processing, and to examine whether this is more pronounced during the spatial compared to the tonal encoding, we analyzed performances in the time bisection task before PA. Subsequently the effect of PA on auditory time bisection task was assessed. Further correlational analyses were performed to better investigate the relation between the effects of PA and the temporal task. Finally, we investigate the spatial location of stimuli and PA effects on the percentage of “long” responses across interval durations in the spatial and tonal experiments.

In the whole results section post-hoc analyses are conducted with the Least Significant Difference test (LSD test) and effect size is provided as partial eta square.

Prismatic Adaptation results

To ensure that pre-PA/post-PA differences in time bisection task were due to the PA procedure we assessed the presence of both error reduction and after-effect.

To verify that participants showed *error reduction* as they adapted to the prisms, we conducted an ANOVA on the mean displacement (expressed as degrees of visual angle) of participants' visible pointing, with Group (LG vs RG) as a between-subjects variable and Condition (pre-exposure condition, first three trials of the exposure condition, last three trials of the exposure condition) as a within-subjects variable (more details on this procedure can be found in Frassinetti et al., 2002). Post hoc comparisons were conducted using the LSD test. The effect of Group was significant [$F(1,26) = 80.41$; $p < 0.0001$; $\eta_p^2 = .756$]: LG showed an overall pointing displacement to the right while RG showed an overall pointing displacement to the left (0.376°, SE = 0.17; -0.553°, SE = 0.26), compatible with the rightward and leftward prismatic deviation respectively. The interaction between Group and Condition was significant [$F(2,52) = 80.41$; $p < 0.0001$; $\eta_p^2 = .756$]: post-hoc analysis revealed that pointing displacement in pre-exposure condition and in first three trials of the exposure condition was significantly different both for LG (0.000°, SE = 0; 1.127°, SE = 0.15; $p < 0.0001$) and for RG (0.000°, SE = 0; -1.661°, SE = 0.27; $p < 0.0001$), whereas it was not different from the pointing displacement in last three trials of the exposure condition (LG = 0.000°, $p = 1$; RG = -0.000°, $p = 1$) (see Figure 10A).

To verify the presence of an *after-effect*, we compared participants' displacement during invisible pointing in the pre-exposure and post-exposure conditions. An ANOVA on the mean displacement of invisible pointing responses was carried out with Group (LG vs RG) as a between-subjects variable and Condition (pre-exposure vs post-exposure) as a within-subjects variable. The interaction between Group and Condition was significant [F (1,26) = 206.37, $p < 0.0001$; $\eta_p^2 = .888$] since as expected, LG and RG showed significant leftward and rightward deviations, respectively, in the post-exposure condition relative to the pre-exposure condition (LG = -4.558°, SE = 0.36; vs -1.773°, SE = 0.31, $p < 0.0001$; RG = 3.060°, SE = 0.50; vs -0.867°, SE = 0.42; $p < 0.0001$) (see Figure 10B).

Figure 10

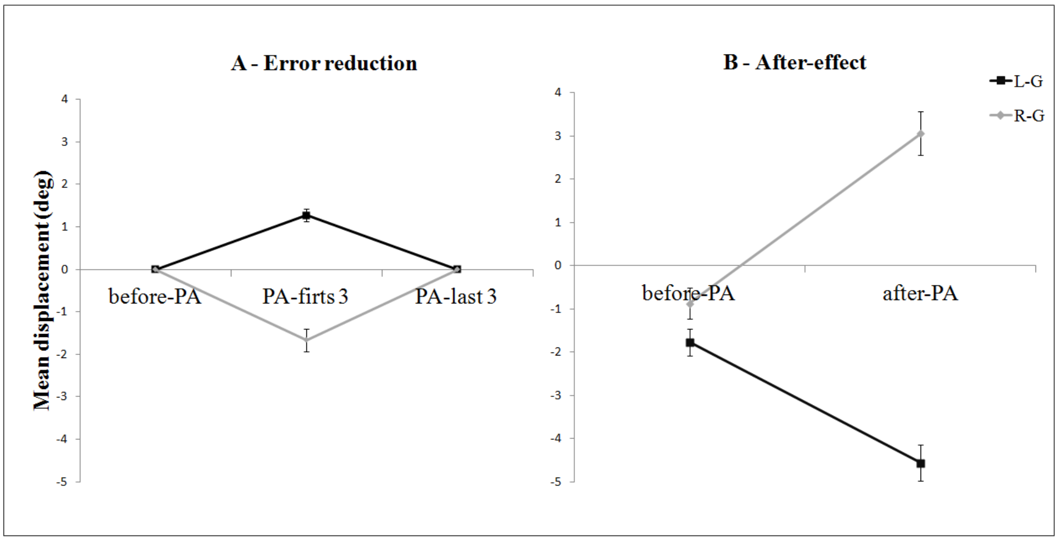


Fig. 10. Mean displacement in degrees of visual angle (deg) of pointing responses in participants with a leftward after-effect (LG) and in participants with a rightward after-effect (RG) induced by rightward and leftward prism adaptation, respectively. Results demonstrating Error reduction shown in (A), which represents mean displacement of participants' visible pointing before prismatic adaptation (before-PA) and in the first three (PA-first 3) and last three trials (PA-last 3) during PA. Results demonstrating After-effect of PA shown in (B), which represents mean displacement of participants' invisible pointing before (before-PA) and after PA (after-PA). Negative values indicate leftward pointing displacement with respect to the target's actual location; positive values indicate rightward pointing displacement.

Representation of auditory temporal stimuli before exposure to Prismatic Adaptation

For each experiment we conducted an Analysis of Variance (ANOVA) on bisection point values before PA, using Stimulus Position (left vs. right) and Stimulus Pitch (high tone vs. low tone) as within-subjects variables.

In the Spatial experiment, a significant main effect of Stimulus Position was found [F (1,27) = 5.45; p = 0.03; $\eta_p^2 = .168$]. Stimuli presented on the left were underestimated compared to stimuli presented to the right (mean = 1898 ms, SE = 42 mean = 1836 ms; SE = 45; see Figure 11A). No other effect reached significance (p = 0.23).

In the Tonal experiment Stimulus Pitch (p = 0.09), Stimulus Position (p = 0.80) (see Figure 11B) and their interaction (p = 0.67) were not significant.

Effect of Prismatic Adaptation on the representation of auditory temporal stimuli

For each experiment an ANOVA was conducted on bisection point values obtained in the experimental sessions before and after PA, using Group (LG = leftward after-effect group or RG = rightward after-effect group) as between-subjects variable and Condition (before-PA, or after-PA), Stimulus Position (left or right) and Stimulus Pitch (high tone or low tone) as within-subjects variables.

In the Spatial experiment, a significant main effect of Stimulus Position was found [F (1,26) = 8.21; p = 0.008; $\eta_p^2 = .240$] showing that stimuli presented to the left were underestimated compared to stimuli presented to the right (mean = 1878 ms, SE = 41; mean = 1816 ms, SE = 40). A significant effect of the interaction between Group and Condition was also found [F (1,26) = 7.93; p = 0.009; $\eta_p^2 = .234$]. Post-hoc analysis (LSD test) revealed that the two groups were not statistically different before PA (LG= 1841, SE = 45; RG= 1893, SE = 74; p = 0.16), whereas after PA opposite effects were observed as a function of prismatic shifts, with the two groups providing significantly different bisection points(LG: 1873, SE = 50; RG: 1783, SE = 55; p = 0.02). However, the effect of PA on time was asymmetric: RG overestimated time after PA with respect to before PA (p = 0.005), whereas this difference was not significant for LG (p = 0.37; see Figure 11C) despite a numerical trend toward time underestimation. No other main effect or interaction reached significance. In particular, there was no interaction involving Stimulus Position, revealing that a similar difference in duration estimation as a function of sound location was maintained after PA.

In the Tonal experiment, a significant effect of the interaction between Group and Condition was also found [F (1,26) = 6.35; p = 0.02; η_p^2 = .196]. Post-hoc analysis (LSD test) revealed that the two groups were not statistically different before PA (LG= 1858, SE = 34; GR= 1830, SE = 56; p = 0.45) whereas after PA opposite effects emerged as a function of prismatic shifts, with the two groups providing significantly different PSE (LG: 1917, SE = 56; RG: 1757, SE = 57; p = 0.0002). Again, the effect of PA on time was asymmetric: the rightward after-effect group overestimated time after PA with respect to before PA (p = 0.05), whereas this difference was not significant for leftward after-effect group (p = 0.12; see Figure 11D) despite a numerical trend toward time underestimation. The absence of any main effect or interaction involving the Stimulus Position variable shows that PA did not enforce any difference in duration estimation as a function of sound location both before PA and after PA.

Figure 11

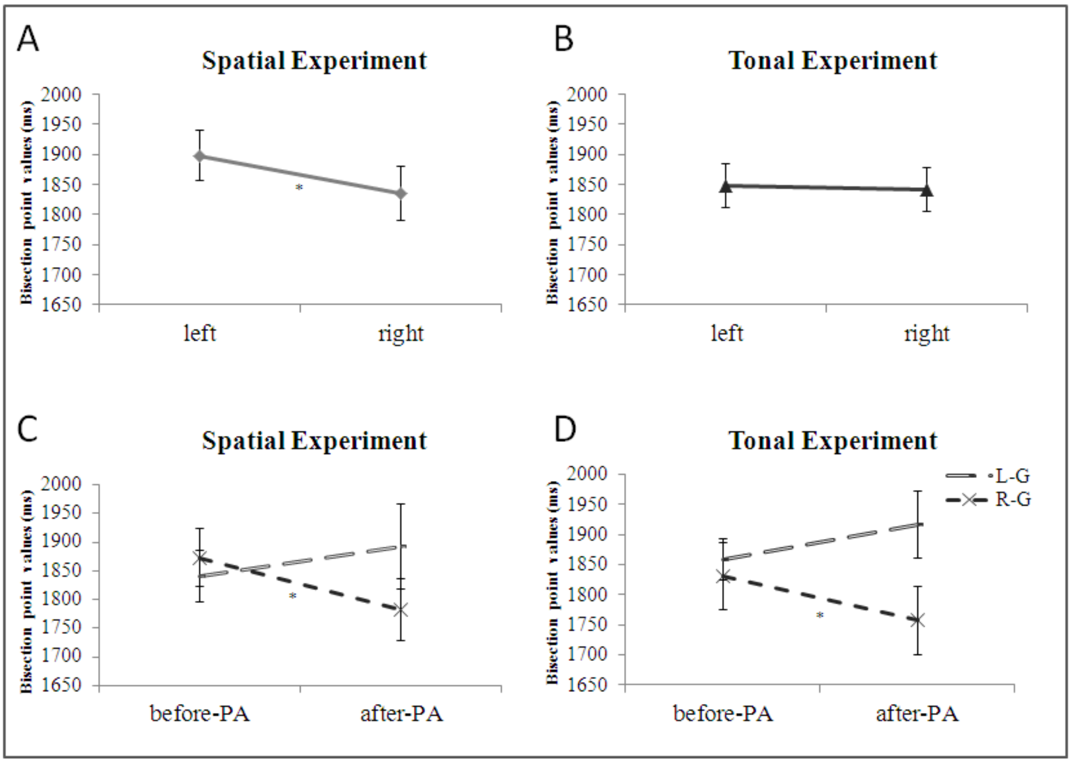


Fig. 11. Bisection point values in milliseconds (ms). Effect of Stimulus Position (left, right) in the Spatial Experiment (A) and in the Tonal Experiment (B). Effect of interaction between Group (LG-leftward after-effect, RG-rightward after-effect) and Condition (before-PA, after-PA) in the Spatial experiment (C) and in the Tonal experiment (D). Asterisks indicate significant differences.

Correlational Analysis

To assess if PA influenced time perception, we conducted a Pearson correlation analysis. As a measure of PA effect on time we took the difference between bisection point before and after PA, separately for the Spatial and the Tonal experiment. Negative values indicate underestimation after PA compared to before PA, whereas positive values indicate overestimation. As measure of error reduction during PA, we computed the difference between the mean pointing displacement in the first three trials minus the mean pointing displacement in the last three trials in the exposure condition. Since pointing displacement in the last three trials was always zero, this difference corresponds to the mean pointing displacement in the first three trials (i.e., the starting pointing displacement). As a measure of after-effect, we took pointing displacement in the post-exposure condition.

The analysis revealed a negative correlation between starting pointing displacement and after-effect ($r = -0.82$; $p < 0.0001$) suggesting that the larger the pointing displacement in the direction of lenses deviation, the larger the after-effect in the opposite direction. Most interestingly, the analysis indicated a negative correlation between starting pointing displacement and auditory duration processing both in the Spatial ($r = -0.60$; $p = 0.001$) and in the Tonal ($r = -0.43$; $p = 0.02$) experiment (see Figure 12A). Specifically, the larger the pointing displacement in the direction of lenses deviation, the larger the effect of PA on time: when pointing displacement was positive (lenses to the right inducing leftward after-effect) the effect on time was an underestimation, when pointing displacement was negative (lenses to the left inducing rightward after-effect) the effect on time was an overestimation. Finally, a positive correlation was found between after-effect and time both in Spatial ($r = 0.52$; $p = 0.005$) and Tonal ($r = 0.38$; $p = 0.05$) experiment (see Figure 12B): the larger the after-effect to the left the larger the underestimation, the larger the after-effect to the right the larger the overestimation.

Figure 12

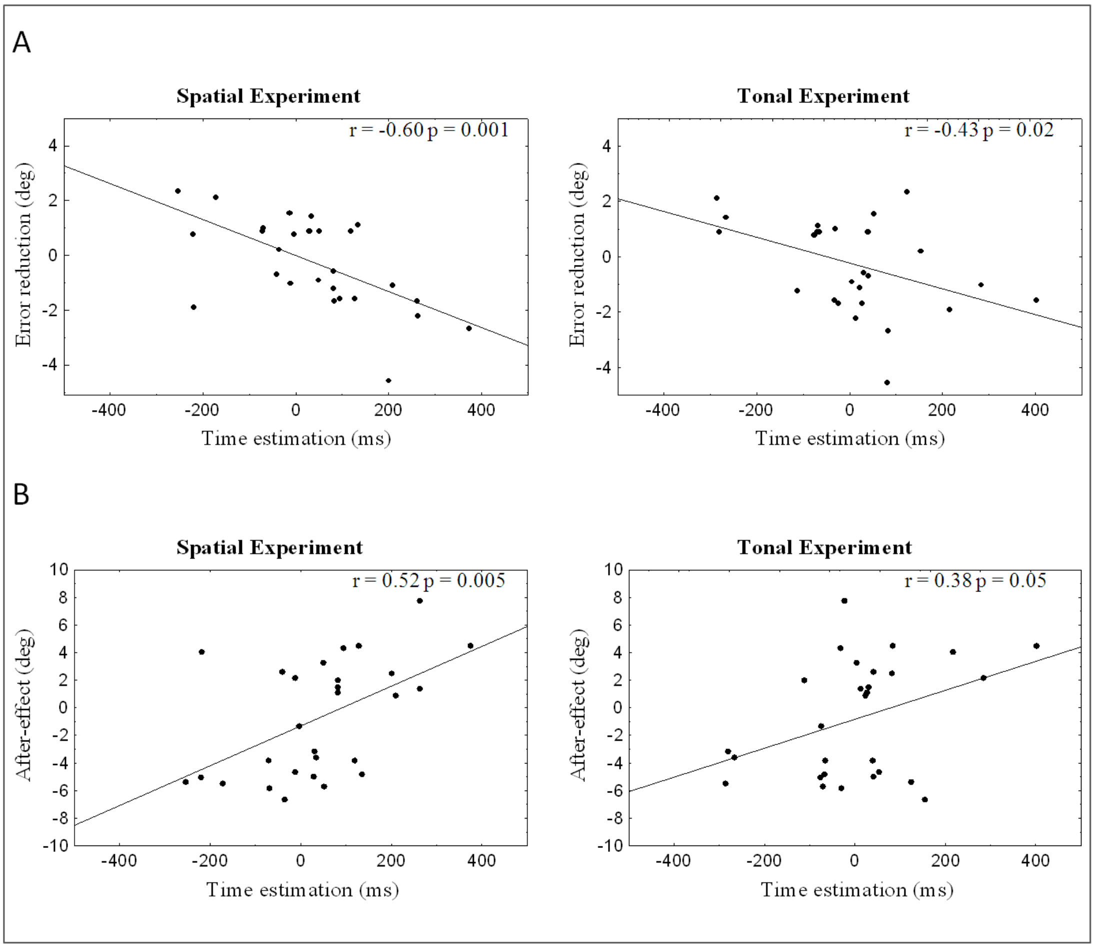


Fig. 12. Correlational analysis between: (A) Error reduction (in deg) and the effect of PA on Time estimation expressed in millisecond (ms), in the Spatial Experiment and in the Tonal Experiment; (B) After-effect (deg) and the effect of PA on Time estimation (ms), in the Spatial Experiment and in the Tonal Experiment. Each graph reports *r* and *p* values. Note that the effect of PA on Time estimation was calculated for each experiment as the difference in bisection point before and after PA. Negative values mean underestimation of time; positive values mean overestimation of time.

Percentage of "long" responses

Finally, we wanted to investigate whether the spatial location of presented stimuli and PA effect, influences the **percentage of "long" responses** in the different interval durations and whether this may be more pronounced during the spatial compared to the tonal encoding. To this aim, the percentage of "long" responses for each interval duration (1400, 1700, 2000, 2300, 2600, ms) was calculated for each participant and each condition. Then, for each experiment we conducted an Analysis of Variance (ANOVA) on percentage of “long” responses, using Group (LG = leftward after-effect group or RG = rightward after-effect group) as between-subjects variable and Condition (before-PA, or after-PA), Stimulus Position (left vs right) and Intervals (1400, 1700, 2000, 2300, 2600, ms) as within-subjects variables. Post-hoc analyses were conducted using the Least Significant Difference (LSD) test and effect size is provided as partial eta square.

In the Spatial experiment the effect of Stimulus Position was significant [F (1,26) = 5.69; p = 0.03; ηp2 = .179]. Means indicated that percentage of “long” responses was higher (overestimation of time) for right stimuli (61%, SE = 8%) than for left stimuli (58%, SE = 8%). The effect of the interaction between Stimulus Position and Intervals was also significant [F (4,104) = 2.73; p = 0.03; ηp2 = .094]. Post-hoc analyses revealed that even if the percentage of “long” responses was higher for right stimuli than for left stimuli, this difference was significant for the middle interval (2000 ms) (right, 77% vs left, 67%, p < 0.001), but not for the other intervals (1400 ms, 1700 ms, 2300 ms, 2600 ms, p > 0.07 for all comparisons) (see Figure 13 for means and SE).

Figure 13

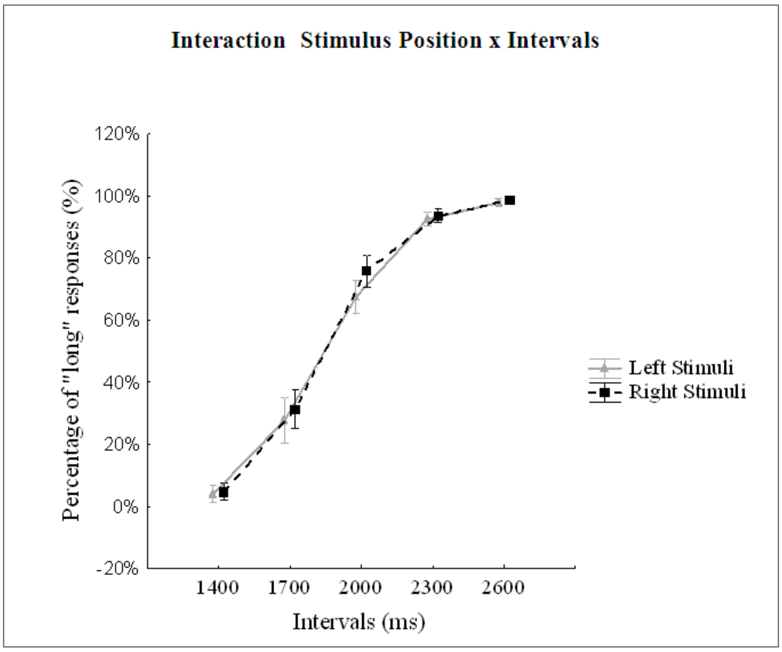


Fig. 13. Results of the interaction between Stimulus Position and Intervals. Percentage of “long” responses (%) for each interval duration expressed in millisecond (Intervals - 1400, 1700, 2000, 2300, 2600 ms), for stimuli presented on the left (Left Stimuli) and right (Right Stimuli) side of space.

As far as the effect of PA, a significant main effect of Condition [F (1,26) = 6.35; p = 0.02; ηp2 = .196] and of the interaction between Group and Condition [F (1,26) = 9.74; p = 0.004; ηp2 = .273] was found. An effect of the interaction between Group, Condition and Intervals was found [F (4,104) = 2.97; p = 0.02; ηp2 = .102]. Figure 14 shows that in RG group there was a tendency, for all intervals, toward a higher percentage of “long” responses after PA relative to before PA, that was significant for the two central intervals (1700 ms, 41% vs 27%; 2000 ms, 78% vs 66%; p< 0.001 for both comparisons). By contrast in LG group, even if means suggest a tendency toward a lower percentage of “long” responses after PA relative to before PA, for the two central intervals (1700 ms and 2000 ms), this difference was not significant.

However, for the 1700 ms interval, the higher percentage of “long” responses of RG group after PA was significantly different from the lower percentage of “long” responses of LG group after PA (RG, 41% vs LG, 24%, p = 0.03) (see Figure 14 for means and SE).

Figure 14

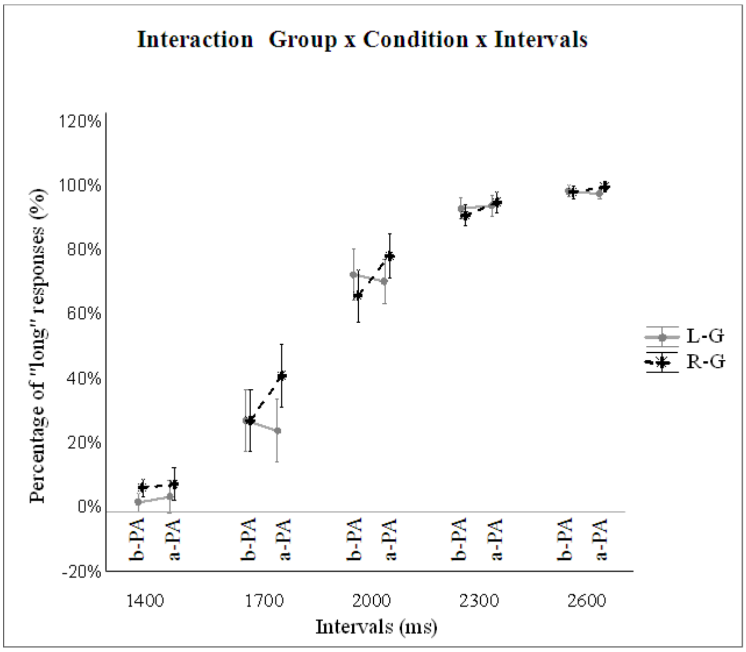


Fig. 14. Results of the interaction between Group (L-G, R-G), Condition (b-PA, a-PA) and Intervals (1400, 1700, 2000, 2300, 2600 ms). Percentage of “long” responses (%) for each interval duration expressed in millisecond.

In the Tonal experiment, the effect of Stimulus Position (p = 0.53) and its interaction with other variables were not significant (p > 0.06). As far as the effect of PA the interaction between Group and Condition was significant [F (1,26) = 6.46; p = 0.02; ηp2 = .199]. Post-hoc analysis revealed that the two groups were not statistically different before PA (LG= 59%, SE = 11%; RG= 60%, SE = 11%, p = 0.96), whereas after PA the effect on time was asymmetric: RG group showed a higher percentage of “long” responses (overestimation of time) after PA with respect to before PA (66% , SE = 11%, vs 60%, p = 0.005), whereas this difference was not significant for LG group (57%, SE = 11%, vs 59%, p = 0.36). Moreover a significant effect of the interaction between Group and Intervals was found [F (4,104) = 2.62; p = 0.04; ηp2 = .092]. Post-hoc analyses revealed a higher percentage of "long" responses in RG relative to LG group, for the central intervals (1700 ms, 39% vs 27%, p = 0.03; 2000 ms, 79% vs 68%, p = 0.05) (see Figure 15 for means and SE).

Figure 15

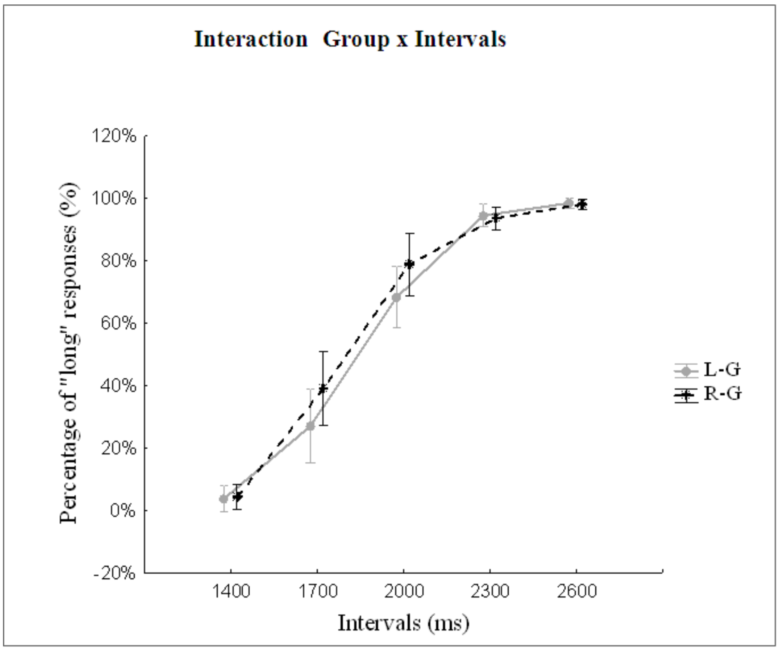


Fig. 15. Results of the interaction between Group (L-G, R-G) and Intervals (1400, 1700, 2000, 2300, 2600 ms). Percentage of "long" responses (%) for each interval duration expressed in millisecond.

In sum these results show that the spatial location of stimuli influences the percentage of "long" responses toward an overestimation of right stimuli relative to left stimuli, in the spatial and not in the tonal experiment. This effect of spatial location is significant for the very central interval of the distribution (2000 ms), suggesting that the spatial location exerts its effect in the point of maximum uncertainty when judging a time interval.

However, parallel to what found with the analyses on bisection point, prismatic adaptation influences the percentage of “long” responses in both the spatial and tonal experiment. This influence was asymmetric: prisms inducing a rightward after-effect significantly increased the percentage of “long” responses while prisms inducing a leftward after-effect did not significantly change the percentage of “long” responses despite a trend of means toward a decrease. Similarly, the effect of PA on time intervals was significantly evident in the central stimuli of the distribution, suggesting that the effects of a spatial manipulation (whatever spatial location or PA) occurs when the participant is uncertain about the response when judging a time interval.

7.1.4 Discussion

The present study examined the spatial representation of auditory time focusing on two novel aspects: first, the role of spatial vs tonal coding of sound in enhancing such a representation; second, the role of prismatic adaptation as modulatory effect. If auditory time is spatially represented on a mental time line (MTL) left-to-right oriented, underestimation of stimuli presented to the left and overestimation of stimuli presented to the right was expected. The present findings confirmed this prediction by showing that duration of auditory stimuli was underestimated when they were presented to the left side of the participant, with respect to when they occurred on the right side. Most important, this effect was evident only when the auditory stimuli required previous spatial encoding (Spatial experiment), but not when they required tonal encoding (Tonal experiment). When participants were asked to respond taking into account the stimulus spatial location (left or right), space influenced duration estimation. This suggests that when auditory stimuli were coded as ‘left’ or ‘right’, this information about their location in external space was reflected in their representation on the mental temporal line. As a result, duration of left stimuli was underestimated with respect to the duration of right ones. By contrast, when subjects were asked to respond taking into account the stimulus tonal frequency, the actual location in space (left or right) did not influence duration estimation.

