TESIS DOCTORAL

Déficit en Orientación Temporal tras daño frontal

Temporal Orienting deficit after frontal damage

DOCTORADO EUROPEO

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A César e Isabel

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ÍNDICE

PREFACIO

La neuropsicología es una disciplina apasionante que conjuga el conocimiento sobre las funciones cognitivas y emocionales del cerebro sano y dañado. Trabajar en la clínica, atendiendo a pacientes con secuelas neuropsicológicas tras daño cerebral, genera la necesidad de llevar a cabo intervenciones válidas y eficaces que permitan a los pacientes tener la mayor funcionalidad posible en su vida diaria.

A lo largo de mi experiencia clínica, cientos de pacientes han mostrado importantes dificultades para responder en el momento oportuno, lo cual se manifestaba de muy diversas maneras tales como impulsividad, inatención o baja tolerancia a la demora. Creo firmemente en la necesidad de investigar y estudiar los procesos que se encuentran alterados y que conforman el déficit central o básico de dichas conductas observables, así como las bases neurales que sustentan esos procesos, puesto que dará lugar a un conocimiento más acertado del problema, permitiendo su evaluación, diagnóstico y el diseño de una intervención más eficiente y ecológica.

El objetivo de esta investigación, por tanto, ha sido profundizar en el conocimiento de los procesos de preparación temporal y, mediante la administración de las tareas experimentales propias de este área, realizar un acercamiento a su base neural, con el propósito de avanzar en la comprensión e intervención de los déficit que en procesamiento temporal presentan los pacientes con daño cerebral.

Ellos han sido el motor de mi investigación.

SINOPSIS

El tiempo es un proceso complejo que está presente en nuestra vida diaria, siendo necesario en múltiples actividades. Cuando las capacidades temporales se ven afectadas, la conducta se ve alterada y las personas responden de forma desadaptativa. En relación con el procesamiento temporal o *timing* se han distinguido procesos de percepción del tiempo y procesos de preparación temporal, dentro de los cuales se pueden diferenciar procesos más controlados (i.e. efecto de orientación temporal y efecto de foreperiod) y procesos más automáticos (i.e. efectos secuenciales).

El estudio de las bases neurales del procesamiento temporal, en general, así como de la preparación temporal controlada vs. automática, profundizando en cada uno de los efectos descritos en la literatura, ha constituido el objetivo principal de la presente tesis.

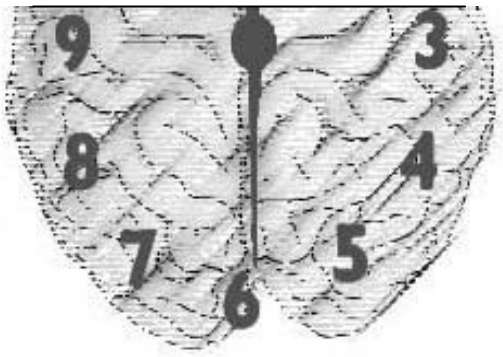
La exposición de la tesis se estructura en cuatro partes: introducción, investigación experimental, discusión general y conclusiones. La *introducción* revisa los conceptos fundamentales para la presente investigación respecto al procesamiento temporal. Esta introducción se divide en tres capítulos que proponen, en primer lugar, una revisión de los modelos teóricos más relevantes sobre procesamiento temporal; en segundo lugar, una revisión de los estudios neuropsicológicos sobre estimación temporal tras daño cortical; y en tercer lugar, una revisión de los estudios sobre preparación temporal.

Fruto de esta revisión son los objetivos que han motivado la *Investigación Experimental*. Esta parte comienza con el planteamiento del grupo de hipótesis que ha guiado la realización de dos estudios con pacientes que habían sufrido daño cerebral. Estos estudios se

corresponden con artículos independientes, el primero ya publicado y el segundo en proceso de revisión.

Finalmente, la *Discusión General* pretende la integración del conocimiento alcanzado a partir de cada uno de los artículos, mediante un resumen global de los resultados y aportaciones más relevantes de la tesis, y poniéndolo en relación con las ideas centrales de la introducción. La tesis culmina con una reflexión acerca del procesamiento temporal y la relación existente entre los procesos de percepción del tiempo y los de preparación temporal, y las principales *Conclusiones* que se derivan de las investigaciones presentadas.