Spatial coding of auditory time is task-dependent, but independent of motor response

These findings corroborate and extend the results of a recent work on auditory time by Ishihara and colleagues (2008), showing that left-side responses were faster for early-onset timing than late-onset timing, whereas right-side responses were faster for late-onset timing than early-onset timing. These results supported the idea that time and space metrics interact in action (Walsh, 2003; Bueti and Walsh, 2009). The present work extends the findings of Ishihara and colleagues (2008) in several ways. First, we show that spatial interference on time processing for sounds requires previous spatial encoding of the stimulus. The auditory system is not inherently spatial, because information is initially encoded tonotopically and space is not immediately available on receptor surface (Barker et al., 2011; Hall et al., 2009). To encode the spatial location of auditory stimuli the brain implements additional processes, based on interaural and monaural auditory cues (Blauert and Lindemann, 1986). As a result, the output of this computation is typically more complex and less precise than the localization of a visual stimulus. Our results indicate that the spatial representation of auditory time emerges more strongly whenever a spatial encoding of the auditory stimuli is enforced. Second, differently from Ishihara et al.’s study, we examined duration instead of timing expectancy. Third, we did not use a motor response and our findings show that a spatial representation of auditory time emerges also without interactions with a spatial motor response. The observation that time and space can interact even in the absence of motor actions is particularly relevant. One possible explanation is that the brain develops spatial metric maps during action interactions with the environment. Once this metric system has completed its development, it is used as a code to compute other cognitive operations and not just for measuring quantity dimensions useful for action (Bueti and Walsh, 2009). The existence of tight links between motor spatial maps and cognitive spatial maps has been widely demonstrated. On one hand, the findings described so far, including the present study, indicate that a manipulation of spatial attention influences the spatial representation of time both with or without motor response (Vicario et al., 2007; 2008; Oliveri et al., 2009a). On the other hand, the reversed condition has also been demonstrated: a manipulation of the representation of time influences spatial attention orienting and motor preparation in space. For example, Ouellet and colleagues (2010) examined the nature of the space–time conceptual metaphor, by testing whether the temporal meaning of words presented centrally on screen can orient spatial attention and/or prime a congruent left/right motor response. They found that the mere exposure to past or future words both oriented attention and primed motor responses to left or right space, respectively. Similarly, a recent ERP study by Vallesi et al. (2011) found that centrally presented time intervals, pre-activated the corresponding motor cortex and speeded up a response mapping compatible with a short/left and long/right order. This evidence of a multidirectional influence among spatial attention orienting, spatial representation of time and spatial motor responses, suggest that spatial metric is a very centralized representation that is employed for spatial operations at other different levels of the cognitive system, and that a perturbation in the spatial metric at one level reflects in the same perturbation at all other levels.

Prismatic adaptation modulates spatial coding of auditory time

A further novel result of the present study is that representation of auditory durations was modulated by prismatic adaptation. More precisely, leftward and rightward attentional shift induced by PA resulted in opposite effects on the estimation of auditory time intervals, regardless of the side of space in which stimuli were presented (left or right) and irrespective of whether the task required a spatial or a tonal coding of the sound. Strikingly, our correlational analysis indicates a relationship between PA parameters (namely, starting pointing displacement and after-effect) and the PA effect on duration processing, both in the Spatial and in the Tonal experiment. Finally, we found that this effect was asymmetric in magnitude. PA affected time estimation more strongly when attention was shifted to the right, compared to when it was shifted to the left.

The strong effects of PA on spatial coding of auditory time has several relevant implications. First, it provides evidence that adaptation of visuo-motor coordination can affect performance on a sensory modality (audition) that is not directly implicated in PA. In this respect, there is a parallel between PA effects on auditory time and PA effects on auditory spatial processing (Eramudugolla et al., 2010; Jacquin-Courtois et al., 2010). In brain-damaged patients with visual and auditory neglect, Eramudugolla and co-workers (2010) found that the overall auditory detection performance improved after PA relative to before PA. Similarly, Jacquin-Courtois et al. (2010) found that PA improved discrimination of auditory stimuli delivered at the contralesional ear. Jacquin-Courtois and colleagues explain their data suggesting that the lateralized remapping of visuo-motor information induced by prism could subsequently alter attention orienting in the auditory modality. In our opinion, and in accord with the present data showing an effect of prismatic adaptation on auditory time stimuli, the results of Jacquin-Courtois et al., suggest that PA transferred benefit to the auditory modality that is orthogonal to the visual, proprioceptive and motor modalities directly implicated in the visuo-motor adaptive process. This implies that effects of PA can extend to unexposed sensory systems, suggesting implication of a supra-modal effect. Once the sensory representation of duration is translated at high cognitive level in a spatial representation, it is not auditory featured anymore. In this sense, PA may have not affected audition but rather a spatial supra-modal representation of temporal stimuli.In this respect, it is important to note that a shift of spatial attention to opposite sides have produced opposite effects on time, independently on the stimuli location (left or right) and independently on the kind of encoding (spatial or tonal). This result reinforces the hypothesis that PA affects the spatial representation of any auditory duration once it has been encoded and translated into a cognitive one. The resulting effect of PA is similar to a "distortion" of the representation of any auditory duration, by shortening or extending it according with the leftward or rightward attentional deviation.

Concerning the asymmetric effects of PA deviation on auditory time, it should be emphasized that such asymmetries are not new in the literature on PA. Previous studies showed that rightward shifts of spatial attention induced by prismatic adaptation are stronger than the leftward ones, as we also document here (Goedert et el., 2010; Colent et al., 2000). As we explained in chapter 4, Colent and colleagues (2000) demonstrated that after a session of PA shifting spatial attention to the right, participants bisected horizontal lines more to the right relative to before PA. The opposite effect was not found with leftward PA deviation. Since rightward line bisection is a typical behavior of patients with hemispatial neglect, the authors considered their results in terms of a simulation of neglect in neurologically healthy individuals. Because neglect syndrome is more likely to occur after right rather than left hemispherical lesions, inducing a rightward bias of spatial attention, Colent and colleagues proposed that the asymmetrical effect of rightward and leftward PA on space might reflect an inherent bias of the brain's structural organization in directing attention to the right. Accordingly, some studies suggest that neglect (post-lesion in patients) and pseudo-neglect (physiological bias that is observed in some tasks in healthy subjects) could be expressions of common cognitive and neural mechanisms (McCourt and Jewell, 1999). In other words, cognitive performances of healthy subjects after PA could be considered as correct approximation of a neglect-like behavior, with common main characteristics (i.e. directional bias, directional specificity, predominance of perceptive effects; Michel et al., 2003).

An explanation that is not in contrast but complementary to the last one, is that the left-to-right shift of spatial attention (and of temporal representation) is easier to be induced than the right-to-left shift, because it has been acquired more extensively in a culture adopting a left-to-right writing/reading system. Therefore it would be difficult to overcome with a short prismatic adaptation training phase. Our participants were all Italian native language speakers, learning exclusively a left-to-right writing/reading habit. Supporting this explanation there is evidence about the strong influence of the writing/reading habits on the congruency effects involving space (Dehaene et al., 1993). Alternatively, the asymmetrical results on the line bisection task could be attributed to sensory-motor after-effect. However, this can be excluded because in the present study, similarly to the study of Colent et al. (2000), we observed symmetrical sensory-motor after-effects, regardless of prismatic deviation side, despite an asymmetrical effect on the representation of duration.

Whatever the interpretation of the asymmetry of PA effects found in the present study, our findings strongly suggest that the engaged process concerns some supramodal level of spatial representations. These effects confirm that sensory-motor integration can structure spatial cognition and hence that sensori-motor and cognitive representations of space are not fully dissociated, supporting our hypothesis that PA has affected the high cognitive spatial representation of time for auditory modality.

In conclusion this study indicates that the spatial representation of auditory time emerges more strongly whenever a spatial encoding of the auditory stimuli is enforced and that this spatial representation of auditory time can be modulated by a shift of spatial attention obtained through the PA procedure.

CHAPTER 8. NEURAL CORRELATES OF THE SPATIAL REPRESENTATION OF TIME AND ITS RELATIONSHIP WITH SPATIAL ATTENTION

8.1 Time and spatial attention: effects of prismatic adaptation on temporal performance in unilateral brain damaged patients

8.1.1 Introduction

According to the demonstrations that moving attentive focus, by PA, along the mental time-line can bias time perception, an open question in cognitive neuroscience remains how the two dimensions of space and time interact with each other in the brain. Neuropsychological studies in stroke patients (Basso et al., 1996; Danckert et al., 2007; Harrington et al., 1998; Koch et al., 2002) and neuroimaging studies in healthy subjects (Bueti et al., 2008; Bueti and Walsh, 2009; Ivry and Spencer, 2004; Koch et al., 2009, 2003; Lewis and Miall, 2003b; Wiener et al., 2009) have explored the neural correlates of spatial–temporal interactions, suggesting a critical role of fronto-parietal structures with a preference for right hemisphere (see also chapters 1, 2 and 3). The present study was designed to investigate, by using PA procedure to directionally manipulate spatial attention, the neural mechanisms subserving the effects of spatial attention on time perception in a model of brain damage. We were interested to address two questions: (1) studying the effects of PA on temporal deficits in brain damaged patients and (2) investigating which hemisphere mediates the effects of PA on time processing. To this aim two experiments were conducted. In a first experiment (Experiment 4), two groups of patients with right and left brain lesion (RBD and LBD) and a group of age-matched healthy subjects were submitted to a time reproduction task before and after rightward or leftward PA (between-group design). In a second experiment (Experiment 5), RBD and LBD patients were submitted to the same task before and after rightward and leftward PA (within-group design). In both experiments, participants were required to reproduce half of the duration of a previously studied visual stimulus (time reproduction/bisection task). The logic subserving this task is that setting the midpoint of a temporal interval requires a spatial computational processing: in fact, the task of bisecting a physical interval measures the spatial ability of computing extent along the lateral dimension. This spatial component becomes crucial when we apply PA, which typically directionally shifts spatial attention. Moreover, the temporal bisection task documented deficits in time perception in RBD patients similar to the line bisection deficits observed in spatial tasks (Oliveri et al., 2009a). We expected that RBD, but not LBD patients, should be impaired in time bisection task before PA as compared with healthy subjects. Moreover, if the effects of spatial attention on time processing are mediated by the right hemisphere, RBD patients should not show the effects of PA on time processing. On the other hand, if the effects of spatial attention on time processing are mediated by the left hemisphere, LBD patients should not show the effects of PA on time processing.

8.1.2 Experiment 4

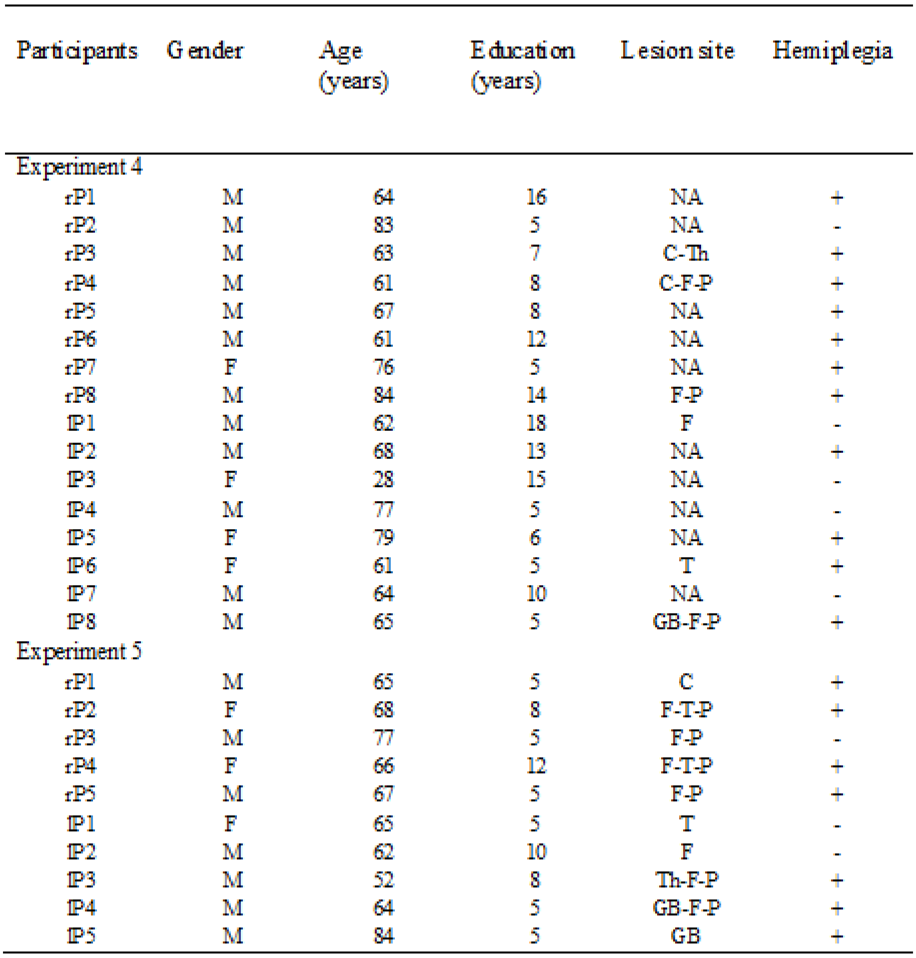
8.1.2.1. Methods

Participants and Neuropsychological assessment

Sixteen patients with unilateral brain-damage, eight RBD (7 male; mean age = 69.9 years) and eight LBD (5 male; mean age = 63 years) and sixteen participants without history of neurological or psychiatric disease (6 male, mean age = 64.8 years) gave their informed consent to participate in the study, which was approved by the local ethics committee. All procedures were in agreement with the 1975 Helsinki

Declaration. Patients were recruited consecutively at the Fondazione Maugeri Hospital (Castel Goffredo, Italy) and at San Giacomo Hospital of Ponte dell'Olio (Piacenza, Italy). The criterions for exclusion from the study were the presence of cognitive impairment (score lower than 24 at the Mini-Mental State Examination; Folstein, et al., 1975) and the presence of visual field deficits. RBD patients were not affected by neglect (as assessed by Bell cancellation test –Gauthier et al., 1989 – and line bisection test) and LBD patients had no comprehension impairment (as assessed by Token test) (data of each patient are provided in Table 1).

Table 1. Summary of clinical and demographic data for RBD patients group (rP) and LBD patients group (lP) in Experiment 4 and in Experiment 5



Participants	Gender	Age (years)	Education (years)	Lesion site	Hemiplegia
Experiment 4					
rP1	M	64	16	NA	+
rP2	M	83	5	NA	-
rP3	M	63	7	C-Th	+
rP4	M	61	8	C-F-P	+
rP5	M	67	8	NA	+
rP6	M	61	12	NA	+
rP7	F	76	5	NA	+
rP8	M	84	14	F-P	+
lP1	M	62	18	F	-
lP2	M	68	13	NA	+
lP3	F	28	15	NA	-
lP4	M	77	5	NA	-
lP5	F	79	6	NA	+
lP6	F	61	5	T	+
lP7	M	64	10	NA	-
lP8	M	65	5	GB-F-P	+
Experiment 5					
rP1	M	65	5	C	+
rP2	F	68	8	F-T-P	+
rP3	M	77	5	F-P	-
rP4	F	66	12	F-T-P	+
rP5	M	67	5	F-P	+
lP1	F	65	5	T	-
lP2	M	62	10	F	-
lP3	M	52	8	Th-F-P	+
lP4	M	64	5	GB-F-P	+
lP5	M	84	5	GB	+

Tab. 1. F: frontal; T: temporal; P: parietal; O: occipital; C: capsule; BG: basal ganglia; Th: thalamus. (+) hemiplegia; (−) no hemiplegia; NA: data not available.

Time bisection task

Subjects sat at a distance of 54 cm from a 14” computer monitor, with their responding hand (left or right depending on experimental group) placed on the space bar of the keyboard. The visual-stimulus was a square (1°×1° of visual angle) presented on the center of the monitor. A blue square was presented on the monitor for a variable time interval: 1600, 1800, 2000, 2200 and 2400 ms (time encoding phase). Immediately after the encoding phase, a red square was presented on the monitor. Subjects were required to press the space bar of the computer when they judged that half the duration of the previously encoded stimulus had elapsed (time bisection phase). Patients pressed the space bar with their ipsilesional hand: RBD patients and 8 control subjects (right controls: RC) performed the task using their right index finger; LBD patients and other eight control subjects (left controls: LC) performed the task using their left index finger. Control subjects were assigned randomly to the two groups. The computer program recorded the reproduced time with 1-ms resolution. No feedback was given on accuracy. Fifty trials were randomly presented, ten for each time interval. Before starting the experimental session, subjects were presented with 100 practice trials. All subjects performed the time bisection task before and after PA.

Prismatic Adaptation procedure

Prismatic adaptation procedure is the same used in the previous experiments 1, 2 and 3 (Chapters 6, 7 and 8). RBD patients and RC, were submitted to ipsilesional (rightward) deviating prisms according to the literature describing the effects of such prisms on spatial tasks in RBD patients (Frassinetti et al., 2002; Rossetti et al., 1998). LBD patients and LC, were submitted to ipsilesional (leftward) deviating prisms. Therefore, following the description of time bisection task, RBD patients and RC performed the

PA procedure wearing rightward-deviating prisms and pointing with their right hand; LBD patients and LC performed the PA procedure wearing leftward-deviating prisms and pointing with their left hand.

8.1.2.2 Results

Since leftward and rightward deviation by PA are expected to induce opposite effects on time (see chapters 6, 7 and Frassinetti et al., 2009), for the time bisection task, we separately analyzed the data from RBD patients and RC and from LBD patients and LC. After the exposition of PA effect on the time task we will present data on PA error reduction and aftereffect.

PA effect on time bisection task

RBD patients and RC (leftward attentional shift). In order to verify the effects of leftward shifts of spatial attention on time processing, an ANOVA was performed with Group (RBD vs RC) as between-subjects factor and Condition (B-PA: before prism-adaptation vs A-PA: after prism-adaptation) and Interval (800–900–1000–1100–1200 ms) as within-subjects factors. Results showed a significant effect of Group [F(1,14) = 8.85; p <0.01]: RBD patients underestimated time durations as compared with RC (1237 ms vs 985 ms) (Fig. 16a). The Condition factor was also significant [F(1,14) = 4.63; p <0.05]: in the A-PA condition, time was underestimated as compared with B-PA condition (A-PA: 1169 ms vs B-PA: 1054 ms). Time underestimation following PA was similar in both groups, as revealed by the lack of significance of the interaction Group x Condition (p = 0.49; RBD: 1314 ms vs 1161 ms; RC: 1024 ms vs 947 ms) (Fig. 16b) (see Table 2 for RT values). The factor Interval [F(4,56) = 5.66; p <0.0007] and the interaction Group x Interval [F(4,56) = 3.02; p<0.02] were significant. In RC, reproduced time in the time bisection task increased as the intervals to-be-timed increased (800ms vs. 1000, 1100 and 1200ms:p <0.03; 900ms vs. from 1200ms: p <0.03) whereas in RBD patients there was not any difference between intervals. Furthermore, RBD patients underestimated all time intervals as compared with RC (p < .04) (Fig. 16c).

Figure 16

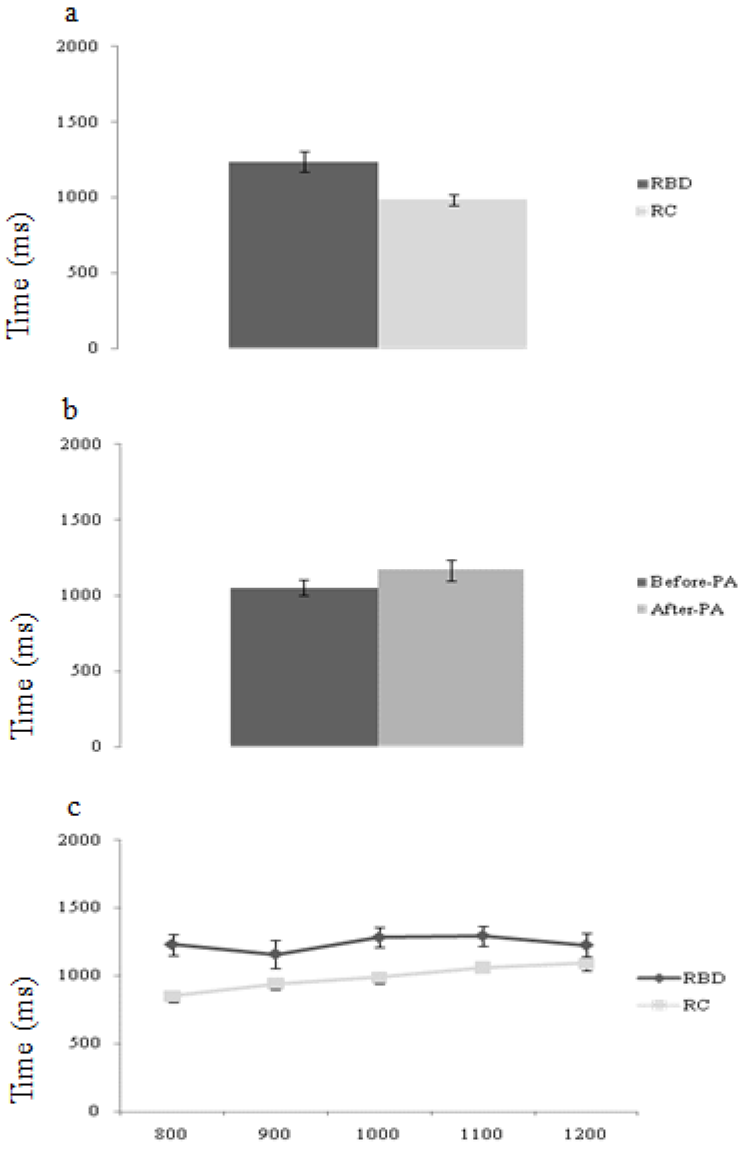


Fig. 16. Experiment 4. (a) Mean reproduced time (ms) in RBD patients vs. right-controls (RC). (b) Mean reproduced time before and following rightward prismatic adaptation in RBD patients and right-controls (RC) together. (c) Mean reproduced time as a function of the five

time intervals in RBD patients and right-controls (RC). Error bars indicate standard error of mean.

LBD patients and LC (rightward attention shift). An ANOVA was performed with Group (LBD vs LC) as between-group factor and Condition (B-PA: before prism adaptation vs A-PA: after prism adaptation) and Intervals (800–900–1000–1100–1200ms) as within-subjects factors. Results showed no differences in timing between patients and controls (LBD: 1062 ms vs LC: 1086 ms: p = 0.86) (Fig. 17a). Condition and the interaction Group x Condition (p = 0.89) were not significant: leftward PA (rightward after-effect) did not influence time processing both in LBD patients (1085 ms vs 1039 ms) and LC (1104 ms vs 1067 ms) (Fig. 17b) (see Table 2 for RT values). The factor Interval was significant [F(4,56) = 9.70; p <0.00001]: in fact, reproduced time in the time bisection task increased as the intervals to-be-timed increased: 800ms vs. 1000, 1100 and 1200ms: p <0.01; 900ms vs1100 and 1200ms: p <0.01). The interaction Group x Interval was not significant (p = 0.39), indicating that this effect was similar in LBD patients and controls (Fig. 17c).

Figure 17

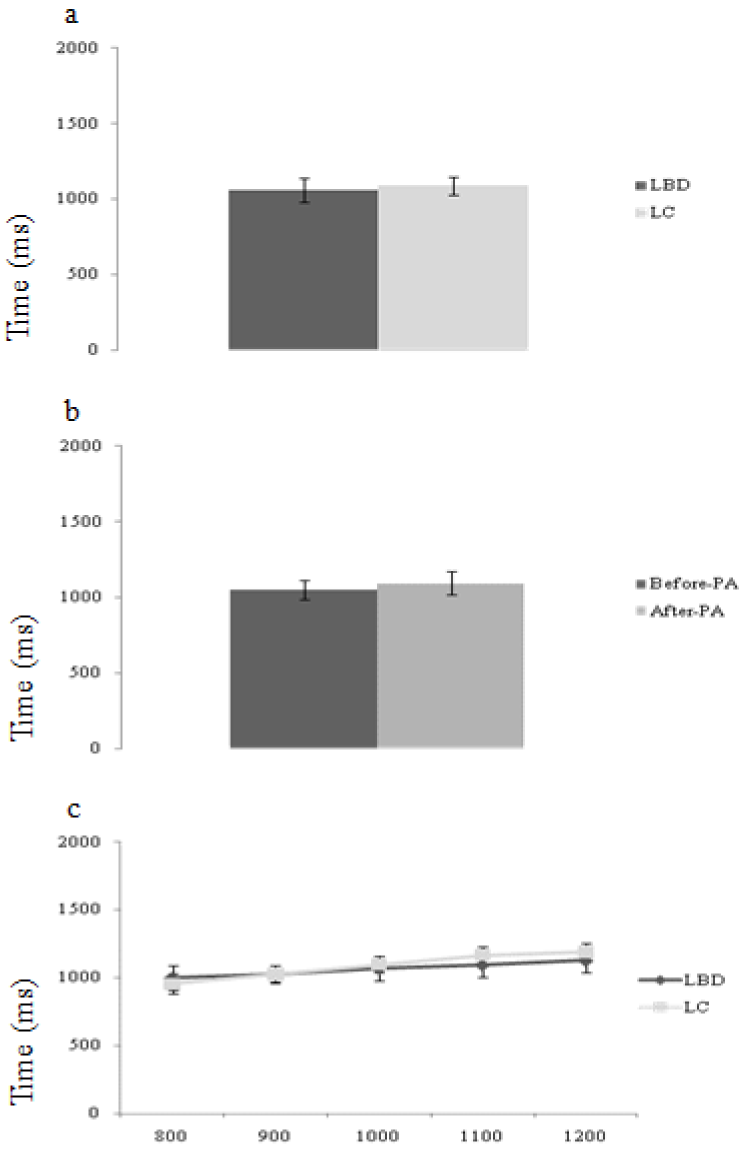
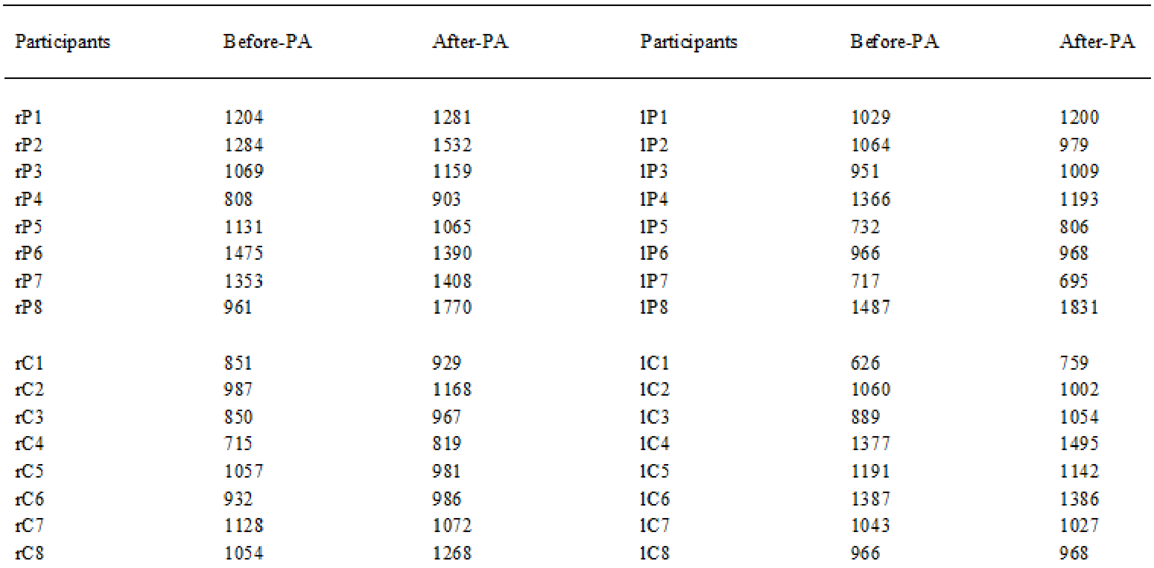


Fig. 17. Experiment 4. (a) Mean reproduced time (ms) in LBD patients vs left-controls (LC). (b) Mean reproduced time before and following rightward prismatic adaptation in LBD patients and left-controls (LC) together. (c) Mean reproduced time as a function of the four time intervals in LBD patients and left-controls (LC). Error bars indicate standard error of mean.

To control for the role of the responding hand, a new control-group of six age-matched healthy subjects (4 male; mean age = 66 years) was submitted to the time bisection task using their right hand, before and after leftward PA (rightward after effect). The performance of subjects performing the pointing task with their right hand (LC-RH) was compared with the performance of subject performing the pointing task with their left hand (LC-LH). An ANOVA with Group (LC-RH vs. LC-LH) as between-subjects factorand Condition (B-PA vs. A-PA) as within-group factor, showed that Group, Condition and their interaction were not significant. This result rules out a crucial role of the responding hand in mediating the effects of PA on time processing.

Table 2. Summary of RTs in time bisection task in RBD patients (rP), right-controls (RC), LBD patients (lP) and left-controls (LC) in Experiment 4.



Participants	Before-PA	After-PA	Participants	Before-PA	After-PA
rP1	1204	1281	lP1	1029	1200
rP2	1284	1532	lP2	1064	979
rP3	1069	1159	lP3	951	1009
rP4	808	903	lP4	1366	1193
rP5	1131	1065	lP5	732	806
rP6	1475	1390	lP6	966	968
rP7	1353	1408	lP7	717	695
rP8	961	1770	lP8	1487	1831
rC1	851	929	lC1	626	759
rC2	987	1168	lC2	1060	1002
rC3	850	967	lC3	889	1054
rC4	715	819	lC4	1377	1495
rC5	1057	981	lC5	1191	1142
rC6	932	986	lC6	1387	1386
rC7	1128	1072	lC7	1043	1027
rC8	1054	1268	lC8	966	968

Tab. 2. RT values (milliseconds) of RBD patients (rP), right-controls (RC), LBD patients (lP) and left-controls (LC) in the time bisection task before prismatic adaptation (Before-PA) and after prismatic adaptation (After-PA) in Experiment 4.

Prismatic Adaptation results

To ensure that any potential difference in time processing were due to prism exposure, error reduction and after-effect were assessed[2].

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[2] The error-reduction is the tendency to compensate, during prism exposure, for prism-induced spatial errors in pointing. The after-effect is the subsequent tendency to point to the direction opposite to the optical displacement induced by prism, after prisms removal. Pointing displacement measure carries a

Error reduction: To demonstrate the presence of error displacement, in the first trials, and of error reduction, in the last trials of prisms exposure condition, visible pointing performance during pre-exposure and exposure condition were compared with the following predictions. First, if subjects were influenced by prisms exposure, a difference should be found between the first trials of the exposure condition and the pre-exposure condition. Second, if subjects were actually able to adapt to the prisms, no difference should be found between the last trials of the exposure condition and the pre-exposure condition, i.e. 0◦ or close to 0◦ pointing displacement should be registered in both conditions. Two different ANOVAs were performed for subjects (patients and controls) submitted to rightward and leftward prismatic deviation respectively, taking Group as between-group variable and Condition (pre-exposure, exposure first three trials and exposure last three trials) as within-subjects variable.

Rightward-deviating prisms (RBD patients and RC). ANOVA indicated a significant effect of Condition [F(2,28) = 57,19; p < 0.0001]. Post hoc analysis reveals that pointing displacement before PA (−.001) was different from exposure condition in the first three trials (2.19, p <0.0001) but not from exposure condition in the last three trials (.16, p = 0.47). This effect was present both in RBD and in RC, as proven by the lack of significance of the interaction Group x Condition (p = 0.16).

Leftward-deviating prisms (LBD patients and LC). ANOVA indicated a significant effect of Condition and of the interaction Group x Condition [F(2,28) = 4.50; p <0.02]. Post hoc analysis reveals that in both LBD patients and LC, pointing displacement before PA was different from that in the first three trials of exposure condition (LBD: .02 vs −1.15; LC: .01 vs −2.06, p <0.0001 for both comparisons) but not from that in

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negative sign (−) when directed to the left and a positive sign (+) when directed to the right with respect to the target actual location.

the last three trials of exposure condition (LBD: .03, p = 0.99; LC: −.01, p = 0.92). Pointing deviation in the first three trials was smaller in LBD than in LC (p <0.0001) (see Fig. 18a).

After-effect: To show the presence of an after-effect, invisible pointing was compared between the post-exposure condition and the pre-exposure condition. If PA produced a leftward visuo-motor bias in response to the rightward deviation induced by prism, a leftward (i.e. negative) or rightward (i.e. positive) error during pointing, after rightward or leftward prisms respectively, should be found when prismatic goggles have been removed, whereas this effect should not be present during pre-exposure condition. To verify this prediction, an ANOVA was performed taking Group as between-group variable and Condition (pre-exposure invisible pointing and post-exposure invisible pointing) as within-subjects variable.

Rightward-deviating prisms (RBD patients and RC). ANOVA revealed a significant effect of Condition [F(1,14) = 146.73; p <0.0001]. Post hoc analysis showed that pre-exposure invisible pointing condition was different from post-exposure invisible pointing condition (after-effect) (.02 vs −2.3). The interaction Group x Condition was not significant (p = 0.60).

Leftward-deviating prisms (LBD patients and LC). ANOVA revealed a significant effect of Condition [F(1,14) = 209.2; p <0.0001]. Post hoc analysis showed that pre-exposure invisible pointing condition was different from post-exposure invisible pointing condition (after-effect) (.07 vs. 2.5). The interaction Group x Condition was not significant (p = 0.13) (see Fig. 18b).

Figure 18

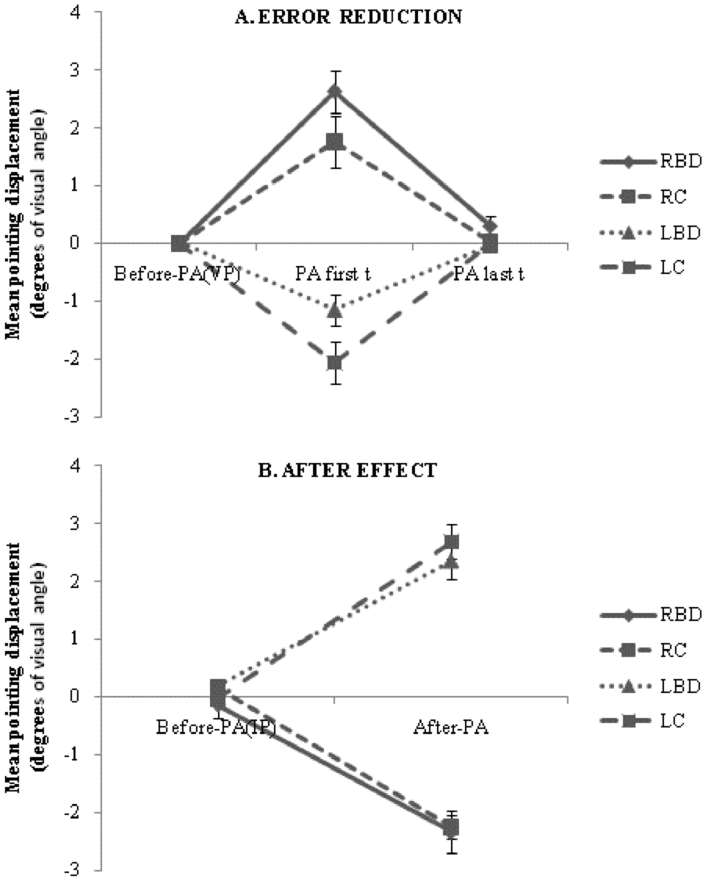


Fig. 18. Pointing deviation. (A) Mean pointing displacement (expressed in degrees of visual angle) of subjects' visible pointing (VP) responses before prism adaptation (Before-PA) and mean pointing displacement of the first three (PA-first t.) and the last three trials (PA-last t.) during prism adaptation. (B) Mean displacement (expressed in degrees of visual angle) of subjects' invisible pointing (IP) responses before prism adaptation (Before-PA) and mean pointing displacement after prism adaptation (After-PA). RBD, right brain damaged patients; RC, right controls; LBD, left brain damaged patients; RC, left controls.

8.1.3 Experiment 5

8.1.3.1 Methods

Participants and lesions mapping

Ten patients with unilateral brain-damage, five RBD (3 male; mean age = 68.6 years) and five LBD (4 male; mean age = 65.4 years), who did not take part in the previous experiment, performed the time bisection task before and after both rightward and leftward PA, following the same procedure of experiment 4. The order of the direction of prismatic deviation was counterbalanced across subjects. Subjects were examined in two sessions, separated by an interval of one week. The exclusion criterions used for Experiment 4 were also applied for selecting patients for Experiment 5 (data of each patient are provided in Table 1). In the first session, they performed the task before PA (baseline), then they underwent PA procedure and then performed the task again (as in Experiment 4). One week later, in the second session, subjects were submitted to the same procedure with prisms inducing the opposite deviation with respect to the first session. In all experiments, in line with previous findings (Frassinetti et al., 2009), when reproduced time is longer than the real time we refer to underestimation; when reproduced time is shorter than the real time, we refer to overestimation. Reproducing a time interval longer than the real time is considered time underestimation because subjects press the key later as if they believed that time is elapsing slower. In line with this interpretation, if participants reproduced a time interval longer after than before PA, the effect induced by prisms is toward an underestimation of time.

CT/MRI digitalized images of five RBD and four LBD patients, who participated in Experiment 5, were mapped using MRIcro software (available on http://www.cabiatl.com/mricro, Rorden C.) The region of maximum overlap, which contained the overlap of at least three patients' lesions, was extracted. Thereafter, the mean number of voxels of patients' lesions overlapping was calculated. The Brodmann areas involved by the lesion for more voxels than the mean were identified.

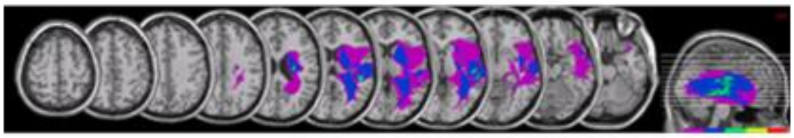
In RBD patients the Brodmann areas identified were in frontal (BA 47), parietal (BA 7, 39 and 40), temporal (BA 20, 21, 38, 41 and 42) and occipital (BA 19) areas and the region of maximum overlap was located in the deep white matter in a temporo-parietal region.

In LBD patients the Brodmann areas identified were in frontal (BA 4, 6, 44, 45 and 47), parietal (BA 2 and 40), temporal (BA 22, 32 and 38) areas and the region of maximum overlap of at least two patients' lesions was located in the frontal cortex (Figure 19).

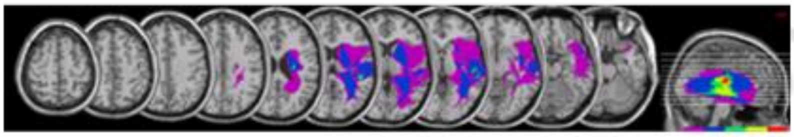
Figure 19

a **RBD:** Region of maximum overlap

True overlapping

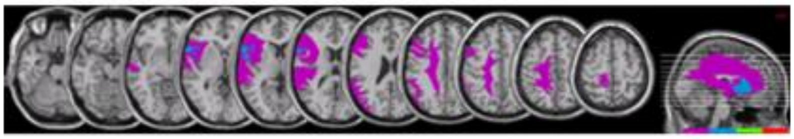


Overlapping



b **LBD**: Region of maximum overlap

True overlapping



Overlapping

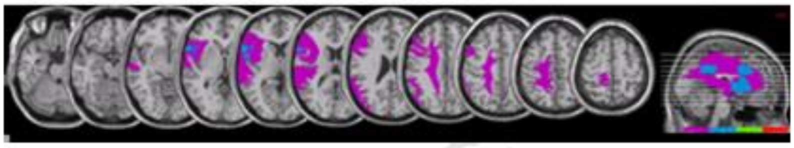


Fig. 19. CT/MRI digitalized images of five RBD (a) and of four LBD (b) patients mapped using MRIcro software. One color refers to one patient. Dark violet: one ROI (region of interest); red: all ROIs. See text for details.

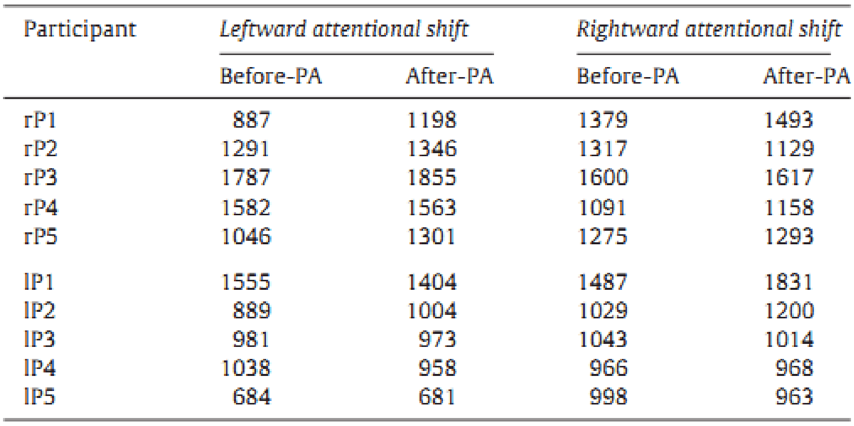
8.1.3.2 Results

PA effects on time bisection task

A shift of spatial attention to the left space induced time underestimation as compared with before PA in RBD patients (1453 ms vs 1318 ms; $p < 0.05$) but not in LBD patients (1004 ms vs 1029 ms; $p = 0.30$). A shift of spatial attention to the right space did not influence time perception either in RBD (1338 ms vs 1332 ms,

$p = 0.45$) or in LBD patients (1195ms vs 1105ms $p = 0.14$). Before PA, RBD patients tended to underestimate time durations as compared with LBD patients (1325 ms vs. 1067 ms, $p = .08$) (see Table 3 for RT values).

Table 3. Summary of RTs in time bisection task in RBD patients (rP) and LBD patients (lP) in Experiment 5.



Participant	*Leftward attentional shift*		*Rightward attentional shift*	
	Before-PA	After-PA	Before-PA	After-PA
rP1	887	1198	1379	1493
rP2	1291	1346	1317	1129
rP3	1787	1855	1600	1617
rP4	1582	1563	1091	1158
rP5	1046	1301	1275	1293
lP1	1555	1404	1487	1831
lP2	889	1004	1029	1200
lP3	981	973	1043	1014
lP4	1038	958	966	968
lP5	684	681	998	963

Tab. 3. RT values (milliseconds) of RBD patients (rP) and of LBD patients (lP) in the time bisection task before prismatic adaptation (Before-PA) and after prismatic adaptation (After-PA), for leftward shift of spatial attention (Leftward attentional shift) and rightward shift of spatial attention (Rightward attentional shift) in Experiment 5.

Prismatic Adaptation results

Error reduction: To verify that subjects showed an error reduction, we conducted an ANOVA with Group (RBD and LBD patients) as between-group variable and

Prismatic Deviation (right and left) and Condition (pre-exposure condition, first three trials of the exposure condition, last three trials of the exposure condition) as

within-subjects variables. The interaction Group x Prismatic Deviation x Condition was significant [F(1,16) = 24.26; p < 0.0001]. This analysis revealed a significant pointing deviation, in the first three trials of the exposure condition, relative to the pre-exposure condition, in RBD patients for rightward (.04 vs. 2.08) and leftward prisms (−.06 vs. −2.42, p <0.0001 for both comparisons) and in LBD patients for rightward (0 vs. 1.02, p <0.01) but not for leftward prisms (0 vs. −.56, p = .27). No difference was found between pre-exposure condition and the last three trials of the exposure condition in RBD as well as in LBD patients, for both rightward and leftward prismatic deviation. Thus, LBD patients did not exhibit the expected pointing deviation during leftward prisms exposure. Moreover, in the first three trials of the exposure condition, LBD patients showed a smaller pointing deviation than RBD patients, both with rightward (1.02 vs. 2.08 p <0.0001) and with leftward prisms (−.56 vs −2.42).

To better investigate the beginning pointing deviation and the rapidity to correct the pointing deviation, RBD and LBD patients' pointing displacement (absolute values) was submitted to an ANOVA with Group as between-group variable and Prismatic Deviation and Blocks (trials 1–3 = block 1; trials 4–6 = block 2; 7–9 = block 3) as within-subjects variables. The deviation in the first three trials is a measure of the immediate effects of prismatic lenses on pointing accuracy, whereas the deviation in the following trials is a measure of the ability to correct the pointing deviation. Indeed, if patients rapidly correct their pointing deviation, a difference should be found between the first and the second block of trials; on the other hand, if patients slowly correct their pointing deviation, the difference should not be found between the first and the second block, but rather between the second and the third block of trials. The variables Group and Blocks and their interaction were significant [F(2,16) = 21.28; p <0.0001]. The pointing deviation in the first block of trials was bigger in RBD than in the LBD patients (.22 vs .79, p <0.0002). No differences between RBD and LBD patients were found in the second (.21 vs .02, p = 0.50) and in the third block (.04 vs 0, p = 0.97). The rapidity of error reduction was similar in RBD and LBD patients, since pointing deviation was significantly reduced in the second (as well as in the third), compared with the first block of trials, in both groups of patients (p <0.001, in all comparisons) (see Fig. 20).

Figure 20

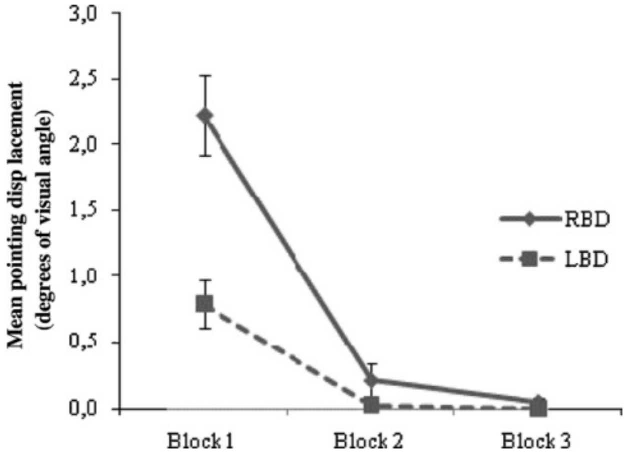


Fig. 20. Mean pointing displacement (absolute values, expressed in degrees of visual angle) of trials 1–3 (block 1), trials 4–6 (block 2) and trials 7–9 (block 3), during prism adaptation in RBD patients and LBD patients. RBD, right brain damaged patients; LBD, left brain damaged patients.

After-effect: To verify the presence of an after-effect, we conducted an ANOVA on displacement in invisible pointing with Group (RBD and LBD) as between-group variable and After-Effect (left and right) and Condition (pre-exposure and post-exposure condition) as within-subjects variables. This analysis showed a significant interaction Group x After-Effect x Condition [F(1,8) = 22.5; p <0.001]:with prisms inducing a leftward after-effect, RBD and LBD patients showed a leftward pointing deviation in the post-exposure rightward pointing deviation in the post-exposure condition, relative to the pre-exposure condition (RBD 2.13 vs .13; LBD 2.21 vs −.04, p <0.0001 in both comparison). Crucially, the leftward after effect in LBD patients was smaller than in RBD patients (−1.49 vs −3.36, p <0.0001) whereas the rightward after effect was not significantly different in LBD and RBD patients (2.21 vs 2.13, p = 0.68).

8.1.4 General discussion

The first aim of the research was to study the effects of PA on temporal deficits in brain damaged patients. Prismatic adaptation shifting spatial attention to the left induces time underestimation in both healthy subjects and RBD patients. Prismatic adaptation shifting spatial attention to the right fails to affect timing in healthy subjects or in patients. LBD patients do not present any distortion of timing following prismatic adaptation. Time underestimation following a right hemisphere damage was found in previous patients' and TMS studies (Danckert et al., 2007; Harrington et al., 1998; Koch et al., 2002, 2003; Oliveri et al., 2009a). Mapping of the distribution of brain lesions in our RBD patients presenting temporal deficits showed involvement of temporo-parietal cortex. These data are in agreement with studies suggesting a specific role of the inferior parietal cortex in time processing (Battelli et al, 2008; Bueti and Walsh, 2009; Harrington et al., 1998; Oliveri et al., 2009a). Interestingly, a greater involvement of posterior brain regions (parietal and/or temporal cortex) is reported in studies employing temporal tasks that emphasize the use of spatial codes, such as the present study and the study by Oliveri, et al. (2009a). As to the phase of time processing impaired in RBD patients, in the adopted time bisection task the supposed timing deficit could operate in the encoding phase, when the temporal interval is first presented, or in the reproduction phase, when the same interval (i.e. half of it) has to be reproduced. The more probable hypothesis is that right hemispheric damage impairs selection of response in the reproduction phase as suggested by recent data (Oliveri, et al., 2009a), showing that time is underestimated when the activity of the right hemisphere is disrupted with transcranial magnetic stimulation during the reproduction and not during the encoding phase. The time deficit showed by RBD patients is in the direction of a time underestimation. The tendency to underestimate time in RBD patients could depend on impairment of a timing mechanism per se (Wiener et al., 2009), as well as on impairment of other cognitive functions such as attention (Oliveri, et al., 2009a; Casini and Ivry, 1999), working memory or long-term memory (Koch et al., 2002, 2003). In particular, working memory deficits could have played an important role in the present study, where the temporal task required subjects to hold in mind the interval before bisecting it. The memory load is indeed greater in this task compared to a classical line bisection task, where the line's length is immediately available. For this reason, the correlation between working memory abilities and time processing in brain damaged patients should be considered in future studies. As far as the role of attention in time processing, a debated point in the literature is whether temporal processing deficits in RBD patients are correlated with the presence of contralesional spatial neglect. In fact, time underestimation in time bisection tasks was found in patients with spatial neglect (Basso et al., 1996; Danckert et al., 2007; Oliveri et al., 2009a). In Danckert et al.'s study (2007), RBD patients with and without neglect estimated time intervals as shorter compared to controls. To estimate a time interval as shorter corresponds to reproduce it as longer, that is to underestimate time interval. On the other hand, in the RBD patients of the above mentioned studies, the lesion was larger in patients with neglect compared to those without neglect. This different lesion pattern could explain the presence or absence of time underestimation. Data of the present paper suggest that time underestimation can follow lesion of the right hemisphere per se regardless of the presence of neglect, as suggested by other authors (Harrington et al., 1998; Koch et al., 2002). However, this does not exclude that spatial attention could influence time processing. Indeed, a manipulation of spatial attention by PA influences time processing: after prismatic deviation inducing a leftward shift of spatial attention, RBD patients and healthy subjects showed a significant underestimation of time duration (relative to before PA). This result is in line with the hypothesis of the existence of a mental temporal line, where short durations are represented on the left side of space and long durations on the right side of space (Frassinetti et al., 2009; Vicario et al., 2007, 2008). According to the proposed mechanism of action of prismatic adaptation procedure on time perception (Frassinetti et al., 2009), one could hypothesize that the leftward shift of spatial attention biases the temporal encoding phase of the time bisection task. Because of this bias, subjects would perceive the first part of the presented temporal interval as shorter, such that when asked to reproduce it they would produce an interval longer than the real half. In RBD patients the bias in encoding produced by rightward prismatic adaptation interacts with the bias in reproduction dependent on right brain damage, leading to a greater underestimation of the reproduced time as compared with control subjects. On the other hand, after leftward prismatic deviation (inducing a rightward shift of spatial attention) neither RBD patients nor controls showed the attended time overestimation. This finding only partially confirms previous data obtained in healthy subjects, where time underestimation and overestimation were observed respectively following leftward and rightward attentional shifts (Frassinetti et al., 2009; Vicario et al., 2007).

A possible explanation could be related to the subjects' age, being significantly higher in the control subjects of the present as compared with those of previous studies. Indeed, aging can influence mechanisms involved in cognitive functions, and it has been associated with a reduction of hemispheric asymmetries (Cabeza, 2002) and with a progressive reduction in the activity of posterior brain regions (Davis et al., 2008). Interestingly, in spatial attention tasks, Fujii, Fukatsu, Yamadori, and Kimura (1995) examining old, middle aged, and young subjects in a traditional line bisection task, found a trend of greater rightward error with increasing age. The effect of age on bisection performance has been ascribed to asymmetrical decline of hemispheres, with greater decline of the right as compared with the left hemisphere. Further studies conducted on subjects of several ages could better clarify any role of age in mediating the spatial attentional effects on time perception. As regards the second aim of the study, that was to investigate which hemisphere mediates the effects of PA on time processing, the novel finding was that LBD patients did not show any effects of PA on time processing, regardless of the side of prism deviation. In fact, there were differences in the effects of PA procedure in LBD as compared with RBD patients and controls: LBD patients presented less pointing deviation during leftward and rightward prism exposure as compared with controls and RBD patients respectively. The reduced pointing deviation with rightward prism was followed by a reduced leftward after-effect in LBD than in RBD patients. It is important to note that even though LBD patients show a reduced pointing deviation during rightward prism exposure, they are able to adapt to prismatic lenses likewise RBD patients. Moreover, the rapidity of error reduction was similar in RBD and LBD patients, as shown by the analysis conducted on the blocks of first trials during adaptation procedure. This interesting result, that was never reported in previous studies on prismatic procedure, puts forward the hypothesis of a role played by the left hemisphere in PA. Left hemisphere mediates prismatic effect on the first phase of visuo-motor adaptation. Thus, LBD patients are less sensitive to the visuo-motor shift induced by prism, independently from the side of prismatic deviation. Our hypothesis is consistent with a recent neuroimaging study showing a role of the left hemisphere in the initial pointing errors during PA (Luauté et al., 2009). The authors found that the left anterior intraparietal sulcus was activated in direct proportion to pointing deviation, while the superior temporal cortex was selectively activated during the later phase of prism exposure. Interestingly, brain lesions in our LBD patients mainly involved parieto-temporal and premotor cortex. Furthermore, studies on RBD patients with unilateral neglect (Frassinetti et al., 2002; Rossetti et al., 1998), showing an amelioration of the visual spatial deficit after rightward PA, suggest the contribution of the left intact hemisphere in mediating the effects of prism on spatial representation. Ongoing neurophysiological studies could better clarify the specific contribution of the right and the left hemisphere in mediating the effects of prismatic adaptation on spatial and temporal perception and the potential of PA to manipulate temporal in addition to spatial deficits.

Experiment 6 - Posterior Parietal Cortices role in relating spatial attention and time representation

8.2.1 Introduction

Similarly to the previous work, the present study is aimed to investigate neural correlates responsible of the interaction between spatial attention and spatial representation but here we used rTMS technique. We stimulated posterior parietal cortex (PPC), as the best candidate to discharge this integrating function since it is known to be involved both in spatial representation of time (Walsh et al. 2003; Bueti and Walsh 2009; Oliveri et al. 2009a) and in shifting spatial attention by PA (Chambers et al. 2004; Rushworth et al. 2001; Pisella et al. 2006).

Neural substrates of spatial representation of time

PPC in the right hemisphere has been described as a critical region in the spatial representation of time. Walsh's (2003) theory pointed out the right inferior parietal cortex (right IPC), as the locus of the shared metric system between space and time. As we revised in chapters 1 and 2, a lot of neuroimaging studies, searching for neural correlates of time processing, indicate a right hemispheric fronto-parietal network for cognitively controlled time in this network, frontal areas would be related to working memory functions, while parietal cortex would be related to the encoding of the metric to measure time intervals (see Chapter 1, 2 and Lewis and Miall 2006a,b, 2003b; Rao et al., 2001; Maquet et al., 1996). Moreover, neuropsychological studies show that right parietal patients are impaired in both time and space (Critchley 1953; Basso et al. 1996; Danckert et al. 2007), while frontal patients are impaired in time only (Koch et al., 2002). Together, these results, raise a suggestion: an involvement of a right fronto-parietal network for time with a specific role of parietal cortex in encoding the metric, supposed as spatially organized, of the length of time intervals, that is the spatial representation of time.

Neural substrates of Prismatic Adaptation

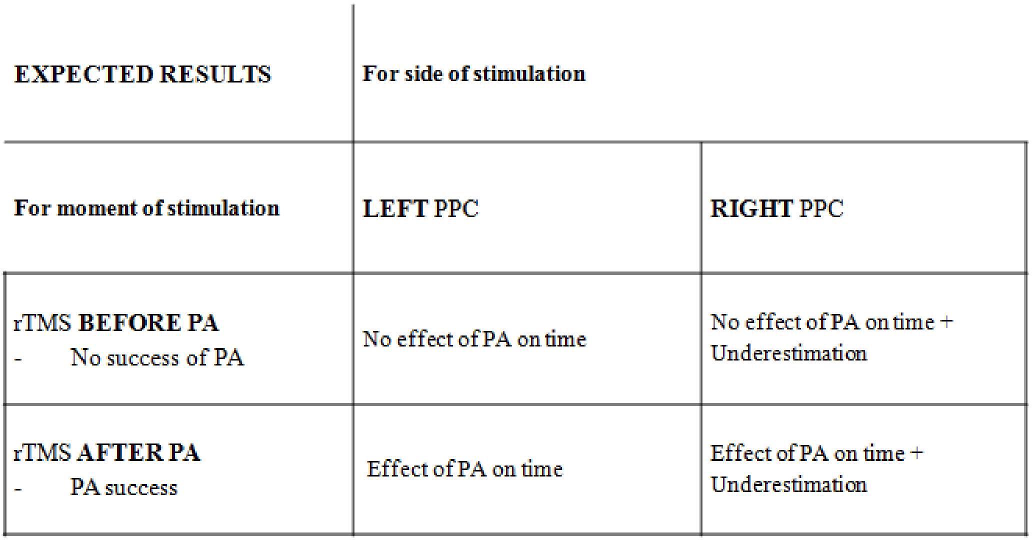
As in the previous experiments, we used PA to shift spatial attention. As far as research on cortical areas implicated in PA, neuroimaging and neuropsychological studies have described a wide cortical-subcortical network in both hemispheres. However, the most critical region in both hemispheres seems to be the Posterior Parietal Cortex (PPC). As the ending component of the *dorsal system*, also called “vision-for-action system”, PPC is consistently involved in shifting spatial attention in relation to action, making saccadic eye movements and reaching to a visual target (Corbetta and Shulman, 2002; Connolly, 2003).

In a recent fMRI study, Luauté and colleagues (2009) investigated dynamic changes in brain activity during the whole procedure of PA. An activation of bilateral PPC was found. In particular, left PPC activation was related to the detection and correction of discrepancy induced by prisms displacement between vision and proprioception. The role of the left PPC in the visuo-motor coordination in a pointing-to-target task, was already found in a pioneer PET study (Clower et al., 1996) and in a TMS study (Desmurget et al., 1999). On the other side, the role of the right PPC on visuo-spatial processing effects induced by PA is widely accepted. A recent fMRI study by Chapman and colleagues (2010), revealed a specific activation of right PPC after the adaptation to prisms. Moreover, in a previous PET study, Luauté and colleagues (2006) searched for the regions responsible of the recovery of visuo-spatial deficit after PA in a group of neglect patients. Authors found that the activity of the right PPC was related to the improvement of neglect consistent with a role of this region in the recovery of spatial representation after PA. This result suggests that right PPC is the key structure which compiles dynamic spatial mental representation as a consequence of PA attentional shift.

Here we studied the role of the right and left PPC in mediating PA procedure and the effects of PA on time. Repetitive TMS (rTMS) has been used to inhibit the left or right PPC during a well proved paradigm constructed like this: time task - PA - time task (Frassinetti et al. 2009; Magnani et al. 2010, 2011; Oliveri et al. in press). Time task consisted in encoding the duration of a visual stimulus and then in reproducing half the duration encoded before, by pressing a key. In a baseline condition, subjects performed the time task before and after PA inducing a rightward or a leftward attentional shift. According with previous findings (Frassinetti et al. 2009), in such a baseline condition, a time overestimation will be observed following a rightward attentional shift and a time underestimation will be observed following a leftward attentional shift. Then, subjects were submitted to the condition with the experimental manipulation by using rTMS: rTMS condition. They were randomly assigned to one of the groups raising from two rTMS factors: the side of TMS stimulation (left or right PPC); the moment of rTMS stimulation (before or after PA). With respect to the last point, we assumed that rTMS applied before PA interferes with the success of PA procedure, while rTMS applied after PA does not interfere with PA success.

Our hypothesis is that, if PPC (right and/or left) plays a direct role on PA procedure and/or in mediating the effects of PA on time, we expect an abolition or a reduction of PA effects on time found in the baseline condition (rightward attentional shift – overestimation; leftward attentional shift – underestimation). By contrast, when rTMS is delivered after PA, since it does not interfere with PA success, we expect an effect of PA on time (overestimation or underestimation) analogous to that found in the baseline condition. However, given the role of the right PPC in encoding the spatial representation of time described in the first paragraph, rTMS of the right, but not the left, PPC should induce an effect on the representation of time regardless of the use of PA. Indeed, a previous rTMS study using the same time task used here, demonstrated a significant underestimation of time after stimulation of the right PPC (Oliveri et al. 2009a). Consequently, when rTMS is applied after PA on the right PPC we expect an effect of PA on time analogous to that found in baseline, summed with a direct effect of rTMS on time that is an underestimation of time. The same result should not be expected for rTMS applied on left PPC. This apparent puzzling expectations can be schematized in an easier two-by-two conditions table (See Table 4).

Table 4.



EXPECTED RESULTS	**For side of stimulation**	
For moment of stimulation	**LEFT** PPC	**RIGHT** PPC
rTMS **BEFORE PA** - No success of PA	No effect of PA on time	No effect of PA on time + Underestimation
rTMS **AFTER PA** - PA success	Effect of PA on time	Effect of PA on time + Underestimation

Tab. 4. Expected results of the influence of rTMS on the effects of prismatic adaptation (PA) on time representation, schematized according to the two rTMS stimulation factors: 1) side of stimulation (LEFT or RIGHT Posterior Parietal Cortex – PPC); 2) moment of stimulation (rTMS BEFORE or AFTER PA).

8.2.2 Methods

Participants

Forty-eight right-handed healthy subjects (range = 19 to 35 years; mean age = 22 years; SD = 3.03 years) with normal or corrected vision and no history of neurological diseases, took part in the experiment. All participants were naïve as to the purpose of the study and gave their informed consent to participate in the study. All procedures were in agreement with the 1975 Helsinki Declaration.

Experimental procedure

Experimental design

All the forty-eight subjects were submitted to a time task before and after PA in a *baseline condition.* Half subjects were submitted to PA inducing a rightward attentional shift while the other half were submitted to PA inducing a leftward attentional shift. Moreover, to study the contribution of parietal cortices in mediating the effect of PA on time, subjects were submitted to *rTMS condition.* In the *rTMS condition* subjects were submitted to the time task before and after PA, as in the *baseline condition,* but applying rTMS before or after PA on the left or right PPC. Subjects were submitted to the baseline and rTMS conditions in two different sessions with an interval of at least one week.

Time reproduction/bisection task

The time bisection task was the same used in experiment 1, 2, 4 and 5. A blue circle (1°x1°) was presented in the center of a white screen with a variable duration (encoding phase) around a standard interval of 2000 ms (1600, 1800, 2000, 2200, 2400 ms). The different interval lengths were used to prevent learning. Immediately after the encoding phase, a red circle of the same size and position was presented. Subjects had to press a response button when they considered that half the duration of the previously encoded time interval (800, 900, 1000, 1100, 1200 ms) was elapsed (reproduction phase). Subjects used their right index finger to respond and they were explicitly required not to count aloud or sub-vocally during encoding and reproduction phase. Inter-trial interval was of 1000 ms. A complete run consisted of 50 trials, 10 trials for each duration. The software selected interval length pseudo-randomly. Task was first described to the subjects and they attempted two runs as practice sessions, to reach a good level of performance as demonstrated in a previous study of our group (Oliveri et al. in press).

Prismatic Adaptation procedure

Prismatic adaptation was administered following the same procedure as previous experiments. As already mentioned, half of the forty-eight subjects (range = 19 to 26 years; mean age = 22 years; DS = 2,35 years) were randomly submitted to prismatic lenses shifted to the left and inducing a rightward shift of spatial attention. The other half (range = 19 to 35 years; mean age = 22 years; SD = 3,64 years) were submitted to prismatic lenses shifted to the right and inducing a leftward shift of spatial attention.The two samples of subjects did not differ in age [t(23) = 0; p = 1].

rTMS protocol

A MagStim Rapid magnetic stimulator (MagStim, Whitland, UK), connected with a figure-of-eight coil with a diameter of 70 mm was used to deliver rTMS over two different scalp sites corresponding to the right and left PPC.

The coil was placed tangentially to the skull, over the parietal scalp sizes corresponding to P3 and P4 position of the 10-20 EEG system. The coil was held tangentially to the scalp, with the handle pointing posteriorly so as to induce a current flowing parallel to the sagittal axis with a posterior to anterior direction. rTMS was applied at 1 Hz frequency for 10 min, at an intensity of 90% of motor threshold. Motor threshold was defined as the lowest rTMS intensity (as assessed with single-pulse TMS of the motor cortex) able to induce a visible muscle twitch of the controlateral hand at least 50% of a sequence of 10 consecutive trials. The adopted rTMS is known to induce an inhibition of the stimulated cortical area lasting beyond the duration of the train.

8.2.3 Results

We initially analyzed data on prismatic adaptation procedure in the baseline condition (without rTMS), to ensure that subjects reached adaptation to prismatic lenses and showed after-effect.

Then, we analyzed performances in the time task before and after PA, in the baseline condition (without TMS), for two reasons. One reason was to ensure that subjects performed the time task properly and that PA exerted the effects on the time bisection task, in line with previous data (Frassinetti et al. 2009). Another reason was to compare a measure of PA effects on time task without and with rTMS. We also compared data of the effects of PA on time, in the baseline and rTMS conditions.

Since the expected effects of PA on time are opposite for the two sides of attentional shift (rightward attentional shift – overestimation; leftward attentional shift – underestimation), we separately analyzed the results for rightward and leftward attentional shift.

Prismatic Adaptation results

Parallel to previous experiments, for both prismatic deviations, we assessed the presence of error-reduction and after-effect in baseline condition.

Error-reduction

To verify whether subjects showed an error-reduction following rightward or leftward deviation induced by prism exposure, we compared their displacement measure in the Pre-Exposure (Visible-Pointing) Condition with that of the first three and the last three trials of the Exposure-Condition (more details on this procedure can be found in Frassinetti et al. 2002). A difference between Pre-Exposure Condition and the first three trials of the Exposure-Condition is expected due to the rightward or leftward displacement induced by prism exposure whereas, in the assumption of almost perfect error-reduction, no difference is expected between Pre-Exposure Condition and the last three trials of the Exposure-Condition. The dependent measure under consideration in this analysis was the mean displacement (expressed as degrees of visual angle) of subjects' visible pointing. For both prismatic displacements, an ANOVA was carried out with Condition (Pre-Exposure Condition, Exposure Condition-first three trials and Exposure Condition-last three trials) as within-group variable. Whenever necessary, post-hoc comparisons were conducted using the LSD test. Effect size is provided as partial eta-square.

Leftward prismatic deviation (rightward attentional shift)

The effect of Condition was significant [F (1,46) = 73,31; $p < 0.0001$; $\eta_p^2 =0,76$]. Post hoc analyses showed that pointing displacement in the Pre-Exposure Condition was significantly different from the Exposure Condition- first three trials (-0.002° vs. -1.91°, p< 0.0001) but not from Exposure Condition-last three trials (0.00°, p = 0.99) (Figure 21A).

Rightward prismatic deviation (leftward attentional shift)

The same pattern of results was found in this experiment. The effect of Condition was significant [F (1,46) = 105,52; $p < 0.0001$; $\eta_p^2 =0,82$]. Post hoc analyses showed that pointing displacement in the Pre-Exposure Condition was significantly different from the Exposure Condition- first three trials (0.003° vs. 1.83°, p< 0.0001) but not from Exposure Condition-last three trials (0.00°, p = 0.98) (Figure 21B).

Figure 21

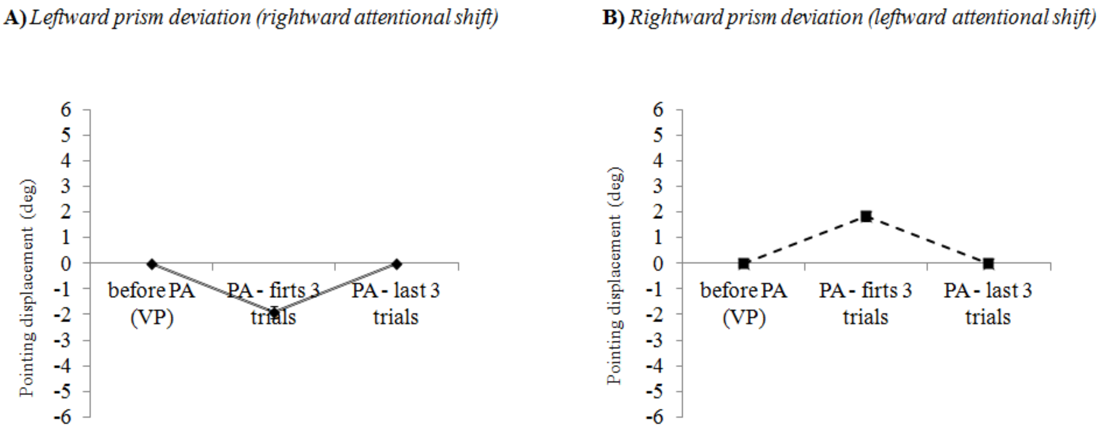


Fig. 21. Pointing deviation for A) leftward prism deviation (rightward attentional shift) and B) rightward prism deviation (leftward attentional shift). Mean pointing displacement (expressed in degrees of visual angle - deg) of subjects' visible pointing responses before prism adaptation (PA), "before PA (VP)", and mean pointing displacement of the first three (PA – first 3 trials) and the last three trials (PA – last 3 trials) during prism adaptation. Error bars indicate standard error of mean.

After-effect

To verify the presence of after-effect, we compared the subjects' displacement in the Invisible-Pointing in the Pre-Exposure and Post-Exposure Conditions. If, after prism exposure, subjects point to the direction opposite the displacement induced by prism, a difference is expected between the Pre- and the Post-Exposure Conditions (after-effect). The dependent measure was the mean displacement (expressed in degrees of visual angle) of the subjects' invisible pointing responses in the Pre-Exposure Condition and in the Post-Exposure Condition. For both prismatic displacement, a paired-samples t-test (two tailed) was conducted to compare Pre-Exposure Condition and the Post-Exposure Condition.

Leftward prismatic deviation (rightward attentional shift)

As expected, participants showed a significant [t(23) = -13,46; p <0.0001] rightward deviation in the Post-Exposure as compared to the Pre-Exposure Condition (3.73° vs -0.61°) (Figure 22A).

Rightward prismatic deviation (leftward attentional shift)

As expected, participants showed a significant [t(23) = 9,58; p <0.0001] leftward deviation in the Post-Exposure as compared to the Pre-Exposure Condition (-5.02° vs -1.03°) (Figure 22B).

Figure 22

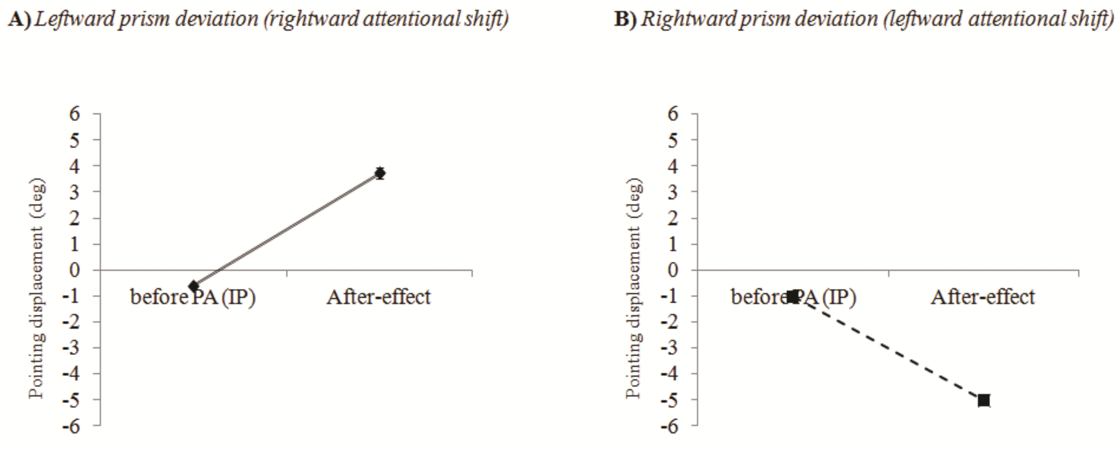


Fig. 22. Pointing deviation for A) leftward prism deviation (rightward attentional shift) and B) rightward prism deviation (leftward attentional shift). Mean pointing displacement (expressed in degrees of visual angle - deg) of subjects' invisible pointing responses before prism adaptation (PA), "before PA (IP)", and after prism adaptation (After-effect). Error bars indicate standard error of means.

Baseline condition – effects of PA on time

Performances in the time task, before and after PA, were calculated for each subject. For each prismatic deviation the means obtained before and after PA were compared by using a paired-samples t-test (two tails). The dependent measure was the mean (in milliseconds - ms) of reproduced intervals. Reproduced time intervals longer than the encoded ones were interpreted as time underestimation; reproduced intervals shorter than the encoded ones were interpreted as time overestimation (For additional details see Frassinetti et al. 2009; Magnani et al. 2011; Oliveri et al. in press).

Rightward attentional shift

As expected a time overestimation was observed [t(23) = 5,90; p < 0.0001] since subjects reproduced shorter time intervals after PA (977 ms) relative to before PA (1052 ms). The amount of overestimation (75 ms), calculated as the difference between values before PA minus after PA, is represented in Figure 23.

Leftward attentional shift

Symmetrically, a time underestimation was observed [t(23) = -5,74; p < 0.0001] since subjects reproduced longer time intervals after PA (1114 ms) relative to before PA (1022 ms). The amount of underestimation (-93 ms), calculated as the difference between values before PA minus after PA, is represented in Figure 23.

Figure 23

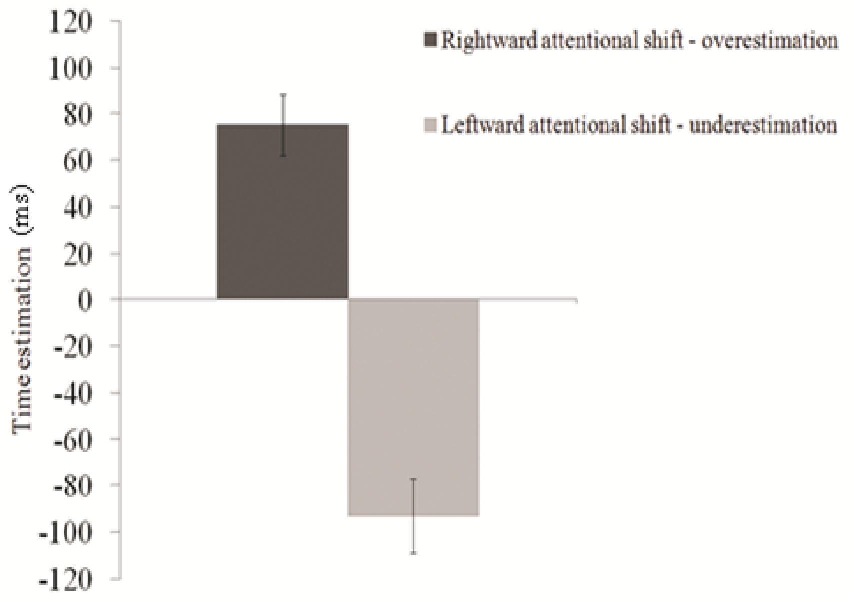


Fig. 23. Time estimation in milliseconds (ms) calculated as the mean of reproduced time before PA minus after PA, for rightward and leftward attentional shift by PA. Positive values indicate overestimation of time, while negative values indicate underestimation of time, as respectively shown for rightward and leftward attentional shift. Error bars indicate standard error of mean.

rTMS influence on PA effects on time

As a measure of PA effect on time, we considered the difference of mean reproduced intervals (ms) before PA minus after PA (negative values – underestimation; positive values – overestimation). For each attentional deviation, rightward and leftward, a first ANOVA was conducted when rTMS was applied before PA, taking Hemisphere (left vs. right) as the between-groups variable and Condition (baseline condition vs. rTMS condition) as the within-subjects variable. A second identical ANOVA was conducted when rTMS was applied after PA. Post-hoc analyses were conducted, where necessary, with the LSD (Least Significant Difference) test. Effect size is provided as partial eta-square.

Rightward attentional shift – overestimation of time

rTMS before PA

An effect of Condition was found [F (1,10) = 13,34; p = 0.004; η_p^2 =0,57]. Mean values indicate a reduction of PA effect on time (i.e. a reduction of overestimation) in the rTMS condition (13 ms) relative to baseline condition (80 ms). As expected, the absence of an effect of hemisphere (p = 0.64) and of its interaction with condition (p = 0.30), suggests that rTMS reduces the effect of PA on time relative to baseline condition, both when it is delivered on the left PPC (-6 ms vs 82 ms, t-one-tail (5) = -2,88, p = 0.02) and on the right PPC (32 ms vs 79 ms, t-one-tail (5) = 1,91, p = 0.06) (Figure 24A).

rTMS after PA

The interaction Condition x Hemisphere was significant [F (1,10) = 11,42; p = 0.007; η_p^2 =0,53]. Post-hoc analyses revealed an enhancement in the effect of PA (i.e. an increased overestimation) on time when rTMS is delivered on the left PPC relative to baseline condition (158 ms vs 42 ms, p = 0.02), and a reduction of the effect of PA on time when rTMS is delivered on the right PPC relative to baseline condition (23 ms vs 103 ms, p = 0.08) (Figure 24B). Surprisingly, when rTMS was delivered on the left PPC we obtained the effects of PA on time (overestimation) plus an additional overestimation. As expected, when rTMS was delivered on the right PPC we obtained the effects of PA on time (overestimation) plus an additional underestimation.

Figure 24

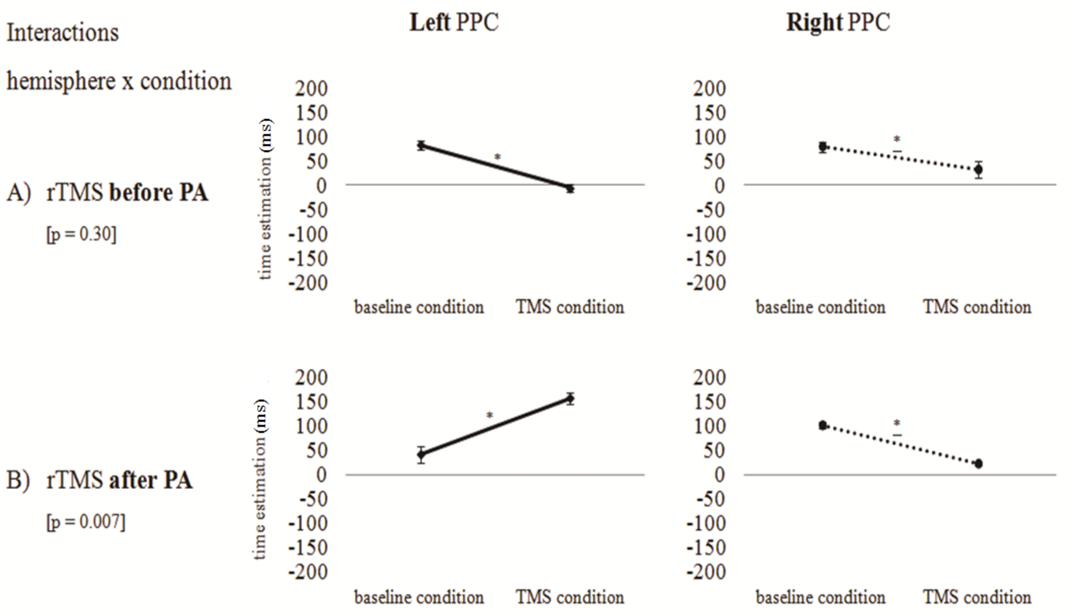


Fig. 24. Data for PA inducing a **rightward attentional shift**. Effect of the interaction between condition (baseline condition – rTMS condition) and hemisphere (Left PPC – Right PPC), when A) rTMS was applied before PA (rTMS before PA) and when, B) rTMS was applied after PA (rTMS after PA). Graphs represent the effect of PA on time (time estimation – in milliseconds) measured as the mean reproduced intervals (ms) before PA minus after PA (negative values – underestimation; positive values – overestimation). Error bars indicate standard error of mean.

Leftward attentional shift – underestimation of time

rTMS before PA

The interaction Condition x Hemisphere was significant [F(1,10) = 5,30; p = 0.04; η_p^2 =0,35]. Post hoc analysis revealed a reduction of the effect of PA (i.e. a reduction of underestimation) and a tendency toward an overestimation in the rTMS condition relative to baseline condition (69 ms vs -116 ms, p = 0.02) when left PPC was stimulated, while no difference in the underestimation was found in the rTMS condition and baseline condition when right PPC was stimulated (-75 ms vs -44 ms, p

= 0.65) (Figure 25A). In sum, we obtained the expected result of no effect of PA, for the left PPC, and no effect of PA (underestimation) plus an additional effect of underestimation for the right PPC.

rTMS after PA

The interaction Condition x Hemisphere was significant [F(1,10) = 11,10; p = 0.008; η_p^2 =0,53]. Post hoc analysis revealed a reduced effect of PA (i.e. a reduction of underestimation) in the rTMS relative to baseline condition (-36 ms vs. -138 ms, p = 0.02) when left PPC was stimulated, while an increased underestimation was found in the rTMS relative to baseline condition when right PPC was stimulated (-132 ms vs. -61 ms, p = 0.08) (Figure 25B). In sum, for rTMS on the left PPC we obtained the effects of PA on time (i.e. underestimation) plus an additional overestimation, while for rTMS on the right PPC we obtained the effects of PA on time (i.e. underestimation) plus an additional underestimation.

Figure 25

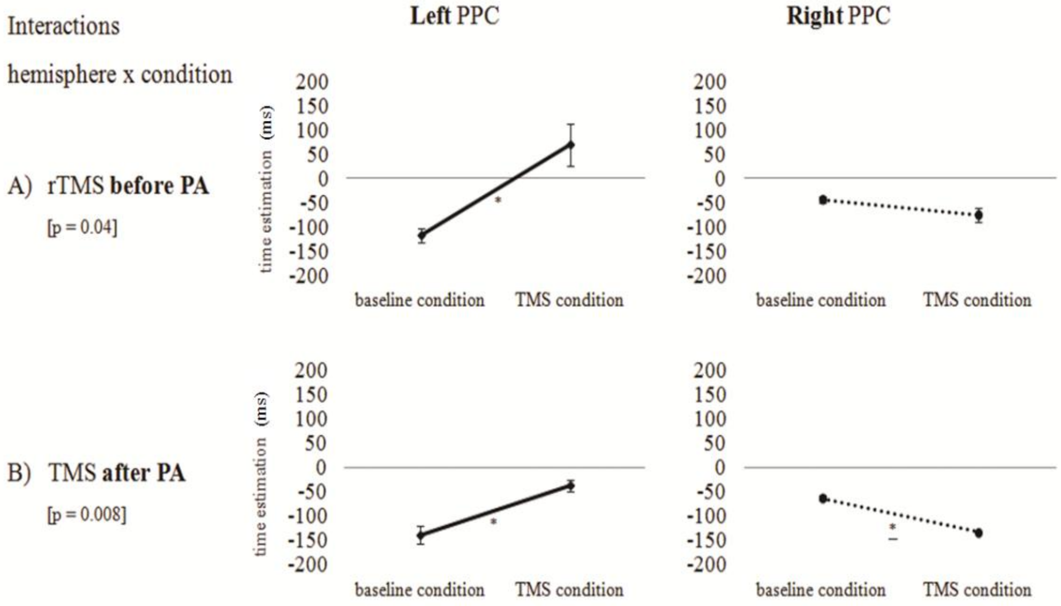


Fig. 25. Data for PA inducing a **leftward attentional shift**. Effect of the interaction between condition (baseline condition – rTMS condition) and hemisphere (Left PPC – Right PPC), when A) rTMS was applied before PA (rTMS before PA) and when, B) rTMS was applied after PA (rTMS after PA). Graphs represent the effect of PA on time (time estimation – in milliseconds) measured as the mean reproduced intervals (msec) before PA minus after PA (negative values – underestimation; positive values – overestimation). Error bars indicate standard error of mean.

rTMS influence on PA parameters

To verify the direct effects of rTMS on PA procedure, we also analyzed PA parameters, i.e. error-reduction and after-effect.

Error-reduction

To verify whether rTMS applied before PA influenced the error-reduction (ER), analyses were performed to compare ER in the baseline and in rTMS condition when rTMS was applied to the left or right PPC. As a measure of ER, we calculated the difference in the mean pointing displacement (in degrees of visual angle – deg) between the first three and the last three trials of Exposure condition (see methods chapter 1). Pointing displacement measure carries a negative sign (-) when directed to the left and a positive sign (+) when directed to the right with respect to a target actual location.

For rightward and leftward attentional shift, an ANOVA was conducted to compare the effects on the left and right PPC when rTMS was applied before PA, taking Hemisphere (left vs right) as the between-groups variable and Condition (baseline condition vs rTMS condition) as the within-subjects variable. Effect size is given as partial eta square.

Rightward attentional shift

The effect of Condition was significant [F(1,10) = 13,61; p = 0.004; η_p^2 =0,58] indicating that ER was reduced in the rTMS condition relative to baseline condition (-0.82° vs. -2.06°). The lack of effect of hemisphere (p = 0.62) and the interaction condition x hemisphere (p = 0.85) suggests that rTMS influence on ER is independent from the stimulated hemisphere.

Leftward attentional shift

The effect Condition was significant[F(1,10) = 8,68; p = 0.01; η_p^2 =0,47] indicating that ER was reduced in the rTMS condition relative to baseline condition (0.99° vs. 1.51°). The lack of effect of hemisphere (p = 0.63) and the interaction condition x hemisphere (p = 0.14) suggest that rTMS influence on ER is independent from the stimulated hemisphere.

These results indicate that rTMS applied before PA interferes with error-reduction, regardless of the side of stimulation.

After-effect

To verify whether rTMS applied before PA influenced the after-effect (AE), analyses were performed to compare after-effects in baseline and in rTMS condition when rTMS was applied to the left or right PPC. As a measure of AE, we calculated the difference in the mean pointing displacement (in degrees of visual angle – deg) between Post-Exposure condition minus Pre-Exposure condition (Invisible-Pointing)..

For rightward and leftward attentional shift, an ANOVA was conducted to compare effects on the left and right PPC when rTMS was applied before PA, taking hemisphere (left vs right) as the between-groups variable and condition (baseline condition vs rTMS condition) as the within-subjects variable.

Rightward attentional shift

The effects of hemisphere ($p = 0.10$), condition ($p = 0.21$) and their interaction were not significant ($p = 0.23$).

Leftward attentional shift

Equally, the effects of hemisphere ($p = 0.83$), condition ($p = 0.65$) and their interaction were not significant ($p = 0.11$).

These results indicate that rTMS, even if it is applied before PA does not interfere with after-effect, regardless the side of stimulation.

8.2.4 Discussion

Here we investigated the possible role of the left and right PPC on Prismatic Adaptation (PA) procedure and/or in mediating the effects of PA on the spatial representation of time. We inhibited the PPC in the two hemispheres, by using rTMS, in healthy subjects performing a time task – PA – time task paradigm (Frassinetti et al. 2009; Magnani et al. 2010, 2011; Oliveri et al. in press). In these experiments, rTMS could be applied either before or after PA. The assumption was that rTMS applied before PA interferes with the success of PA procedure, while rTMS applied after PA does not interfere with PA success.

The first result which captures the attention, is that rTMS applied on PPC before PA impairs the effects of PA on time without altering the after-effect, that is the parameter of PA we consider as related to the shift of spatial attention (Pisella et al. 2006; Serino et al. 2006; Frassinetti et al. 2002). This apparent contradiction is not in disagreement with previous evidence. During PA procedure, two primary mechanisms are responsible for producing spatially accurate movements to compensate for the discrepancy between vision and proprioception. These are the strategic control mechanism and the spatial realignment mechanism (for a detailed reviews see Redding and Wallace, 2006). The strategic control is more related to error-reduction parameter, while the spatial realignment is more related to after-effect (Redding and Wallace, 2002). Strategic control and realignment are considered two independent processes that interact with each other but that can be dissociated (Redding and Wallace, 2001) and selectively impaired (Newport and Jackson, 2006). For instance, Newport and Jackson (2006), showed a double dissociation between strategic control and realignment in the same patient with a bilateral posterior parietal damage. Authors proposed a model for the role of PPC in these two processes, suggesting a parieto-cerebellar loop for strategic control and a premotor-cerebellar loop for realignment. Our results with rTMS on error-reduction and after-effect are in line with this model, supporting a role of PPC of both hemispheres on strategic control (error reduction) and not in spatial realignment (after-effect). Indeed, we found an interference of rTMS on bilateral PPC on error reduction and not on after-effect. Thus, we can state that realignment (after-effect) occurred even following an interference with strategic control induced by rTMS on PPC in both hemispheres. In this vein, Newport and Jackson (2006) suggested that for successful realignment (after-effect) the ability to implement control strategies is not necessary.

More interestingly and in line with the aim of the study, we found that rTMS applied before PA reduces the effect of PA on time perception, regardless of the side of attentional shift induced by PA, as well of the side of PPC stimulation. This finding suggests a role of PPC of both hemispheres on PA procedure and/or in mediating the effect of PA on spatial representation of time. Indeed, the interference of rTMS with the component of strategic control would suggest a direct role of bilateral PPC on PA procedure. However, a more direct role of both PPCs in mediating the effects of PA on spatial representation of time cannot be excluded. Regarding this point, in their review on the role of PPC in the visuo-motor behavior, Rushworth and Taylor (2006) suggested that bilateral PPC is crucial in orienting what they call “motor attention” (or “motor-intention”). A recent study by Fortis et al., (2011) suggested that the effects of PA on spatial representations could be explained in terms of a shift of motor-attention behaviour. The terms “motor-attention” (Rushworth et al. 1997) or “motor-intention” (Andersen and Buneo, 2002; Boussaoud and Wise, 1993), refer to the visuo-motor behaviour by which the shift of attention and movement are closely linked (Rizzolatti et al. 1985). Our opinion in this regard is that after PA, attention and movement are inextricably directed toward the same side of space in a way that “the side where I’m going to act is the side where I’m going to pay attention” and vice-versa. This general orientation of the whole spatial behaviour would reflect both on perceptual-motor responses to the external word and on any kind of spatial representations, including the spatial representation of time. In this perspective, our results in line with previous ones, suggest that left and right PPC interact with each other to allow the “motor-perceptual attentional” shift, necessary to manipulate spatial representations, including that of time.

We also found a specific effect of rTMS of the right PPC on time perception task. Indeed, when we stimulated right PPC we found a constant effect of underestimation of time regardless of the moment of rTMS application. This finding is in line with an exclusive implication of the right PPC in encoding (Walsh 2003; Bueti and Walsh

2009) and manipulating the metric of the spatial representation of time (Oliveri et al. 2009a). In support of this hypothesis, previous studies showed that TMS on the right PPC affects the rotation and manipulation of visuo-spatial mental images in several contexts (Bestmann et al. 2002; Sack et al. 2005). Therefore, the right PPC could play a double role in the relation between PA and time: 1) mediating the effect of PA on time directing the motor-perceptual attention induced by PA together with the left PPC, 2) affecting the spatial representation of time per se.

Surprisingly, we also found an effect of overestimation of time, when rTMS was applied on the left PPC. This unexpected result would raise the possibility of a direct involvement of this area in the representation of time. Prior studies support the hypothesis of a role of the left hemisphere in timing (Pouthas et al., 2005; Praamastra et al., 2006). However, they implicate the left hemisphere in timing processes different from those studied here. In a recent review, Coull and Nobre (2008) clarified the apparent inconsistency and confusion in the literature about hemispheric lateralization of different timing processes. They retained that the main distinction we have to keep in mind, when studying the neural correlates of time, is that between implicit and explicit timing. The crucial difference between implicit and explicit timing is whether or not the task instructions require subjects to provide an overt estimation of time durations. For *implicit* timing tasks, the interval duration is not the goal of the task, but, for example, timing information about inputs are used to build an *expectation* of when the next stimulus will appear. By contrast, for *explicit* time tasks, subjects are aimed to provide an accurate estimation of *elapsed* time. Revising literature, based on this distinction, Coull and Nobre (2008) concluded that implicit timing (temporal expectation) relies upon a circuit involving left parieto-frontal network. By contrast the cortical network enrolled by explicit timing would be a right parieto-frontal network.

In line with this conclusion, recent findings suggest a strong involvement of the left parietal cortex in the “temporal expectation” function defined as the allocation of attentional resources in time (Cotti et al., 2011). Therefore, one could speculate that time overestimation following rTMS of the left PPC after PA reflects a direct role of the left PPC in orienting attentional resources in time expectation (implicit timing). However, this speculation can be excluded for at least two reasons. The former is that a reduction, by rTMS on left PPC, in attentional resources to time would have provoked an underestimation, rather than overestimation, of time (Rao et al., 2001; Wearden, 2004). The latter is that the paradigm we used was an explicit timing task, well demonstrated to involve right hemispheric circuit (Lewis and Miall, 2006b; Oliveri et al., 2009a). Furthermore, we think that the task we employed here, preferentially recruits the right PPC, since subjects were required to bisect the interval representation to set the correspondent midpoint, similar to what happens for line bisection (Oliveri et al., 2009a). Accordingly, Oliveri et al. (2009a), stimulating right and left PPC with rTMS, using the same time bisection task, found a significant underestimation of time following right PPC stimulation, whereas no significant effects were found following left PPC stimulation. The only difference between Oliveri et al.’s (2009a) paradigm and the present one is the use of PA. Therefore, we favour an explanation of the effects of left PPC rTMS in terms of imbalance of excitability between left and right hemisphere induced by the combined action of PA and PPC rTMS. We think that in normal conditions, left PPC inhibits the activity of the right PPC. Thus in our paradigm, when left PPC is deactivated, right PPC could be over activated both by the lack of inhibition by the left PPC and by PA effects on spatial attention orienting. As a result, an over activation of the right PPC would induce an overestimation of time opposite to the underestimation of time induced by its inhibition.

Our findings reveal an interactive role of the posterior parietal cortices in the two hemispheres in the implementation of the effects of a shift spatial attention by means of PA on the spatial representation of time. These findings and previous evidence, can be summarized and explained with a speculative model of the neural correlates of PA effects on time.

We suggest that the representation of a temporal interval is coded and stored in the right PPC. The spatial realignment during prismatic procedure (measured by after-effect) involves a different network, that is a premotor-cerebellar loop (Newport and Jackson, 2006). Following realignment, both left and right PPC are involved in the orientation of spatial (motor and perceptual) behavior induced by PA. This orientation of the whole spatial behaviour would reflect on any kind of spatial representations. As a consequence of this orientation of the spatial behaviour, a modification of the spatial representation of time takes place in the right PPC. The modified representation of time intervals is now available in the right PPC for the response required by the task.

In conclusion, the present study attempted to understand the neural correlates subtending the effects of prismatic adaptation on the spatial representation of time, focusing on posterior parietal cortices. We suggest a model implying a close interaction between left and right PPCs, for the PA procedure success, for the PA effects on time and for the direct influence of PPC on time. Future studies will help to investigate more deeply this interaction and to prove the validity of the model proposed.

8.3 Experiment 7 – Functional imaging of the interaction between spatial attention and time

8.3.1 Introduction

After exploring the contribution of the two hemispheres and of the two parietal cortices in mediating the effect of PA on time, here we searched for the cortical areas responsible of such effect. We implemented an fMRI study where healthy participants underwent a time-experimental task and a visual-control task during scanning and a session of PA outside the scanner. The two task employed were identical with the exception that in the time task, subjects pressed a key according with the time duration of a visual cue. In the visual task subjects had not encode any duration and pressed a key according with the appearance of a visual cue. Subjects were scanned while performing the two tasks combined in a block-design, before the PA session, after the PA session and after 30 minutes from the PA session. The effect on time immediately after a session of PA are well known (see experiments 1, 2 and 6). The necessity to scan after 30 minute from the PA manipulation, came from the pilot study of the present experiment. A group of participants, who did not take part to the experiment, was submitted to a session of time-task and visual-task before PA, immediately after PA and after 30 minutes from PA. The goal was to understand the moment of the maximal effect of PA on time, in order to design the scanning procedure. We found the classical underestimation of time immediately after PA inducing a leftward aftereffect (Frassinetti et al., 2009) and null effect of PA on the visual task. Surprisingly, we found a significant increased effect of PA (i.e. an increased underestimation) after 30 minutes relative to immediately after. For this reason we decided to investigate the activations related to PA effects on time both immediately and after 30 minutes from the manipulation.

In line with previous studies (Bueti et al., 2008; Lewis and Miall 2003a,b, 2006b; see also chapter 1, 1.2 para) we expect to find an activation of a wide circuit for the time task before PA manipulation, including basal ganglia, parietal temporal and frontal areas especially in the right hemisphere. Then we will explore and discuss the activation in the time task, contrasted with the visual task, after PA and after 30 minutes from PA, relative to before PA.

8.3.2 Methods

Participants

Seventeen healthy volunteers (5 male, aged 18-34 years, mean = 23 years, SD = 4,9 years) were involved. All participants were naïve as to the purposes of the research and gave their written informed consent to participate in the study, which was approved by the Birkbeck-UCL Centre for Neuroimaging Etichs Commette.

Stimuli and Tasks

We designed two tasks (modified version of the Bueti et al.'s (2008) task): one experimental task (time-task) and one control task (visual-task) (Figure 26 for a graphical representation). The stimuli used for the both tasks were identical. A first standard red square (1°x1° degree of visual angle) was presented at the center of the screen for a variable period between five possible durations (1600, 1800, 2000, 2200, 2400 ms). When the square disappeared, it was replaced by a cross that could last from 1000 to 3000 ms.

In the **time-task** (experimental), subjects were instructed to **encode the duration** of the standard red square. Then, after the cross disappeared subjects were instructed to press a key. The key pressing controlled the appearance of a second red square that disappeared when the key was released. Subjects were instructed to hold the key until the target duration matched the standard duration.

In the visual-task (control), subjects were instructed to **not encode the duration** of the standard red square. Then, after the cross disappeared, it was replaced by a second red square that could last one of the five possible durations. Subjects were instructed to press the key when the square appeared and release the key when the square disappeared. We called this task with the name of "visual" since, the instruction to press and release the key is given solely by the appearance of the visual cue. By contrast in the time-task, subjects press and release the key according with a temporal interval encoded. Thus, the visual control task matches the demands of the time experimental task, with exception of the encoding and reproducing a temporal interval.

Figure 26

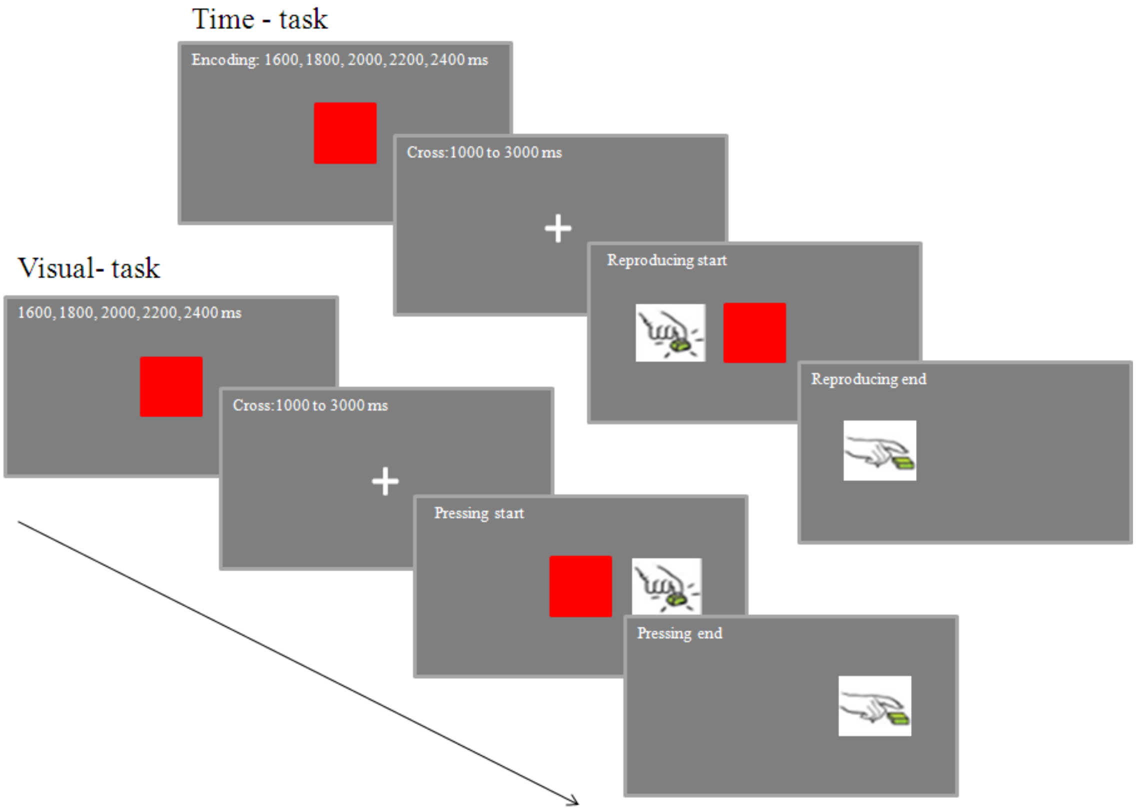


Fig. 26. Graphical representation of sequence of events in each trial for the two tasks. For both tasks, first a red square appeared and lasted 1600, 1800, 2000, 2200 or 2400 ms. In the time task an encoding of this time is requested while in the visual task it is not. Then a cross lasting from 1000 to 3000 ms appeared. After the cross disappearance in the time task subjects were instructed to press a key leading a second square appearance (reproducing start) and to release the key after time reproduction (reproducing end). In the visual task a square appeared instructing subjects to press a key (pressing start) then it disappears instructing subjects to release the key (pressing end).

Prismatic Adaptation procedure

Prismatic adaptation procedure is the same adopted in the previous studies and it was administered out of the scan (see paradigm below). All subjects were submitted to the same rightward prismatic lenses inducing a leftward aftereffect. In agreement with previous experiments (see chapter 6, 7 and 8 and Frassinetti et al., 2009) an underestimation of time is expected after this aftereffect direction after PA relative to before PA.

Paradigm

Subjects performed each of the two tasks in different blocks of trials in a blocked design for fMRI. Each session scanning comprised two runs of 5 blocks each, for a total of 10 block for session. Half blocks were deputed to the time-task and the other half were deputed to visual-task. Blocks order was randomized in each session following the ABBA method. Each block comprised 25 trials, five for one duration (1600, 1800, 2000, 2200, 2400 ms). The block started with a string (“Time task” or “Visual task”), lasting 10 seconds, instructing subjects about the task of next block. Block duration for the time-task varied slightly because it was determined by the subjects’ temporal response (encoding/reproduction) (on average 38.2 sec, SD = 4 sec). For the visual task the variability depends only on RT latency and the block duration was more precise (39 sec, SD = 1).

After the entire separate fMRI protocol, the subject was trained with 10 trials for each task before scanning. The participant was than submitted to three session scanning lasting 10 minutes each (Figure 27). The first session was the pre-PA session. After the pre-PA session the subjects left the scan, to attend the PA procedure off the machine in a separate room, for about 20 minutes. After PA, the subject was rearranged in the scan for the second scanning: the post-PA session. Before the beginning of the third session, the participant lied in the scan for about 13 minutes, while the experimenter recorded the structural images. The aim of this third session was to analyze the activity after 30 minute from PA. For this reason, we computed the sum between the duration of the second session and the structural recording, and we waited for the remaining minutes to reach 30. At this point the third scanning, called post-30-PA, started.

Figure 27

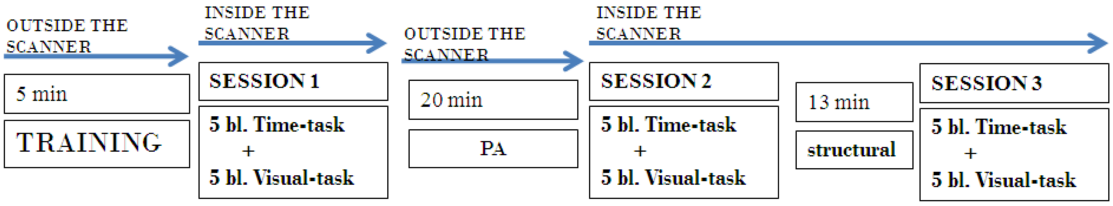


Fig. 27. Graphical representation of experimental paradigm. The three session scanning (session 1, 2 and 3), comprised 5 blocks (bl.) for each task (Time-task, Visual-task). The scanning was preceded by a training phase. Session 1 and 2 were separated by PA procedure. Session 2 and 3 were separated by the recording of structural images.

fMRI scanning

A 1.5-T Siements was used to acquire T2*-weighted echo-planar (EPI) image volumes with blood oxygenation level-dependent contrast. Each EPI volume comprised thirty-eight 2-mm axial slices with an in-plan resolution of 2 x 2 mm positioned to cover the whole brain. For each of the three session two runs were performed. For each run an average of 84 volumes (ranging from 74-90) were recorded. The first four volumes of each run were discarded to led T1 equilibration effects. Volumes were acquired continuously with a TR of 3.32 sec per volume.

Participants all underwent the whole experimental paradigm, but five participant were not included in the analysis. Two participants had problem with the images recordings. Three out of seventeen participants did not show the expected effect of PA on time. Since this is a well-documented effect (Frassinetti et al., 2009; Magnani et al., 2010) and since we are looking for the cortical bases of this peculiar effect, we decide to not analyze functional data of such participants.

8.3.3 Analysis

Behavioral data

The dependent measure for the analyses was the RT of the key pressing. In the time-task it corresponded to the reproduced interval. In the visual-task it corresponded to the length of the second red square. An ANOVA with Session (pre-PA, post-PA, post-30-PA), as a within subjects variable, was conducted for each task. Post-hoc analyses were conducted with the LSD test.

fMRI data

Functional images were analyzed using Statistical Parametric Mapping package (SPM8, Wellcome Department of Imaging Neuroscience, University College of London). Since the subjects moved in and out the scanner, we performed the pre-processing separately for every session, so that for each subject we obtained three sets of imaging data: pre-PA, post-PA and post-30-PA. The pre-processing however followed the same procedure. Images volume were realigned, spatially normalized to a standard EPI template volume based on MNI reference brain in the space of a Talairach and Tournoux (1988) and sampled to a 2-mm isotropic voxels. The normalized image volumes were then smoothed with an isotropic 8-mm full-width half-maximum (FWHM) Gaussian kernel.

Voxel activation was identified using a statistical model containing two regressors representing the two tasks. To model the regressor a boxcar, convolved with a canonical hemodynamic response function, was used. The model also included the motion correction parameters (effects of no interest). To remove low-frequency signal drifts we used a 0.0128 Hz high-pass filter.

A first single-level analysis was performed for all 12 subject, in which linear contrasts were used to test hypothesis of regionally specific tasks effect. For each subjects and each session, statistical parametric maps of the t statistic for the contrast of interest, transformed into corresponding Z value, were computed. For each session (pre-PA, post-PA and post-30-PA) the contrasts of interest were computed:

1-Time-task – baseline

2-Visual-task – baseline

For baseline we intended the lower level of brain activation during scanning sessions. The subjects' minimum activity during tasks, was looking at the instructions for 10 seconds, that were a two-words string ("Time task" or "Visual task") indicating the next block task.

These contrasts maps were entered in a second-level random effect analyses. First we searched for the activations in the time-task and in the visual-task, contrasted with baseline, in the pre-PA session. The activations surviving at a lower threshold of $p<0.001$ uncorrected for multiple comparison in a whole brain volume are listed in Table 5.

Since we were particularly interested to the activations responsible for the effects of PA on time, we compared the signal on time vs visual task in the two sessions after PA relative to the session pre-PA. Statistical inference was derived from two full-factorial ANOVAs with Tasks (Time-task, Visual-task) and Sessions (post-PA vs pre-PA or post-30-PA vs pre-PA) as factors. Then we applied a small volume correction by using a mask including all those voxels that are active in at least one of the two tasks conditions. The activations surviving to a threshold of $p<0.05$, FWE corrected, at a peak level will be discussed.

Table 5. Stereotaxic Brain MNI Coordinates (mm) for Regions Activated in the Time task at p < .001, Uncorrected for Multiple Comparisons at the peak level.

Areas	x	y	z	Z-score
TIME TASK				
Frontal lobe				
Precentral gyrus (BA 4) L	-52	-16	42	3.53
Inferior frontal gyrus (BA 47-9) R	34	24	-10	3.35
	42	10	22	3.46
Middle frontal gyrus (BA 10) R	30	42	8	3.27
Parietal lobe				
Inferior parietal lobule (BA 40) L	-42	-50	52	3.27
Postcentral gyrus (BA 3) R	42	-26	54	3.45
Temporal lobe				
Middle temporal gyrus (BA 39) R	30	-56	22	3.27
Superior temporal gyrus (BA 22) L	-58	-44	10	3.59
Sub-lobar				
Insula R	36	20	0	3.11
Striatum L	-28	-8	10	3.35
	-30	-6	-14	3.34
Striatum R	24	20	0	3.45
Caudate	14	16	-10	3.30
VISUAL TASK				
Frontal lobe				
Inferior frontal gyrus (BA 13) L	-28	16	-16	3.19
Middle frontal gyrus (BA 10) L	-20	46	-6	3.27
	-40	40	10	3.19
Parietal lobe				
Postcentral gyrus (BA 2) L	-50	-22	32	3.34
Temporal lobe				
Superior temporal gyrus (BA 22) L	-56	-44	10	3.33
(BA 41) L	-46	-36	2	3.19
(BA 42) L	-60	-26	12	3.63
Sub - lobar				
Insula L	-44	-38	18	3.29
Caudate L	-12	8	26	4.83
	-8	10	-2	3.37
Claustrum R	30	8	10	3.23

Tab. 5.BA = Brodmann's area; L = left hemisphere; R = right hemisphere.

8.3.4 Results

Behavioral results

ANOVA on the time task revealed a significant effect of Session [F(1,22) = 5,58; p = 0.01; η_p^2 =0,34]. Compared with the pre-PA session (1738 ms), subjects reproduced longer intervals in the post-PA session (1852 ms, $p < 0.05$) and much in the post-30-PA session (1923 ms, p = 0.003). Despite a trend toward a longer reproduction between the post-PA and post-30-PA, this difference was not significant (p = 0.22) (Figure 28A).

ANOVA on the visual task did not reveal a significant effect of session (p = 0.59). Reproduced intervals in the pre-PA session (2044 ms) were equal to that of the post-PA (2063 ms) and post-30-PA (2049 ms) sessions (Figure 28B).

Figure 28

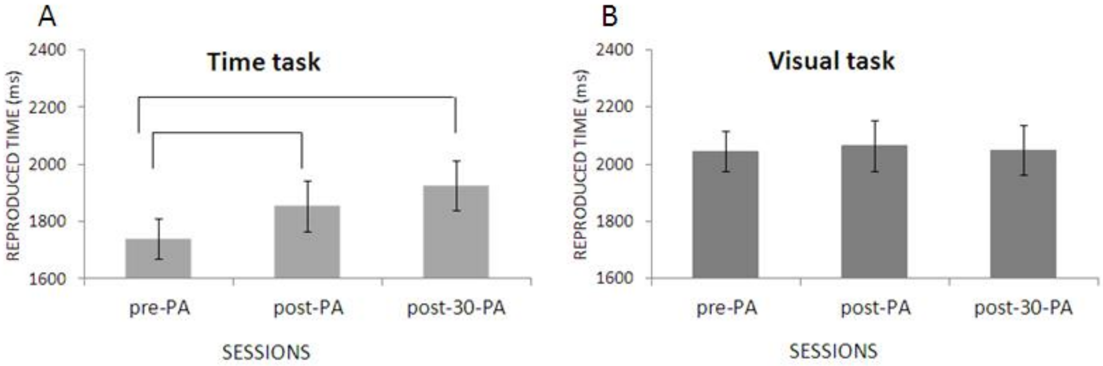


Fig. 28. Interaction between sessions for the Time task and Visual task. Mean of reproduced time (milliseconds - ms) for session pre-PA, post-PA and post-30-PA. Post-hoc were significant between pre-PA and post-PA and also between pre-PA and post-30-PA in the time and not visual task. Error bars represent standard errors of the means.

fMRI results

post-PA – pre-PA

Regions more activation in the time-task relative to the visual-task, in the post-PA session compared to pre-PA, are in the frontal cortex and principally in the left inferior and superior frontal gyrus and the left anterior cingulate cortex (all significant at $p < 0.05$ corrected at peak level) (Figure 29 – for coordinates).

Figure 29

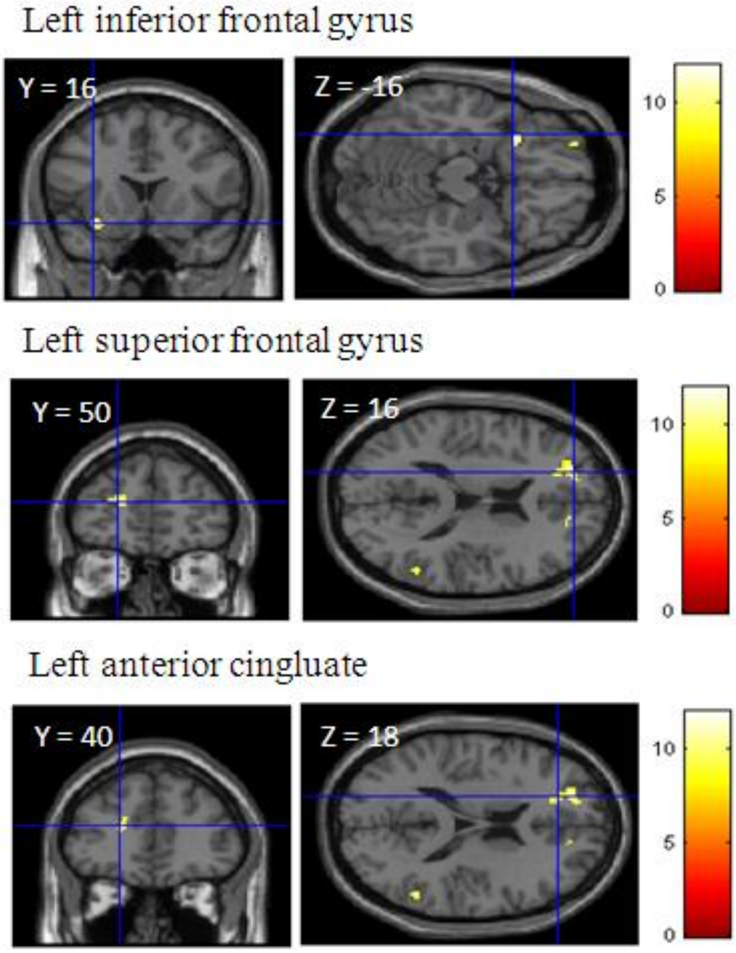


Fig. 29. Loci activated by different statistical contrasts (see Results) overlaid on the average canonical T1-weighted structural image in the stereotactic space of Talairach and Tournoux (1988). Significant activations at a $p < 0.05$ corrected level. Activations are shown in coronal view, in y coordinates, and axial view in z coordinates.

Post-30-PA – pre-PA

Regions more activation in the time-task relative to the visual-task, in the post-PA session compared to pre-PA, are in the frontal cortex and principally in the left middle gyrus and the left anterior cingulate cortex (all significant at $p < 0.05$ corrected at peak level) (Figure 30 – for coordinates).

Figure 30

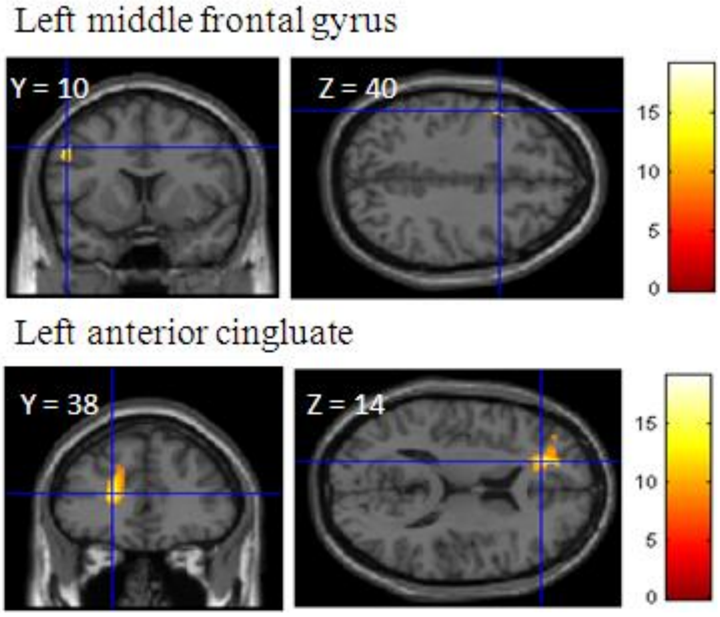


Fig. 30. See Fig. 29.

8.3.5 Discussion

The first results of the present study is the activation of a wide cortical network of areas for time task, in line with the findings of previous studies on time processing neural bases (Bueti et al., 2008; Lewis and Miall 2003a,b; Coull et al., 2004). For example, we found an activation in the right frontal cortex, in the left and right parietal cortices, left and right temporal lobes and in the insula and the striatum (see chapter 1 for the role of each area on time processing). Also the visual task activated a wide circuit of frontal parietal and temporal areas but more lateralized in the left hemisphere. This is in line with a dominance of the right hemisphere in time, relative to the left hemisphere (Lewis and Miall 2003a,b, 2006b; Harrington et al., 1998; Koch et al., 2002, 2003, 2009; Oliveri et al., 2009a; Oliveri et al., in press). Interestingly, from the observation of table 5, is evident that primary motor cortex (M1 - BA 4) is active for the time task and not for the visual task. However, the two tasks required the same kind of motor program and motor response. Moreover, the behavioral results showed that RT were longer in the visual than in the time task. Thus, one should expect that the activation of BA 4 was at least equal for the two tasks. One possible explanation is that the process of encoding a duration reflects on the activity in the primary motor cortex. In other word M1 would be more active for temporal-encoded motor responses than visual-related and repetitive motor responses.

The mere activations related to time were not the main goal of the present study, but searched for areas responsible of the effects of PA on time. The areas found as significantly active in the time task relative to the visual task after PA relative to before PA are intriguing. We found an activation of left frontal lobe especially in the left superior frontal gyrus, left cingulated cortex and left inferior frontal gyrus.

The superior frontal gyrus is associated to higher levels of executive processing especially in spatial cognition, although the domain specificity is not exclusive and is overridden by an increase in executive demand, regardless the domain being processed (du Boisgueheneuc et al., 2006). The activity in this area related to PA effects on time, could be attributed to the involvement of executive resources when processing a time duration after a spatial manipulation. The cingulated cortex is part of a large system of structures that are involved in similar functions. These structures are in the rostral limbic region and include amigdala, striatum, orbitofrontal and anterior insular cortex.

This system is deputed to the motivational content of internal and external stimuli, regulates context-dependent behavior and visceromotor controls. Also the area in the left inferior frontal gyrus we found, is near to this system, close to the insular cortex (see Figure 29). As we exposed in the chapter 1 insular cortex has been recently associated to time processing. Craig (2009), suggested that, through the temporal integration of enteroceptive signals from within the body, the insula provides a series of ‘emotion moments’ in time. The perception of duration would be defined by the integration of these successive moments, formed by information originating within the body. After Craig, Wittmann et al., (2010b) pointed out the insula in time processing. Authors searched for neural basis of time dilatation effect. An object moving towards an observer is subjectively perceived as lasting longer than the same object that is static or moving away. With a fMRI study, Wittmann and colleagues showed that the illusion of temporal dilation is due to activation of the insula. Authors suggested that this area is the locus of the processing of the passage of time and the locus of subjective time dilatation. The activation of these areas related to the effects of PA on time would suggest that PA acts on time by compress and expand the experience of time passage according with the spatial side of attentional manipulation.

Finally, after thirty minutes from PA, left inferior frontal gyrus (next to the insula) was not active. Activations were again in the anterior cingulate cortex and in the middle frontal gyrus. The middle frontal gyrus is associate to working memory especially in sustained mnemonic response and prominently in the storage of spatial information. These findings, suggest that after 30 minutes the effect of PA on time, is more related to a stored representation of time, rather than a dilatation of time experience.

CHAPTER 9. IMPAIRMENT AND REHABILITATION OF THE SPATIAL REPRESENTATION OF TIME

9.1 Experiment 8 - Prismatic adaptation effects on spatial representation of time in neglect patients

9.1.1 Introduction

An interesting model to study the link between spatial attention and time representation is constituted by patients with visual spatial neglect. Indeed, neglect patients, after a lesion of the right hemisphere, show a deficit in orienting spatial attention toward the controlesional space (i.e. the left hemispace) and a severe attentional bias toward the ipsilesional space (i.e. the right hemispace) (Husain and Rorden, 2003; Mesulam, 1999; Driver and Mattingley, 1998). We know that in addition to spatial deficits, time perception deficits have been described in neglect patients (Basso et al., 1996; Becchio and Bertone, 2006; Danckert et al., 2007; Oliveri et al., 2009a). The rightward bias of spatial attention in neglect patients can be reduced by means of one session of PA (Rossetti et al., 1998; Farnè et al., 2002; for a review see Rode et al., 2003). In the chapter 8 (experiments 4 and 5) we described the effects of prismatic lenses on time in right brain damaged patients without neglect (RBD-N-) and in age-matched healthy controls (Magnani et al., 2011). PA inducing leftward attentional deviation biased time perception in RBD-N- patients and in controls, while PA inducing a rightward attentional deviation failed to affect time perception in either group. However the effects of prismatic lenses on time perception in RBD patients with neglect (RBD-N+) were never investigated.

A first aim of this study is to investigate the impact of a spatial attention deficit following a right hemispheric stroke on the *spatial representation of time*. A second aim is to assess if a reduction of the spatial attention deficit by means of PA is able to ameliorate the *spatial representation of time* in right brain damaged patients with neglect. Right brain damaged patients with neglect (RBD-N+), right brain damaged patients without neglect (RBD-N-) and age-matched healthy subjects (HC), were submitted to a time bisection task, before and after a single session of PA. PA inducing a leftward attentional shift was chosen for two reasons: first, according to the side of PA used for the rehabilitation of spatial deficit in neglect patients; second, considering the lack of effect of PA inducing a rightward attentional shift on time in brain damaged patients in our previous study (Magnani et al., 2011). Since right brain damaged patients, regardless of the presence of neglect, are often impaired in temporal tasks (Basso et al., 1996; Danckert et al., 2007; Koch et al., 2002), we expect to replicate the result of a compromised performance of both RDB-N+ and RDB-N- (i.e. underestimation of time) in the time task compared to HC.

However, a crucial involvement of the right, rather than the left, hemisphere in controlling time perception is well established in the literature (Harrington et al., 1998; Koch et al., 2002, 2003; Lewis and Miall, 2006b; Oliveri et al., 2009a). The attempt of the present study is to go beyond the general role of the right hemisphere in time, focusing on the possible and peculiar influence of spatial attention on the representation of time. In this regard, if spatial attention actually plays a role in shaping the spatial representation of time, RBD-N+ are expected to be more impaired on the time task compared to RBD-N- and HC. Concerning the effects of PA on time perception deficit in neglect patients, if PA can actually ameliorate spatial representations, we expected a reduction of the impairment in the spatial representation of time in RBD-N+ patients after PA compared to before PA in the time bisection task.

9.1.2 Methods

Participants and Neuropsychological assessment

Twenty patients with unilateral right brain damage, ten with neglect (RBD-N+ , 3 male; mean age = 69.8 years; SD = 8.3 years; mean education = 7 years) and ten without neglect (RBD-N-, 7 male; mean age = 71.1 years; SD = 8.3 years; mean education = 8.5 years) and ten participants without history of neurological or psychiatric disease (3 male, mean age = 60.7 years; SD = 7.8 years; mean education = 9.1 years) gave their informed consent to participate in the study, which was approved by the local ethics committee. All procedures were in agreement with the 1975 Helsinki Declaration. Patients were recruited consecutively at the Fondazione Maugeri Hospital (Castel Goffredo, Italy). The criterions for exclusion from the study were the presence of cognitive impairment (score lower than 24 at the Mini-Mental State Examination; Folstein et al., 1975). Moreover according with previous evidence of a lack of effect of prismatic adaptation in patients with occipital lesion and visual field deficit (Frassinetti et al., 2002), patients with this characteristic were not recruited for the study. All patients but one (nP10 patient in Table 6) were tested in the acute phase (i.e. after one to two months from the stroke). To assess the presence of neglect, all RBD patients were tested by using BIT Conventional (Wilson et al., 1987). Ten patients, who showed a performance lower than the cut-off at BIT Conventional were selected as RBD-N+ patients and were assessed, before and after PA, with the Bell cancellation test (Gauthier et al., 1989) and the Line bisection test. We wanted also to investigate whether PA exerts its effect on further tasks. Our aim was to assess the possible relationship between the effects of PA on temporal and spatial tasks with that on temporal and attentional non/spatial tasks. To our aim, six out of the ten RBD-N+ patients were assessed with additional tests before and after PA: drawing Copy test

(Gainotti et al., 1972), clock Drawing test (Normative data, Mondini et al., 2003), reading test (Làdavas et al., 1997), spatial span (Corsi Block tapping task, Normative data, Orsini et al., 1987), sustained attention (SART 2000 – Robertson et al., 1997) and selective attention (Attentive Matrix, Normative data, Della Sala et al., 1992; Stroop test, Normative data, Caffarra et al., 2002).

Table 6

	Tests for neglect assessment													*Tests for attention and memory assessment*									
	BIT	BCT		LBT		DC		CT		RT				CBTT		SART		AM		ST			
										Words		Non-Words								TI		EI	
		B-PA	A-PA	B-PA	A-PA	B-PA	A-PA	B-PA	A-PA	B-PA	A-PA	B-PA	A-PA	B-PA	A-PA	B-PA	A-PA	B-PA	A-PA	B-PA	A-PA	B-PA	A-PA
nP1	126*	100*	59	11*	13*	66*	66*	50	70*	2	2	16	34	3,5	4,5	0,8	0,8	32,5	22,5*	74,2*	31,8	9,5*	5*
nP2	113*	100*	88*	20*	23*	78*	89*	100	40	42	30	73	87	2,8*	2,8*	0,8	0,5*	13,3*	10,3*	57,9*	125*	10*	0,5
nP3	132*	18	6	0	-2	11	11	10	15	2	2	14	14	5,3	4,3	0,9	0,8	27,3	29,3	19,1	12,6	2,8	0,3
nP4	42*	71	59	91*	82*	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
nP5	101*	100*	100*	13*	10*	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
nP6	74*	100*	59	82*	36*	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
nP7	42*	100*	65	9	7	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
nP8	56*	35	35	7	5	33	44	60*	65*	0	0	29	36	3,5	3,5	0,7*	0,6*	13,2*	16,2*	33,8	49,8*	14*	4,3*
nP9	101*	6	6	5	-1	22	22	60*	90*	7	0	33	29	3,8	3,8	0,8	0,7*	27,3	32,3	0	0	23*	20*
nP10	129*	23	12	10*	3	0	0	0	0	0	0	8	8	2,9*	3,8	0,6*	0,7*	18,9*	28,8	74,8*	31,7	0	0

Tab. 6. Scores of neglect patients in each test, before prismatic adaptation (B-PA) and after prismatic adaptation (A-PA). BIT = Behavioral Inattention Test, accuracy score (Cut-off > 129); BCT = Bell Cancellation Test, percentage of omissions on the left (Cut-off < 85%); LBT = Line Bisection Test, percentage of mean deviation from the midpoint of the line (cm) (positive values for rightward deviation; negative values for leftward deviation) (Cut-off ≤ 10% or ≥ -10% cm); DC = Drawing Copy test, percentage of errors (Cut-off < 66%); CT = Clock Test, percentage of errors (Cut-off ≤ 50%); RT = Reading Test, percentage of errors; CBTT = Corsi Block Tapping Test, accuracy score (Cut-off ≥ 3,5); SART, accuracy score (Cut-off > 0,7); AM = Attentional Matrices test, accuracy score (Cut-off ≥ 23,9); ST = Stroop Test, effect of Time Interference (TI) (Cut-off ≤ 36,92) and effect of Errors Interference (EI) (Cut-off ≤ 4,24). * pathological values. n.e. = not executed

Time Bisection Task

Time bisection task was the same used before. Participants sat at a distance of 54 cm from a 14” computer monitor, with their right hand placed on the space bar of the keyboard. The standard visual-stimulus was a blue square (1° x 1° of visual angle) presented on the centre of the monitor. The blue square was presented on the monitor for a variable time interval (1600, 1800, 2000, 2200, 2400 ms) and subjects were instructed to encode its duration (time encoding phase).

Immediately after the time encoding phase, the target stimulus, a red square of the same dimensions of the blue one, was presented on the monitor in the same central position. Participants were required to press the space bar of the computer when they judged that the target stimulus had lasted half the duration of the standard stimulus (time bisection phase).

The computer program recorded the reproduced time with 1-ms resolution. No feedback was given on accuracy. Fifty trials were randomly presented, ten for each time interval. Before starting the experimental session, subjects were presented with two practice sessions for a total of 100 practice trials. All subjects performed the time bisection task before and after PA. HC and RBD-N- performed the time bisection task and PA procedure in one single session. Patients with neglect, who also underwent the additional neuropsychological battery before and after PA, were administered the whole experimental procedure in two sessions. In the first session (*baseline session*), run before PA, RBD-N+ patients were submitted to the 100 practice trials of the time bisection task, taking about 10 minutes, to one experimental session of 50 trials of the time bisection task, taking 5 minutes and to the neuropsychological assessment described above, taking about 40 minutes to be completed. In sum, the baseline session took less than one hour to be done. In the second session (*PA session*), run the day after, RBD-N+ patients first underwent the PA procedure (see next paragraph), taking about 15 minutes. Immediately after PA, one experimental session of 50 trials of the time bisection task (5 minutes) and the neuropsychological assessment (40 minutes) were administered. Similarly to the baseline session, the PA one lasted roughly one hour. The administration order of time bisection task and neuropsychological assessment was counterbalanced between subjects, and it was maintained equal before and after PA. For the PA, participants wore ipsilesional (rightward) deviating prisms according to the literature describing the effects of such prisms on spatial tasks in RBD-N+ patients (Rossetti et al., 1998; Frassinetti et al, 2002).

Prismatic Adaptation Procedure

The procedure used for prismatic adaptation is the same used in the previous experiments. However it is worth remembering that all participants were submitted to PA inducing a rightward shift of spatial attention.

9.1.3 Results

Time Bisection Task

Performance in the time bisection task was calculated for each subject. First, performance before and after PA was compared in order to investigate the effects of PA on time bisection task in each group. The dependent measure was the mean (in milliseconds) of reproduced intervals. Reproduced time intervals longer than the encoded ones were interpreted as time underestimation; reproduced intervals shorter than the encoded ones were interpreted as time overestimation. Reproducing a time interval longer than the actual interval to-be-reproduced is considered time underestimation because subjects press the key later as if they believed that time is elapsing slower. Reproducing a time interval shorter than the actual interval to-be-reproduced is considered time overestimation because subjects press the key earlier as if they believed that time is elapsing faster.

Effect of PA on Time Bisection Task

An ANOVA was conducted to compare the performance of RBD-N- patients and controls with the performance of RBD-N+ patients, taking Group (HC, RBD-N-, RBD-N+) as a between-group factor and Condition (before PA vs. after PA) and Interval (800-900-1000-1100-1200 ms) as within-subjects variables. Post-hoc analyses were conducted, where necessary, with the Newman-Keuls test. Effect size is indicated as partial eta square.

A significant effect of Group [F(2,27) = 7,68; p = 0.002; η_p^2 =0,36] was found. Post-hoc analysis revealed that RBD-N+ patients reproduced longer intervals (3885 ms, SD = 3271 ms) with respect to both RBD-N- patients (1272 ms, SD = 295 ms; p = 0.005) and HC (995 ms, SD = 130 ms; p = 0.004). Condition [F(1,27) = 5,99; p = 0.02; η_p^2 =0,18] and the interaction between Group and Condition were significant [F(2,27) = 10,49; p = 0.0004; η_p^2 =0,44]. PA reduced the duration of reproduced intervals in RBD-N+ patients with respect to before PA (3078 ms, SD = 2575 ms vs 4692 ms, SD = 3810 ms; p = 0.0002); PA did not modify the duration of reproduced intervals with respect to before PA in RBD-N- (1375 ms, SD = 284 ms vs 1168 ms, SD = 283 ms; p = 0.51) or in HC (1034 ms, SD = 127 ms vs 956 ms, SD = 126 ms; p = 0.80) (see Figure 31A).

A significant Group x Interval interaction was found [F(8,108) = 3.9; p = 0.0004; η_p^2 =0,22]. In RBD-N+ patients, reproduced time was greater for the shortest interval (4624 ms, SD = 4383 ms) than for all other intervals (3640 ms, SD = 2790 ms; 3942 ms, SD = 3187 ms; 3640 ms, SD = 3323 ms and 3577 ms, SD = 3242 ms; p < 0.002

for all comparisons). In RBD-N- patients and in HC no difference was found among intervals. In RBD-N+ patients all intervals were reproduced as longer with respect to RBD-N- patients (1219 ms, SD = 332 ms; 1230 ms, SD = 394 ms; 1306 ms, SD = 343 ms; 1319 ms, SD = 316 ms and 1286 ms, SD = 392 ms; $p < 0.002$) and HC (862 ms, SD = 151 ms; 954 ms, SD = 157 ms; 999 ms, SD = 158 ms; 1068 ms, SD = 127 ms and 1091 ms, SD = 184 ms; $p < 0.002$) (see Figure 31B).

The interaction group x condition x interval was not significant ($p = 0.32$), suggesting that the difference among reproduced intervals before PA and after PA is maintained in all three groups.

Since RBD-N+ patients reproduced so much longer time intervals with respect to RBD-N- patients and HC, the ANOVA including the three groups might have masked the differences between the other two groups. Thus, a second ANOVA was conducted with Group (HC, RBD-N-) as between-group variable and Condition and Interval as within-subjects variables.

A significant effect of Group [F(1,18) = 9,46; p = 0.006; η_p^2 =0,34] was found, indicating that RBD-N- patients reproduced time intervals as longer with respect to HC (1272 ms vs. 995 ms, see above for SD). Condition was also significant [F(1,18) = 12,93; p = 0.002; η_p^2 =0,42] since reproduced intervals were longer after PA with respect to before PA (1205 ms, SD = 277 ms vs. 1063 ms, SD = 240 ms). The interaction between group and condition was not significant: both groups, RBD-N- and HC, reproduced longer intervals after PA than before PA (RBD-N- = 1375 ms vs. 1168 ms; t-test two tails p = 0.02; HC = 1034 ms vs. 956 ms; t-test-two tails p = 0.02, see above for SD). The effect of Interval was significant [F(3,72) = 7,02; p = 0.0001; η_p^2 =0,28]. The analysis showed that the reproduced time increased as the interval to-be-timed increased (800 ms vs. 1000 ms, 1100 ms, 1200 ms: p = 0.007; 900 ms vs. 1100 ms, 1200 ms: p = 0.03). Interactions between interval and group and condition were not significant.

Figure 31

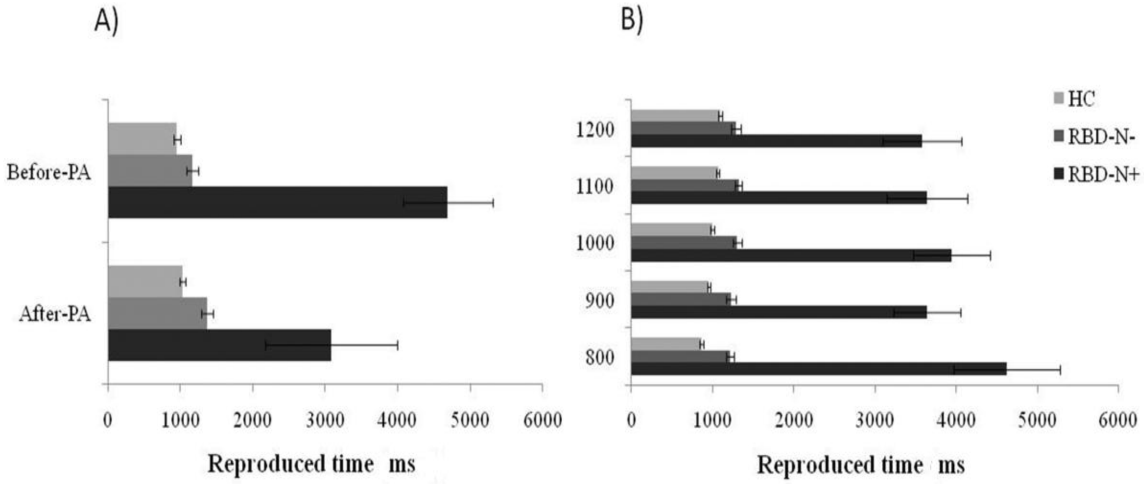


Fig. 31. (A) Mean reproduced time (ms) in right brain damaged patients with neglect (RBD-N+) versus patients without neglect (RBD-N-) versus healthy controls (HC), before prismatic adaptation (Before-PA) and after prismatic adaptation (After-PA); (B) Mean reproduced time (ms), of data collapsed before and after PA, in RBD-N+ patients vs. RBD-N- patients vs. healthy controls (HC) for all experimental intervals (800, 900, 1000, 1100, 1200 ms). Error bars indicate standard error of mean.

Effect of PA on Coefficient of Variation

The **coefficient of variation (CV),** that is the ratio between mean and standard deviation, was calculated as a measure of precision. In order to investigate whether PA had an effect not only on the length of reproduced intervals, but also on the precision in the time bisection task, we conducted an ANOVA to compare CVs before and after PA in all three groups. We took Group (HC, RBD-N-, RBD-N+) as a between-group variable and Condition (before PA vs. after PA) as a within-subjects variable. A significant effect of Group was found [F(2,72) = 14,20; p < 0.0000; η_p^2 =0,51]: post-hoc analysis revealed that RBD-N+ showed the highest CV (0,29 ms, SD = 0,09) among groups (RBD-N- = 0,21, SD = 0,07, p = .01; HC = 0,13, SD = 0,03, p = 0.0001). Moreover, RBD-N- patients' CV was significantly higher than that of HC (p = 0.02). Interestingly, there was not an effect of condition (p = 0.44), and its interaction with group (p = 0.33), indicating that CVs were similar before and after PA in all three groups and that PA did not exert any effect on the precision in the time bisection task.

Neuropsychological Tests and Regression analyses

To verify whether there was a relationship between the severity of spatial and temporal deficits before and after PA, two multiple regression analyses were conducted. We considered a **temporal score**[3]as a measure indicating temporal deficit in neglect patients. The mean and standard deviation of reproduced intervals in the time bisection task of the HC group before (mean = 956 ms; SD = 126 ms) and after PA (mean = 1034 ms; SD = 127 ms) were calculated; the **temporal score** was considered as the number of standard deviations of difference between the performance in the time bisection task of each neglect patient and the corresponding mean value of the HC group.

The two multiple regressions were conducted taking **temporal score** as dependent variable and scores in each spatial test (see Table 1) as regressors. The first regression was conducted with values before PA. A significant correlation with the temporal score was found for the Line bisection task (r^2 = 0,92; β = 1,17; p = 0.004) and for the Reading task (words) (r^2 = 0,74; β = -0,53; p = 0.05). Symmetrically, in the second

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[3] We adopted a method similar to that used to assess the pathologic performance in tests standardization. A pathologic performance is considered as a performance exceeding two Standard Deviations from mean score of controls (Spinnler and Tognoni, 1987).

regression on values after PA, a significant correlation with the temporal score was found for the Line bisection task (r^2 = 0,86; β = 2,26; p = 0.01) and for the Reading task (words) (r^2 = 0,96; β = -0,43; p = 0.001).

To verify whether there was a relationship between the presence of temporal and non-spatial attention deficits before and after PA, two multiple regression analyses were conducted, taking temporal score as dependent variable and scores in each non spatial attentional test (see Table 6) as regressors. No significant correlations were found between scores in temporal test and in attentional tests before and after PA. This result allows us to state that non-spatial attentional functions are not predictive for temporal deficit shown by RBD-N+ patients before PA and for the amelioration of such a deficit after PA.

Prismatic Adaptation results

Error reduction: To demonstrate the presence of error displacement, in the first trials, and of error reduction, in the last trials of prisms exposure condition, visible pointing performance during pre-exposure and exposure condition was compared with the following predictions. First, if subjects were influenced by prisms exposure, a difference should be found between the first trials of the exposure condition and the pre-exposure condition. Second, if subjects were actually able to adapt to the prisms, no difference should be found between the last trials of the exposure condition and the pre-exposure condition, i.e. 0° or close to 0° pointing displacement (degrees of visual angle) should be registered in both conditions.

An ANOVA was performed taking Group (RBD-N+, RBD-N-, HC) as the between-group variable and Condition (pre-exposure, exposure first three trials, exposure last three trials) as the within-subjects variable. Post-hoc analyses were conducted, where necessary, with the Newman-Keuls test. Effect size is indicated as partial eta square.

The variables Group [F(2,27) = 3,5; p = 0.04; η_p^2 =0,21], Condition [F(2,54) = 91,9; p = 0.0001; η_p^2 =0,77] and their Interaction [F(4,54) = 3,27; p = 0.02; η_p^2 =0,19] were significant. Post-hoc analysis revealed that pointing displacement in the first three trials of exposure condition was greater in RBD-N- (2.52°, SD = 1.14°) than in RBD-N+ (1.27°, SD = 0.92°, p = 0.0002) and in HC (1.94°, SD = 1.14°, p = 0.04). The difference between RBD-N+ and HC was also significant (p = .02). As expected, in all three groups, the pointing displacement before PA was different from that in the first three trials of exposure condition ($p < 0.001$ for all comparisons) but not from that in the last three trials of exposure condition (see Figure 32A for means).

After-effect: To show the presence of an after-effect, invisible pointing was compared between the post-exposure condition and the pre-exposure condition. If PA produced a leftward visuo-motor bias in response to the rightward deviation induced by prism, a leftward (i.e. negative) error during pointing should be found when prismatic goggles have been removed, whereas this effect should not be present during pre-exposure condition. To verify this prediction, an ANOVA was performed taking Group as the between-group variable and Condition (pre-exposure invisible pointing and post-exposure invisible pointing) as the within-subjects variable.

The variable Condition was significant [F(2,27) = 186,21 p = 0.0001; η_p^2 =0,84]. The pointing displacement in the post-exposure invisible pointing condition differed from the pointing displacement in the pre-exposure invisible pointing condition (-2,94°, SD = 1.04° vs. -0,96°, SD = 0.60°) (See Figure 32B).

Figure 32

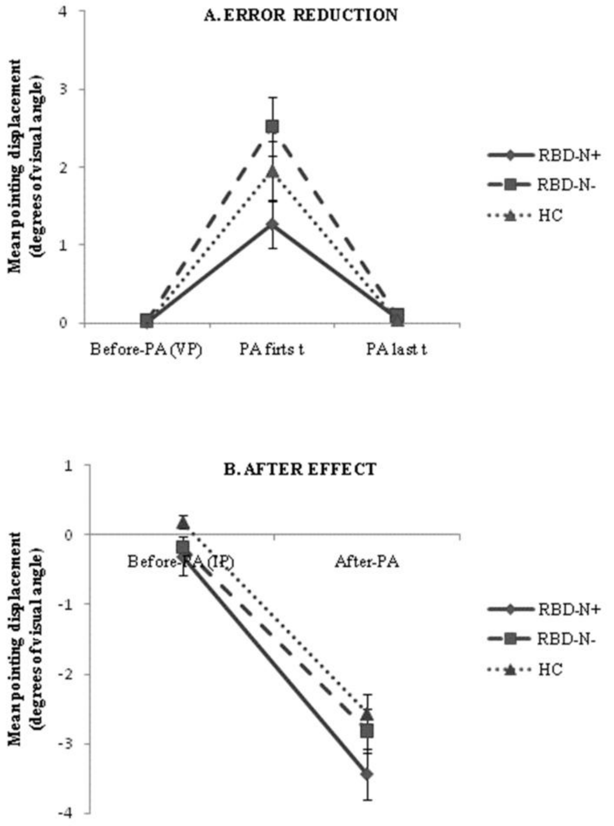


Fig. 32. Pointing deviation. (A) Mean pointing displacement (expressed in degrees of visual angle) of patients' visible pointing (VP) responses before prism adaptation (Before-PA) and mean pointing displacement of the first three (PA-first t) and the last three trials (PA-last t) during prism adaptation. (B) Mean displacement (expressed in degrees of visual angle) of patients' invisible pointing (IP) responses before prism adaptation (Before-PA) and mean pointing displacement after prism adaptation (After-PA). RBD-N+ = right brain damaged patients with neglect; RBD-N- = right brain damaged patients without neglect; HC = healthy controls. Error bars indicate standard error of mean.

In sum, data analysis on prismatic adaptation procedure demonstrated that all groups (HC, RBD-N+, RBD-N-) compensate, during prism exposure, for prism-induced spatial errors in pointing (adaption effect). Moreover, after prisms removal all groups showed the tendency to point to the direction opposite to the optical displacement induced by prism (after-effect).

Anatomical Data

CT/MRI digitalized images of seven RBD-N+ and six RBD-N- patients were mapped using MRIcro software (available on http://www.cabiatl.com/mricro, Rorden C.) (see Figure 33A and 33C for single lesions).

The region of maximum overlap, which contained the overlap of at least three patients' lesions, was extracted. Thereafter, the mean number of voxels of patients' lesions overlapping was calculated. The Brodmann areas involved by the lesion for more voxels than the mean were identified.

In RBD-N+ patients the Brodmann areas identified were in *frontal* (BA 6, 44, 45, 47), *parietal* (BA 3, 39) and *temporal* (BA 20, 21, 22, 37, 38) areas and the region of maximum overlap of at least three patients' lesions was located in the *deep white matter in a fronto-temporal region* (See Figure 33B).

In RBD-N- patients the Brodmann areas identified were in *frontal* (BA 47), *temporal* (BA 20, 21, 22, 37) and *occipital* (BA 19) areas and the region of maximum overlap of at least three patients' lesions was located in the *temporal cortex* (See Figure 33D). For each brain area, the mean number of voxels involved by the lesion in RBD-N- patients was subtracted from that in RBD-N+ patients. RBD-N+ patients' lesions involved parietal and more extensively frontal areas compared to RBD-N- patients' lesions.

In order to quantitatively understand which areas were involved by the lesion in RBD-N+ patients and not in RBD-N- patients, for each patient, a value equal to 0 was assigned to a specific area if it was not involved and a value equal to 1 was assigned if it was involved in patient's lesion. A non-parametric Mann-Withney U test was conducted on these values, to compare the two groups of patients. Areas significantly involved in RBD-N+ patients and not in RBD-N- patients were BA6 (mean rank RBD-N+ = 9,07 vs. RBD-N- = 4,58; p = 0.02), BA45 (mean rank RBD-N+ = 9,07 vs. RBD-N- = 4,58; p = 0.02), BA3 (mean rank RBD-N+ = 9,14 vs. RBD-N- = 4,50; p = 0.01).

In order to exclude that the extent of RBD-N+ patients' lesions was significantly greater than the extent of RBD-N- patients' lesions, the mean of number of voxels for all areas for each patient were calculated and compared by means of an ANOVA taking **group** as a between-group variable. The effect of group was not significant (p = 0.43).

In order to understand which injured area was more associated with the temporal deficit in neglect patients, a multiple regression analysis was conducted, taking **temporal score** (see above) of each neglect patient as dependent variable and the mean of number of voxels for each brain area of each neglect patient as regressors. We considered as significant α value, a $p < 0.001$. The regression revealed a significant correlation with temporal score for BA45 ($r^2 = 0,94$; $\beta = 1,37$, $p < 0.001$) and for BA39 ($r^2 = 0,93$; $\beta = 1,39$, $p < 0.001$), suggesting an involvement of frontal and parietal areas in inducing temporal deficit in neglect patients.

Figure 33AB

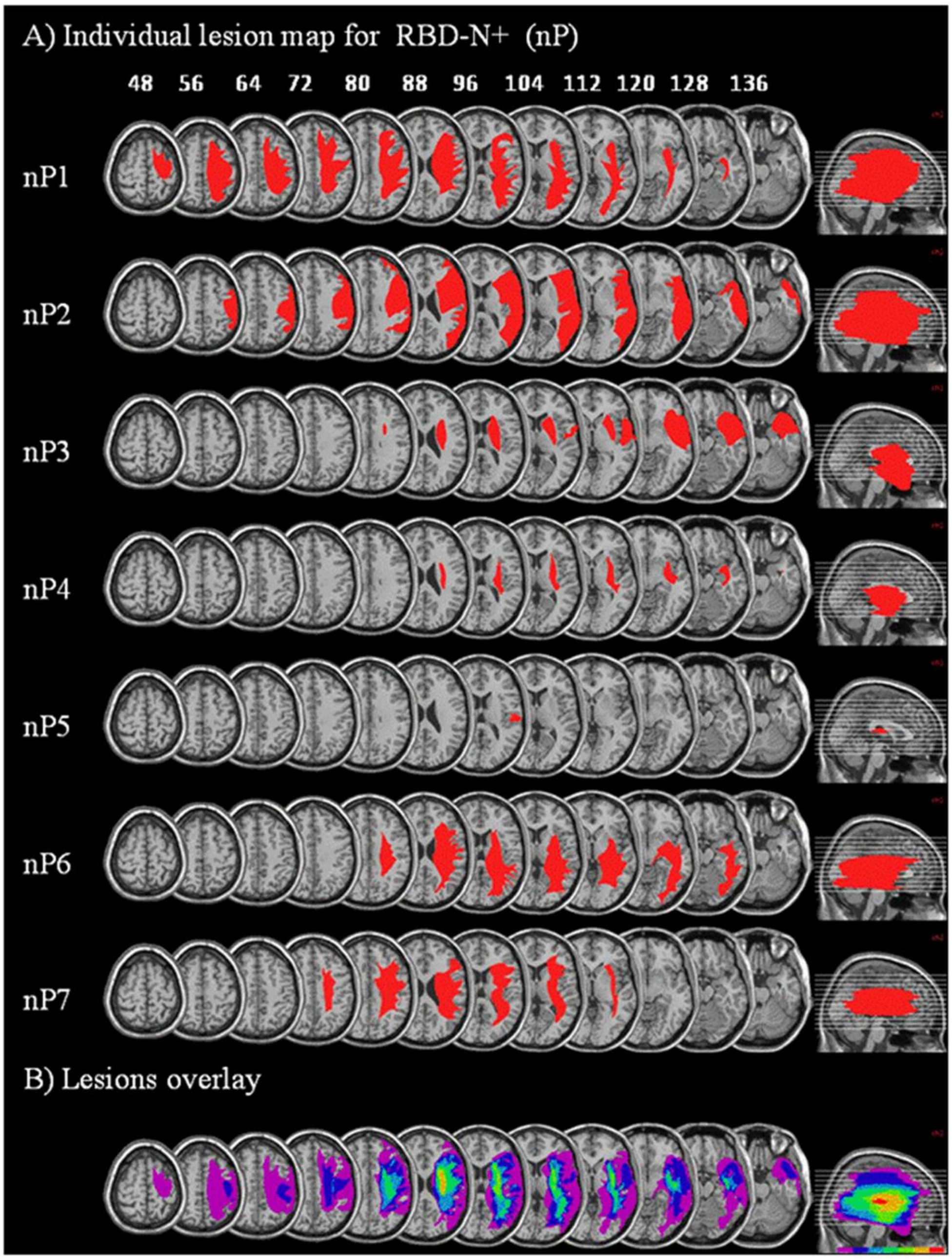


Fig. 33. See next caption

Figure 33CD

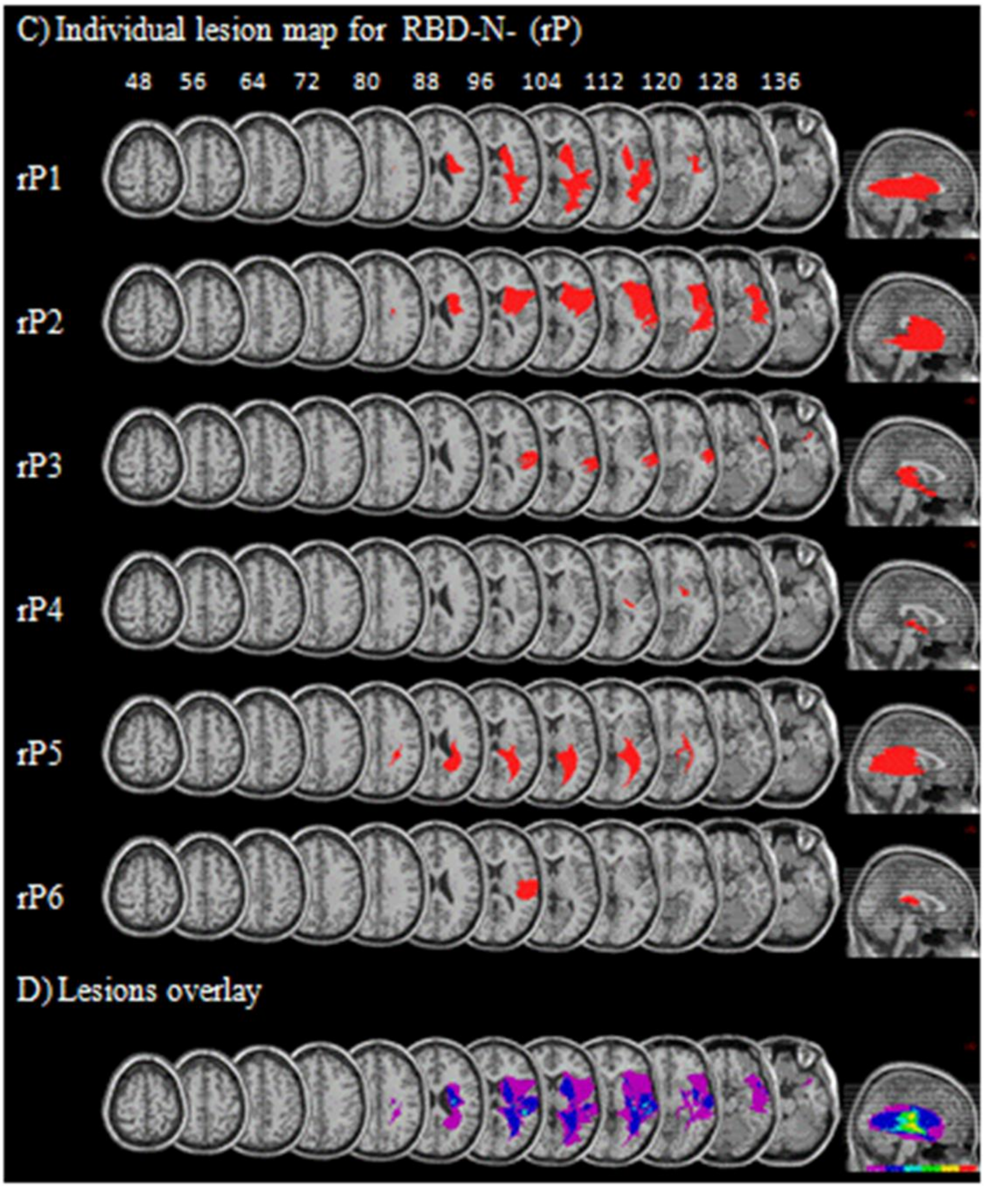


Fig. 33. CT/MRI digitalized images. (A) individual lesions and (B) lesion overlay analysis of seven right brain damaged patients with neglect (RBD-N+) (nP); (C) individual lesions and (D) lesion overlay analysis of six right brain damaged patients without neglect (RBD-N-) (rP). Individual lesions are marked in red. In the lesion overlay, each patient's lesion is given in a distinct color with the region of maximum overlap indicated in red.

9.1.4 Discussion

There are two aspects to the main results of the present study. The first concerns the consequence of a deficit of spatial attention following a brain lesion on the spatial representation of time; the second concerns the effects of prismatic adaptation on spatial representation of time. About the first point, the presence of a spatial attention deficit worsens the temporal deficit emerging following right brain damage. Indeed, RBD-N- patients underestimated time with respect to healthy controls. Moreover, RBD-N+ patients showed greater underestimation of time than RBD-N- patients. About the second point, a *leftward deviation of spatial attention* by prisms caused different effects in right brain damaged patients with and without neglect. Prisms increased time underestimation in RBD-N- whereas they reduced time underestimation in RBD-N+ patients.

Time underestimation following right hemispheric disruption has been found in previous neuropsychological and TMS studies (Harrington et al., 1998; Koch et al, 2002, 2003; Danckert et al., 2007; Oliveri et al., 2009a; Calabria et al., 2011; Magnani et al., 2011). The specific brain regions of the right hemisphere controlling time perception are a matter of controversy in the various lesion studies. Some studies highlight a role for the dorsolateral prefrontal cortex (Koch et al., 2002; Koch et al., 2003) while other studies implicate the inferior parietal cortex (Harrington et al., 1998; Oliveri et al., 2009a; Bueti and Walsh, 2009; Battelli et al., 2008). Differences in the temporal task employed, and in the duration of stimuli to be timed, may account for discrepancies between the various studies. In studies employing temporal tasks that emphasize the use of spatial codes, such as the study by Oliveri et al. (2009a), a greater involvement of posterior brain regions is reported. On the other hand, in studies employing timing tasks that emphasize the working memory load (Koch et al., 2002, 2003), a greater involvement of the dorsolateral prefrontal cortex is justifiable. In the present study, RBD-N- patients' lesion involved frontal and temporal areas. The lesion of these regions might be responsible of the differences between RBD-N- and controls in the temporal task.

The analysis on the lesion extent did not reveal any differences between RBD-N- and RBD-N+ patients. On the other hand, RBD-N+ patients' lesion involved the frontal region more extensively and also the parietal region compared to RBD-N- patients. The difference in the lesion site between RBD-N- and RBD-N+ patients corresponded to two additional behavioural deficits in RBD-N+: a spatial attention deficit (i.e. the visual neglect) and a greater temporal deficit (time underestimation).

We hypothesize that the temporal deficit is linked to the spatial deficit following these specific brain lesions. The correlation between the severity of the temporal and of the spatial deficit support this hypothesis. Moreover, the fact that RBD-N+ patients' lesions involved parietal region (BA39), is in line with a critical engagement of the right inferior parietal cortex as the locus of the common metric system for space and time (Walsh, 2003; Bueti and Walsh, 2009).

Our suggestion is that RBD-N+ patients present a general deficit in timing interacting with a more specific impairment in using spatial codes in temporal tasks. The deficit of spatial attention biases the representation of time along a left-to-right oriented mental time line (Vicario et al., 2007, 2008; Oliveri et al., 2009; Frassinetti et al., 2009). According to this hypothesis, RBD-N+ patients are more likely to underestimate time than RBD-N- patients because the core timing deficit interacts with a distorted spatial attention/representation of the left space. If time is spatially represented as a line, RBD-N+ patients could have neglected the left/first part of such a line in a similar way to which they neglect the left/first part of a spatial line (Berti et al., 1995; for a review see Vallar, 2007).

We interpreted reproduction of a longer interval than the real one as time underestimation. This interpretation assumes that subjects were underestimating the time interval while reproducing it, i.e. in the response phase of the timing task. However, one could alternatively hypothesize that a subject reproduces a longer interval because he actually perceives the interval as longer than the objective one in the initial encoding phase. If this was the case, we should interpret the performance of neglect patients in our temporal task as time overestimation. However, the time underestimation hypothesis in neglect is more supported by the literature (Danckert et al., 2007; Merrifield et al., 2010). Merrifield et al. (2010) show that patients with neglect underestimate time duration in a nonverbal time estimation task, in a verbal auditory time estimation task and in a visual time estimation task. For the same reason, we also think that the great underestimation showed by patients with neglect in the present study is not due to a general difficulty or misunderstanding in performing the task.

Moreover, to us, the use of a spatial code to represent a time interval, that is the peculiar deficit we attribute to neglect patients, emerges principally during the response phase rather than in the encoding phase of the stimuli. Our interpretation is in accord with the theory of magnitude (Walsh, 2003), suggesting that a common metric system shared by time end space is engaged for action. Supporting this interpretation are also results from TMS studies, showing an effect of a deactivation of parietal cortices in impairing the ability to perform a time bisection task only when rTMS is delivered in the response rather than in the encoding phase (Oliveri et al., 2009a).

A “motor” impairment of time perception in neglect patients can also be discussed with reference to models of spatial neglect, according to which this disorder may result from disruption of either sensory-attentional or motor-intentional systems (Na et al., 1998; Heilman, 2004; Ghacibeh et al., 2007). Indeed, the temporal task employed in the present study certainly has a production (i.e. motor) component besides a perception one. From a neural point of view, sensory-attentional and motor intentional components have been correlated respectively with parietal and frontal areas.

According with this explanation, the beneficial effects of rightward prisms in time perception deficits could also be explained according with recent studies, reporting that prism adaptation primarily affects the motor-intentional "aiming" system in both healthy individuals and neglect patients (Fortis et al., 2011).

However, whatever component of spatial attention is considered, i.e. the perceptual or the motor one, the hypothesis that spatial attention influences time perception remains strong.

These data suggest a new model of time perception and of its dysfunctions following right-brain-damage. In the absence of lateralised spatial deficits, real time and perceived time are aligned at the beginning of an interval, represented by the mental time line. In healthy subjects, during the flow of the time interval, the alignment between real and perceived time persists from the beginning to the end of the interval. In RBD patients, the brain lesion interferes with the alignment between real and perceived time during the whole time interval. Specifically, we suggest that following a right brain lesion the perceived time is slowed down resulting in time underestimation. The presence of left spatial neglect shift forwards (i.e. rightwards in terms of spatial representation) the passage of time while the subject is reproducing it along a left-to-right oriented mental time line. When neglect patients start to pay attention to time, a portion of real time corresponding to the neglected space has already elapsed. Our findings suggest that the interaction between space and time along a mental time line to critically requires right parietal regions.

Manipulation of spatial attention by PA influences time processing according with this model. In RBD-N- patients and controls, the leftward shift of spatial attention shifts the spatial representation of time leftwards. The leftward shift implies a backward perception of elapsing time. Because of this bias, similarly to what we found in previous study (Magnani et al., 2011), both RBD-N- patients and controls underestimate time intervals after PA compared to before PA. More interestingly for the aim of this study, in RBD-N+ patients, the leftward shift of spatial attention induced by prisms rebalances the spatial attention bias, thus reducing the part of the time-line previously neglected. The effects of prismatic adaptation procedure in rebalancing spatial attention system and in reducing biases in the spatial representations are well known (Frassinetti et al., 2002; Pisella et al., 2006). However, the way by which the mere visuo-motor adaptation employed in prisms procedure affects high level of space representation is a matter of debate in literature. Redding and Wallace (2006), in their theoretical review, explain that during prismatic adaptation procedure, in the condition of exposure to prisms, two main processes occur. The first is a strategic calibration, which arises a remapping of spatially coded movement commands to rapidly reduce error in the pointing task. The second is a realignment process, which brings spatial maps of coordinate systems into correspondence. This process could be the responsible of a re-shape of the left part of spatial representations in neglect patients after prismatic adaptation. Following this reasoning, in the present study, the reduction of the neglected part of the spatial representation of the time-line improves time underestimation, favouring the alignment between the real and the perceived time. Amelioration of time underestimation parallels amelioration of left spatial deficits, further stressing the link between spatial and temporal dimensions at a clinical and rehabilitative level (Figure 34).

Figure 34

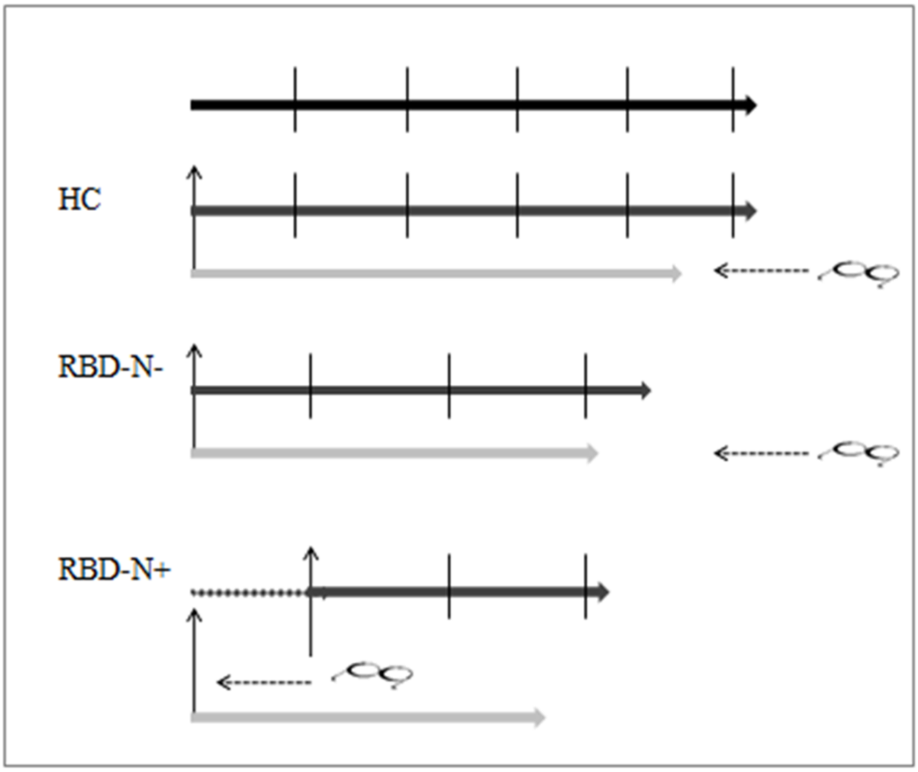


Fig. 34. Theoretical model of spatial-temporal interactions in healthy subjects and in patients with right brain damage.

The horizontal black arrow represents a putative interval to be timed. The horizontal dark grey arrows represent time intervals perceived by participants. The vertical black lines represent time beats indicating the velocity of time flow passage: the greater the distance between the lines, the slower the passage of time flow. The vertical black arrows represent the alignment between the real time interval and the interval perceived by participants. The horizontal dashed arrows represent the leftward shift of spatial attention induced by prismatic adaptation. The horizontal light grey arrows represent the time interval perceived by participants after a prismatic adaptation session. The dashed line represents the neglected part of the temporal line in neglect patients.

HC. Healthy controls. The real time interval and the perceived interval are aligned. The passage of time flow of the perceived interval has the same velocity of the real interval. A leftward shift of spatial attention induces an underestimation of time.

RBD-N-. Right brain damaged patients without neglect. The real time interval and the perceived interval are aligned. The passage of time flow of the perceived interval beats more slowly than the real interval. A leftward shift of spatial attention induces an underestimation of time.

RBD-N+. Right brain damaged patients with neglect. The real time interval and the perceived interval are not aligned because of the rightward bias of spatial attention. The spatial attention bias induces missing of the first part of the perceived interval. The passage of time flow of the perceived interval beats more slowly than the real interval. A leftward shift of spatial attention reduces the initial spatial attention bias and induces a reduction of time underestimation.

The model that we propose is not in contrast with the most known theories of time processing, SET theory (Scalar Expectancy Theory, Gibbon et al., 1984). This theory states that an internal clock mechanism emits pulses, that are subsequently stored in an accumulator where accumulated pulses shape a raw representation of elapsed time. This raw representation is then encoded into a transitory working memory store, which represents the current time, and, over trials, into a long-term reference memory store (memory component). Finally, records of time intervals in working and reference memory are compared by a comparator component, which dictates the response. Previous studies suggested that temporary storage (working memory component) is underpinned by right frontal areas (Koch et al., 2002, 2003). Lesions in this region showed by our RBD-N- patients could have induced a slowdown of the encoding rate from the internal clock and to impairment in keeping the flow of time. Our purpose is that parietal areas are involved at a different level, i.e. the comparator level, where a spatial metric would be engaged to measure and compare representations of time intervals. Our RBD-N+ patients, who showed a lesion of parietal areas further than frontal areas, would show impairment in the comparator component, in the use of spatial metric, in addition to an impairment in the temporary storage component.

To summarize, the novelty of the present study is that it sheds light on the relationship between spatial attention deficits and the spatial representation of time in neglect patients. Our findings provide further evidence that time and spatial attention are strictly linked and are the first to suggest a possible method for the rehabilitation of temporal deficits in neglect patients. Studies on the ecological impact of temporal deficits in neglect patients are necessary and currently in progress.

9.2 Experiment 9 – Prismatic adaptation treatment ameliorates temporal disorders and its ecological impact in a patient with neglect

9.2.1 Introduction

Temporal processing deficits have been widely described in neglect patients (Danckert et al., 2007; Basso et al., 1996). In the previous experiment we showed that the spatial attention bias in neglect, induces a deficit of spatial representation of time, that can be reduced by a session of PA (Oliveri et al., in press). However, this study is the first moving a step toward the treatment of time deficits in neglect, despite a wide literature on space deficits (Rossetti et al., 1998; Frassinetti et al., 2002; Serino et al, 2006, 2009; Làdavas et al., 2011; Farnè et al., 2002). One question is why neuropsychological research has developed a large body of evidence and methods to recover space deficits and not to recover time deficits? One answer could be that we known the negative impact of spatial deficits (see Tham et al., 2000) in everyday life and this has induced researchers to find a solution. Difficulties in time processing, could also have a strong impact on neglect patients daily routine, for example in appreciating how much time an activity takes to be done, but nothing has been written about that. It might be that the ecological impact of time deficit has been less described because, in the hospitalization context, the time deficits are less evident than spatial deficits. A neglect patient can show difficulty in driving his/her wheelchair through hospital corridors, or can be impaired in paying attention to a nurse talking him/her on the left. But the patient does not show temporal deficits because the duration of daily activities in the hospital is organized by external persons. Anyway, when a neglect patient comes back home and he/she needs to organize his/her daily life, temporal deficit could strongly emerge.

Here we studied a single patient (L.L.) with neglect showing time impairments. L.L. left the hospital after a month from the stroke because she did not have motor impairments, despite a not complete recover of neglect symptoms. The aim of the study was twofold. First we explored the impact of time impairments in L.L. everyday activities. Second we investigated whether a treatment with PA of ten daily sessions, that normally is used for neglect rehabilitation, ameliorates temporal deficits not only in a behavioral time task but also at an ecological level. The choice of a PA treatment of ten daily sessions, came from evidence about its efficacy in spatial symptoms rehabilitation in neglect (Serino et al., 2006, 2009) that generalize on daily living activities as guiding the wheelchair (Watanabe and Amimoto, 2010; Jacquin-Cuortois et al., 2008).

To quantify L.L. time deficit, she (and nine healthy controls) was submitted to a time bisection task. Then, the effect of a session of PA on time deficit was verified by submitting L.L. to the time bisection task before and after a session of PA. Finally, L.L. was presented with a time bisection task and a qualitative interview, assessing time deficits impact on daily life, before and after a ten daily PA treatment.

this aim we submitted L.L. and eight healthy controls, to a time bisection task. In addition L.L. was then submitted to time bisection task before, after a session and after a ten daily PA treatment. Moreover, we presented L.L. a qualitative interview on temporal difficulties before and after the ten daily PA treatment.

As previously demonstrated (see experiment 8 and Oliveri et al, in press), we expected that L.L. is impaired in the time task relative to controls and that a session of PA slightly improves the performance in the time bisection task. Moreover we expected that a treatment with PA can strongly reduce the impairment of temporal deficit in time bisection task and can generalize to the quality of life of the patient, assessed by the qualitative interview.

9.2.2 Methods

Participants

Case-report

L.L. is a 52-year-old right handed woman, stylist, with 13 year of education. She was examined 1 month and half after an hemorrhagic stroke due to a right internal carotid aneurysm. The stroke causes hemispatial neglect and no signs of hemianopia and hemiplegia. The CT scan showed a right frontal lesion. L.L. was alert and cooperative, with no general intellectual deficit. Her speech was informative and fluent. When we tested L.L. she was not hospitalized because of the absence of motor deficit and she had came back at work.

A neuropsychological battery revealed that she was oriented in time and space and there was no signs of cognitive deterioration as assessed by MMSE (Folstein et al., 1975). No reasoning deficits were observed by means of Raven's Coloured Progress Matrices (CPM 47) (Raven, 1956). L.L. didn't show any disorder of long-term verbal and spatial memory as assessed by Rey 15-Word Test (Rey, 1958) and Rey-Figure Test (Rey, 1941). However L.L. showed the presence of spatial short-memory impairment (Corsi Block Tapping Test - Milner, 1971) but not of verbal short-memory impairment (Digit Span Test - Milner, 1971). L.L. did not show any deficit of inhibitory control (Stroop Test – Caffarra et al., 2002), of selective attention (Attentional Matrices-Della Sala et al., 1992) and sustained attention deficits assessed by SART-2000 test (Robertson et al., 1997).

The presence of neglect was assessed as follows. In the Bells' Test (Gauthier et al., 1989) she omitted crossing out several items on the left side of the sheet. In Line bisection Test, in which we asked her to bisect several line of two different lengths (long line = 24 cm; short line = 12 cm), L.L. was impaired in bisecting the long line displacing the midline rightward to the true centre. In the Reading Test (Làdavas et al., 1997) L.L. didn't commit any errors in the concrete words stimuli, but she commit some errors in the non-words stimuli. In the Clock Drawing Test (Mondini et al., 2003) and in Drawing test (Gainotti et al, 1972) she didn't show any impairment.

Controls Group

Nine healthy participants without history of neurological or psychiatric disease (5 male, mean age = 51.1 years, SD = 1.8 years) gave their informed consent to participate in the study, which was approved by the local ethics committee. All procedures were in agreement with the 1975 Helsinki Declaration.

Time bisection task

Participants (patient L.L. and controls) performed the same time bisection task used in previous experiments. They were required to reproduce half the duration of a previously encoded visual stimulus (stimulus duration: 1600, 1800, 2000, 2200, 2400 ms). Participants performed the task using their right index finger. Fifty trials were randomly presented, ten for each time interval. Subjects were presented with 100 practice trials before starting the experimental session.

Interview

It was a semi-structured interview composed of open questions that led the patient free to tell her subjective experience. L.L. was recorded with a camera during the interview. Particularly we asked L.L. to tell about her subjective perception of the time flow, her ability to estimate how much time an activity takes, her ability in organize daily activities and weekly activities.The aim of the interview was to investigate the ecological impact of temporal deficit in everyday life and to understand if L.L. could conduce a normal life regardless the presence of temporal deficit.

Prismatic Adaptation procedure

For each PA session the procedure was the same adopted in all the other experiment. L.L. Rightward PA inducing a leftward shift of spatial attention was administered, according with the literature in PA effects on time and space in neglect (Oliveri et al., in press, Frassinetti et al., 2002). PA. L.L. underwent the treatment in 10 sessions, 1 a day, which took about 20 min each, over a period of two weeks (Serino et al., 2006).

9.2.3 Results

Before PA

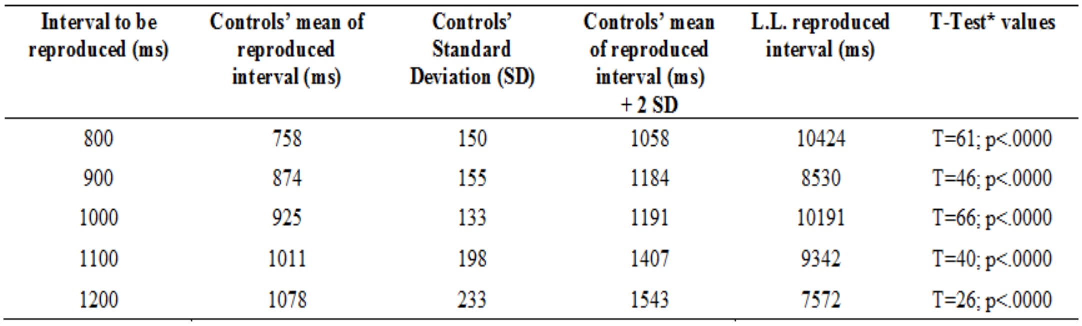
Time bisection task

We first compared patient’s and controls performance in the time bisection task before applying PA procedure. The aim was to estimate the impairment of L.L. against a group of aged matched normal subjects. Comparison between L.L. performance and controls, for each interval duration, was conducted with a modified t-test (Crawford & Garthwaite, 2002) that estimates the abnormality of an individual performance taking into account the size of the control group. The analysis was conducted on the mean of reproduced time.

As in previous experiments, when reproduced time is longer than the time to-be-reproduced we refer to underestimation (Frassinetti et al., 2009).

The patient was significantly less accurate as compared with control subjects in the reproduction of all intervals, showing a tendency to underestimate the real time. Reproduced time of patient for each intervals were more than 2 SD longer compared with the controls’ mean and it was significantly different to each controls’ reproduced interval (See Table 7 for values). Interestingly, while in controls reproduced intervals increase as the interval to-be-timed increases. This was not the case of L.L. (see Figure 34).

Table 7



Interval to be reproduced (ms)	Controls' mean of reproduced interval (ms)	Controls' Standard Deviation (SD)	Controls' mean of reproduced interval (ms) + 2 SD	L.L. reproduced interval (ms)	T-Test* values
800	758	150	1058	10424	T=61; p<.0000
900	874	155	1184	8530	T=46; p<.0000
1000	925	133	1191	10191	T=66; p<.0000
1100	1011	198	1407	9342	T=40; p<.0000
1200	1078	233	1543	7572	T=26; p<.0000

Tab. 7. Table reports mean values, standard deviations (SD) and mean values plus SD, of reproduced intervals, expressed in milliseconds (ms), in the time bisection task for controls group and reproduced intervals (ms) in the time bisection task for patient (L.L.). Finally it is reported the T-Test* (modified t-test - Crawford & Garthwaite, 2002) resulting from the comparison between each L.L. reproduced interval and each mean of reproduced interval of controls group.

Figure 34

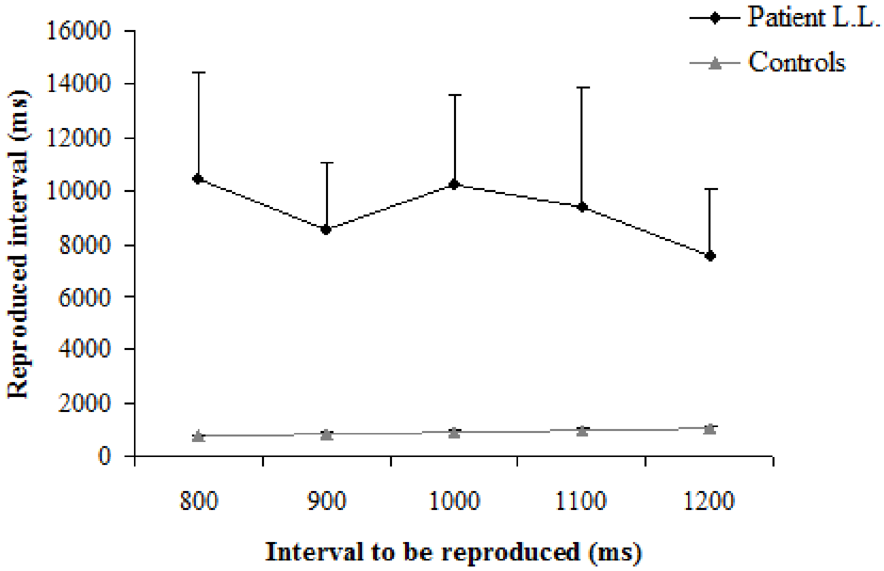


Fig. 34. Reproduced intervals plotted against values of intervals to be reproduced (millisecond) for patient L.L. and controls.

Interview

In the interview about the awareness on the passage of time, patient explained that she has difficulties to estimate the exact hour of the day. Specially she always believes to be forward in time respect to the real time. She also explained that this difficulty to perceive the passage of time embarrasses her when she is among other people. She feels always disoriented about the beginning and the end of an activity, and as a consequence, she is often forced to ask the exact hour. This feeling of disorientation induced a feeling of uncertainty in her social relationship.

L.L. refers that“…in every moment of the day it’s difficult for me to understand the exact hour. For example in the morning I wait for my colleague in an anxious way cause I think she is in late. Sometimes I argue with her about her late, but she remembers me the exact hour and that she is in time. While I believe it’s about 10, in the real time it’s about 8. I really feel uncomfortable with other people especially at work. In the afternoon for example I start to prepare dinner cause I think it’s 7 while it’s 5 in the real time. So it often occurs that dinner becomes cold or too cooked and my husband doesn’t appreciate....”

The extract of the interview shows that L.L. has difficulties in the perception of the passage of time. We interpreted this kind of difficulty as time underestimation. Base on evidence of a linear left-right representation of time, in the previous experiment (8 and Oliveri et al., in press) we explained that neglect patients bisect a temporal interval forward in time as they bisect a spatial line to the right. Moreover we explained that this could be due to the spatial attention bias to right, inducing these patients to ignore the first part of a temporal line as they ignore the first part of a spatial line. Given this lack of the first part, a temporal interval is estimated as shorter than the real one. The evidence reported so far indicate that L.L. underestimates time in the time bisection task as well as the passage of temporal events in daily life. Another crucial point of the extract reported above is that this deficit in perceiving the passage of time has a strong impact on patient’s autonomy at work, on her ability to manage familiar rhythms and on her social behavior.

Time bisection task before and after a session of PA

We observed a decrease of underestimation in all time intervals after PA compared with before PA (see Figure 35 for means and SE). However, patient underestimates time intervals more than two SDs compared to controls (see Table 8), which means that despite a reduction of underestimation, L.L still presents an abnormal time performance after one session of PA.

Table 8

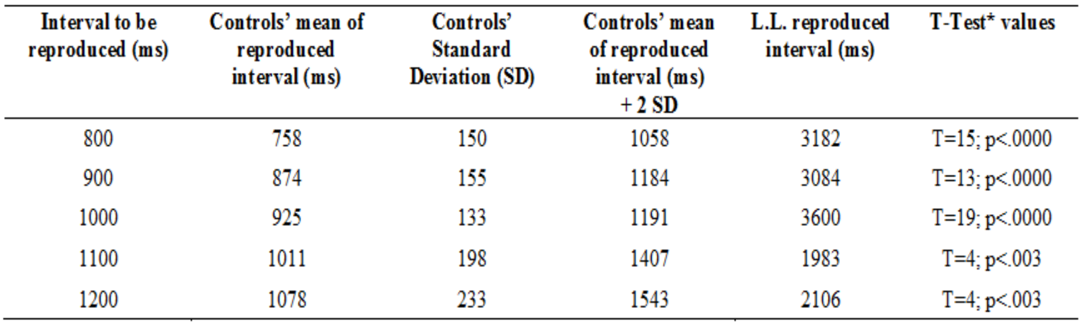
Interval to be reproduced (ms)	Controls’ mean of reproduced interval (ms)	Controls’ Standard Deviation (SD)	Controls’ mean of reproduced interval (ms) + 2 SD	L.L. reproduced interval (ms)	T-Test* values
800	758	150	1058	3059	T=14; p<.0000
900	874	155	1184	3798	T=18; p<.0000
1000	925	133	1191	5309	T=31; p<.0000
1100	1011	198	1407	3129	T=11; p<.0000
1200	1078	233	1543	3512	T=9; p<.0000

Tab. 8. See tab 7 caption.

Time bisection task before and after PA treatment

We observed a further decrease of underestimation in all time intervals after compared with before PA treatment (see figure 35 for means and SE). Again patient still underestimates time intervals more than two SDs compared to controls. However, significant difference with controls is reduced especially for the longer intervals (2200, 2400 ms), relative to the performance after one session of PA (see Table 9 for T values).

Table 9



Interval to be reproduced (ms)	Controls' mean of reproduced interval (ms)	Controls' Standard Deviation (SD)	Controls' mean of reproduced interval (ms) + 2 SD	L.L. reproduced interval (ms)	T-Test* values
800	758	150	1058	3182	T=15; p<.0000
900	874	155	1184	3084	T=13; p<.0000
1000	925	133	1191	3600	T=19; p<.0000
1100	1011	198	1407	1983	T=4; p<.003
1200	1078	233	1543	2106	T=4; p<.003

Tab. 9. See tab 7 caption.

Another interesting difference that we catch in the following Figure 35, is that despite a gradual reduction of time underestimation in L.L. after PA applications, reproduced intervals still do not increase with the interval-to-timed increasing, differently from controls.

Figure 35

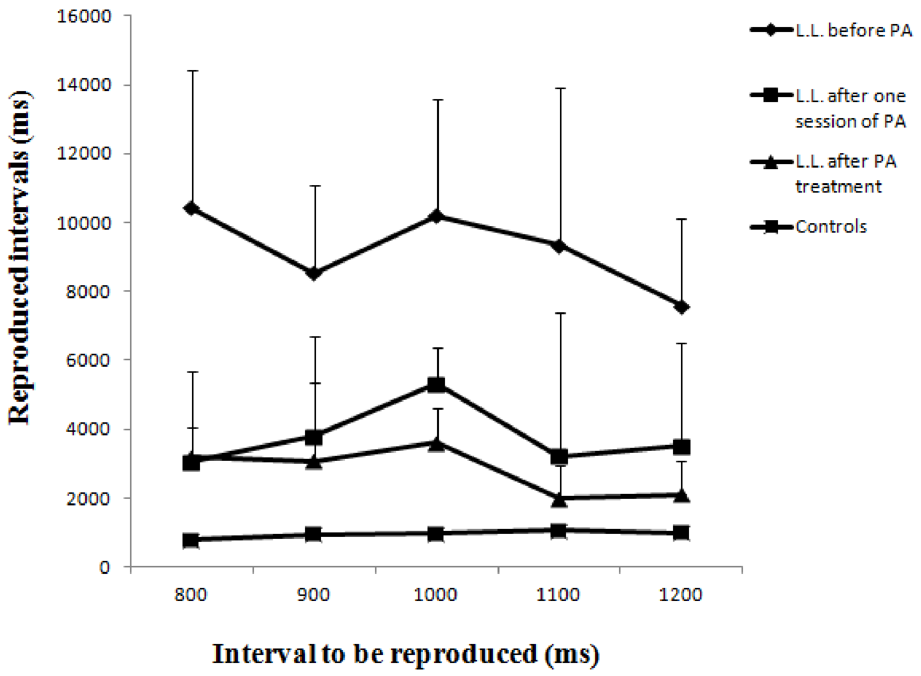


Fig. 35. Reproduced intervals plotted against values of intervals to be reproduced (millisecond) for controls and for patient L.L. before PA, after one session of PA and after PA treatment.

Interview before and after PA treatment

In the interview about the awareness on the passage of time L.L. she told she perceived a discrepancy between subjective flow of time compared to the real flow of time, that we interpreted as an underestimation This aspect is told to be decreased respect to the first interview both in intensity and in frequency. While before the PA treatment she perceived a gap of about two hours between the subjective and the real time, after PA she describes a gap of about one hour. Moreover she told that she feels this discrepancy especially in the afternoon and not in the morning or in the evening.

L.L. "…in the afternoon I usually wait for my daughter coming back from school. She arrives every day at 16,30. Anyway I start to wait for her at about 15,30 and I started to become worry cause she doesn't arrive. So I look at the clock, I realise it's too early and I calm down…"

The extract of the interview shows how the underestimation of time flow still has an impact on behavioral life of the patient, but it is interpreted as reduced respect to before the PA treatment.

Prismatic Adaptation treatment results

Figure 36 shows the adaptation and after-effects values for the ten daily sessions of PA treatment. See chapter 6 for a detailed explanation of PA procedure.

Figure 36

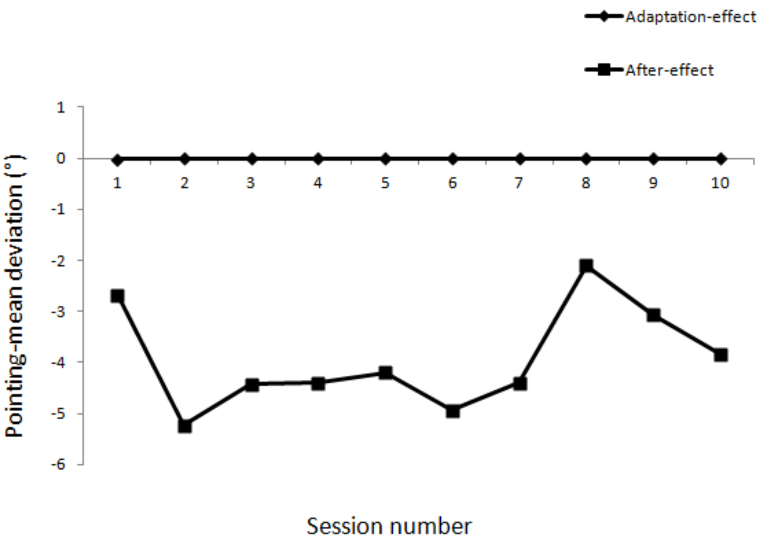


Fig. 36. Adaptation effect and aftereffect over 2 weeks of treatment. Mean displacement (degrees of visual angle) of L.L.'s pointing responses in the exposure condition (i.e. Adaptation-effect) and post-exposure (i.e. After-effect) condition.

9.2.4 Discussion

In summary we found that before PA patient was strongly impaired in the time bisection task and this impairment had a strong resonance on daily life activities. This result is in line with previous studies which show that patients with a right hemispheric lesion underestimate time intervals compared with healthy controls, while neglect patients grossly underestimate time intervals as compared without neglect and controls (Dankert et al., 2007; Oliveri et al., in press). Accordingly to our previous study (Oliveri et al., in press) we interpreted the great underestimation of L.L. of time intervals as the effect of the interaction between the right hemispheric lesion, because of the crucial role of right hemisphere in timing, and the presence of spatial attention deficit, which has a specific role on time perception as well. Since it has been purposed that time intervals are spatially represented on mental time line left-to-right oriented, spatial attention is thought to be crucial in biasing the time along with such spatial representation of time. Therefore neglect patients would largely underestimate time because the core timing deficit is associated with spatial attention/representation deficit of the left space and of the first part of the mental time line. Specially the presence of spatial neglect shift foreword (i.e. rightwards in term of spatial representation) the passage of time along the mental time line while the patient is reproducing the time interval duration.

Regard the effect of PA on time bisection task, we found that a session of PA, inducing a leftward shift of spatial attention, has slightly reduced the tendency of L.L. to underestimate time intervals, while a two weeks treatment of PA, has further reduced the underestimation of time intervals respect to before PA treatment. However L.L., after PA treatment, still shows an abnormal time performance and reproduced time decreased as the intervals to-be-timed increased. A possible explanation of these results could be that PA treatment has reduced the spatial attention bias reflecting on time representation (in terms of underestimation) and not timing deficit caused by right hemisphere lesion.

As far as, the impact of time perception deficit on everyday life we detected, by means a semistructured interview, that the time perception deficit strongly influences daily life. L.L. in the interview tells that she consciously perceives a discrepancy between subjective time flow and real time flow, believing to be forward in time. This aspect induces her to have many difficulties to synchronize herself with external times, inducing a feeling of anxiety and difficulties in social relationship. As for time intervals in the scale of seconds, L.L. would neglect the first part of the time line also for time scale of minute or hours. This could explain why L.L. has always the sensation to be forward in time during the day. These difficulties decreased after PA treatment. We assigned the reduction in time deficit of daily life to a reduction of spatial attention deficit due to PA, which reduces the deficit in neglecting the first part of the spatial representation of time.

GENERAL DISCUSSION

Time cognition is profoundly intermingled with spatial cognition. The process to perceive time occurs thanks to peculiar cognitive functions and neural networks that are selectively deputed to time. However, when the brain needs to represent, measure and manipulate a given time duration, it involves spatial mechanisms. Indeed time is represented via a spatial code, the same used to encode the mere space, and this spatial representation of time is subject to spatial manipulations.

In the last decade numerous researchers studied the spatial code to represent time dimension. All the studies provide results suggesting that time intervals are represented via a spatial line, called Mental Time Line (MTL), with ascending order from left to right, that is, that shorter intervals are represented to the left of longer intervals. Moreover growing evidence demonstrates that this temporal-spatial line left-to-right oriented can be manipulated by manipulating the orientation of spatial attention.

The present thesis contributes to the current debate on the relationship between spatial attention and spatial representation of time by using a well known technique to induce changing in spatial attention plasticity, that is Prismatic Adaptation (PA).

In the first experimental part, the behavioral **mechanisms** of space-time interaction have been addressed. In chapters 6 and 7, three experiments on healthy subjects, have been described to answer the question how the modulation of spatial attention affects the representation of time in normal cognition and in different sensory systems.

In chapter 6, we asked whether directing spatial attention toward a side of space by PA, time representation of visual stimuli is affected in the left-right short-long manner, suggested by literature (Vicario et al., 2007, 2008; Oliveri et al., 2009a,b). Our findings show that, for visual stimuli, the shift of spatial attention via PA induces a modulation of time processing according to the side of attentional shift: PA shifting spatial attention to the left produced an underestimation of , while PA shifting spatial attention to the right produced an overestimation of time. Subsequently, in chapter 7, we investigated whether time representation of auditory stimuli is affected by spatial attention modulation as visual ones. This question is not trivial, since the spatial coding of visual and auditory stimuli is different. Indeed, in the visual modality, space is immediately available in retinotopic coordinates on the receptor surface. By contrast, in the auditory modality, information is initially encoded tonotopically, and space is not immediately available on receptor surface (Barker et al., 2011; Hall et al., 2009). These considerations raised the possibility that auditory time interacts with spatial cognition differently from visual time. We found that the representation of time for auditory stimuli is actually encoded in a spatial way from left to right. But this spatial organization emerges only when it is enforced by the interaction with spatial factors. Indeed, if temporal auditory stimuli are presented in the left or right space of the participant, they are underestimated and overestimated respectively, only when the task requires to encode their spatial location. In a control condition, in which the task did not require to encode the spatial location, left and right stimuli were not underestimated or overestimated respectively. Moreover we found that also the shift of spatial attention by PA influenced the representation of auditory temporal stimuli in a similar way to visual stimuli. Indeed, PA shifting spatial attention to left produced an underestimation of time while PA, shifting spatial attention to right, produced an overestimation of time. The result that a simple visuo-motor adaptation procedure, such as PA, is able to modulate time representation in a modality not directly involved in the procedure, such as audition, is somewhat surprising. This implies that, the effects of PA, can extend to unexposed sensory systems, suggesting implication of a supra-modal effect. Once the sensory representation of duration is translated at high cognitive level in a spatial representation, it is not auditory featured anymore. In this sense, PA may have not affected audition but, rather, the spatial supra-modal representation of temporal stimuli.

In conclusion, in this part of the thesis we have described the effects of a spatial attention modulation on the spatial representation of time. Our findings suggest that spatial metric used to represent time, is a very centralized representation that is affected by spatial operations at high levels of spatial cognition.

In the second experimental part (chapter 8) of this thesis, the **neural bases** of the spatial attention effects on the spatial representation of time have been addressed. The fact that this interaction occurs at high cognitive levels, suggests that areas mediating this interaction are situated in the neocortex. In the study of cortical underpinnings, we started from the hemispheric lateralization. With a neuropsychological study on unilateral patients, we searched for the role of left and right hemisphere in mediating PA effects on time. We found that right brain damaged patients were impaired in time processing relative to age-matched-controls, while left brain damaged patients showed no impairment of time processing. This results confirmed a well established role of right hemisphere in time perception (Danckert et al., 2007; Harrington et al., 1998; Koch et al., 2002, 2003; Oliveri et al.,2009a). Moreover, we found that right brain damaged patients showed the effect of PA on time proved in healthy participants. On the contrary, left brain damaged patients did not show any effect of PA on time, suggesting a crucial role of the left hemisphere in leading PA manipulation to affect the spatial representation of time. In a second study, we wanted to go beyond the mere lateralization searching for the selective role of parietal cortices in mediating the space-time interaction. Since parietal cortices is crucial both in the spatial representation of time (Walsh, 2003; Bueti and Walsh, 2009; Oliveri et al., in press) and in the shift of spatial attention by PA (Luautè et al., 2006, 2009), we assumed that it should be important in the linking process between the two functions. By using repetitive transcranial magnetic stimulation (rTMS) we induced a virtual lesion on the right or left parietal cortex of healthy subjects. Our results suggested a model implying a close interactive neural process between left and right parietal cortex, for the PA procedure success, for the direct influence on time and for the PA effects on time. Particularly we found that left parietal cortex is selectively crucial for the success of PA procedure, while right parietal cortex is selectively crucial for time. In a third study with functional magnetic resonance (fMRI) we found that areas responsible of the PA effects on time are localized in the frontal lobe, supporting the assumption that these effects rely upon high levels of cognition. Moreover this frontal areas are lateralized in the left hemisphere.

The results of the TMS and fMRI experiments support the lateralization results showing that left brain damaged patients do not show time impairment and do not show the effects of PA on time. By contrast right brain damaged patients did show time impairment and also show the effects of PA on time.

This is of particular interest for the study of the **pathology** of the spatial representation of time. Indeed, we know that left brain damaged patients do not benefit of PA effect on time, but actually they do not need. By contrast, right brain damaged patients suffers of time impairment and they also can benefit of PA effects on time.

On this vein, the third experimental part of the thesis, is dedicated to the comprehension of the deficits of the spatial representation of time and the potentiality of PA in the rehabilitation of these deficits.

Given the strict interaction between spatial attention and spatial representation of time, in the chapter 9, first of all, we asked whether a spatial attention deficit following a right hemispheric stroke impairs the function to spatially represent time. The results showed that right brain damaged patients, with and without spatial attention deficits, have an impairment in time relative to controls, but the patients with spatial attention deficit are more impaired than patients without spatial deficits. This suggest that the presence of a spatial attention deficit worsens the temporal deficit, emerging following right brain damage. However, we remember that right brain damaged patients can benefit of PA effect on time. Thus, given the wide evidence of the effects of PA in the recovery of spatial attention deficits we asked whether PA would be a useful technique also for the recovery of time impairments. Results showed that, in patients with spatial attention deficits, a session of PA contrasting this deficit, also reduces the impairment in time, shedding light on PA as a possible instrument for time impairments rehabilitation. However, at this point one could ask why do we have to rehabilitate time deficits? Which is the impact of time deficits in patients' daily life? Actually we do not know anything about it, since the ecological impact of temporal deficits has never been investigate, differently from the ecological impact of spatial deficits (see Tham et al., 2000). Difficulties in time processing, could also have a strong impact on patients daily routine, for example in appreciating how much time an activity takes to be done. It might be that the ecological impact of time deficit has been less described because it is less evident in the hospitalization context than spatial deficit. Then, we explored, for the first time, the impact of temporal deficits on daily functionality in a patient with spatial and temporal deficits that was not hospitalized. The patient showed temporal deficits in an experimental time task, but she also showed difficulties that strongly impaired her daily autonomy, for example in estimating the right hour in the day and in organizing her activities. Thus, we verified whether the use of a ten daily treatment of PA, that normally improves spatial deficit (Watanabe and Amimoto, 2010; Jacquin-Courtois et al., 2008), also improves temporal deficit at an experimental and ecological level. As expected after PA treatment we found a substantial amelioration of the temporal impairment in the time task and, more important, of the daily difficulties, improving the patient's quality of life.

In conclusion the thesis offers a journey from the mechanisms mediating the space-time interaction at a behavioral level, passing through the investigation of the neural basis subtended, arriving to the description of the pathology and rehabilitation of the interaction dysfunctionality. Results exposed in the present dissertation advances the basic knowledge and provide new instruments to take advantage of the space-time relationship in clinical context.

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