INTRODUCTION



CHAPTER 1

THE STARTING POINT: TIME PERCEPTION

Understanding the subjective dimension of time has always been a challenge for neuroscience. As Zakay (1990) proposed, "subjective time is one of the essential dimensions required by humans for orientation in their surrounding world" (p. 59). There is no doubt about the importance of timing in daily activities such speaking, driving, dancing or listening to music. The complexity of this concept has led to multiple models and classifications of timing. Specifically, controlled and automatic temporal processing have been distinguished related to top-down and bottom-up processes, respectively (Michon, 1985).

Other authors have classified controlled and automatic temporal processes in terms of the duration and prediction of stimuli appearance (Lewis & Miall, 2003, 2006). Continuous and predictable stimuli will recruit the automatic timing system related to motor activity, while discontinuous and unpredictable stimuli will recruit the cognitive-controlled timing system related to right prefrontal and parietal cortices. In the same vein, Zelaznik and colleagues (2002) have been dissociated implicit and explicit timing depending on movement initiation and movement duration. Explicit representations of time are needed in pacing and intermittent drawings tasks, where participants have to estimate when exactly start; while the use of time in continuous circle drawings is implicitly. Otherwise, Coull and Nobre (2008) have organized this nomenclature in a model that distinguishes implicit vs. explicit timing as well as automatic vs. controlled processes. As this model proposes, the main distinction between explicit and implicit timing is "whether or not the task instructions require subjects to provide an overt estimate of duration" (p.137). Therefore, implicit timing tasks require subjects to make a non-temporal perceptual or motor response, but

the implicitly use of time information is needed to achieve the task goal. The implicit tasks consist mainly in temporal preparation tasks where time information can be used in a controlled manner (endogenous) or automatically (exogenous). However, in explicit timing tasks, subjects have to estimate explicitly intervals duration. Participants have to estimate the duration of one interval or to discriminate between the duration of two stimuli (*perceptual timing*); or have to produce or reproduce intervals in a sustained, delayed or periodic motor act (*motor timing*). Both perceptual and motor explicit timing refer to what have been traditionally named as "time estimation" or "time perception".

There is an extensive literature on time perception that uses a wide variety of tasks for the assessment of subjective time in range from milliseconds to minutes. Specifically, Bindra and Waksberg (1956) proposed four major methods in time estimation: verbal estimation, time production, time reproduction and comparison (see Table 1.1 for a classification and description of the most widely used).

THEORETICAL MODELS

Several models have been proposed to explain how humans estimate time to adjust their behavior to temporal parameters in the range from milliseconds to minutes. Some of them propose a distributed time representation such as the spectral and network models. The *spectral models* share the idea that decoding time is performed by collections of neurons that differ in temporal properties and activate at different times (Grossberg & Schmajik, 1989; Miall, 1989).

Table 1.1. The classification proposed by Bindra and Waskberg (1959) collects the tasks in range from milliseconds to minutes, also known as *interval timing*. We have also taken into account the tasks definitions provided by Nichelli (1993, 1996) and Grondin (2010). This classification has been divided into perceptual and motor explicit timing tasks, following Coull and Nobre (2008).

Type of Task			Description
Perceptual Timing	Estimation Tasks	Verbal estimation	Subjects have to estimate a time interval with conventional time units.
	Comparison Tasks	Temporal Comparison	Subjects are presented with two consecutive intervals and should indicate verbally or by pressing the appropriate key, if the second interval was shorter or longer than the first. The first interval can be standard or vary trial to trial.
		Temporal Resolution	Subjects are presented with two intervals and must decide whether they are equal or not.
		Magnitude Estimation	Subjects are presented with a standard interval and must judge the duration of another interval by assigning a number (in conventional units of time) or representing the duration drawing a line.
		Single Stimulus	Subject are shown one of two possible stimulus (short vs. long) and they must decide whether the short or the long.
		Temporal Bisection	Subjects are trained to discriminate two standard intervals (short vs. long); then they are presented with intervals of intermediate duration and subjects must classify each interval as more similar to short or long.
		Temporal Generalization	Subjects are trained with a standard interval; then subjects are presented with other intervals and must decide whether or not they are equal to the standard.
		Temporal Order	Subjects are shown two successive stimuli and must decide which came first.
Motor Timing	Production Tasks	Temporal Production	Subjects must produce a specific time interval conducting two answers (at the beginning and end of the interval) or a single response.
	Reproduction Tasks	Temporal Reproduction	Subjects are shown a single interval or a sequence of intervals with a standard length, and they must reproduce that interval or sequence with the same duration.
		Ratio-setting	Subjects are shown a time interval and then asked to generate a specific proportion of it.

The *network or state-dependent models* (Buonomano, 2000; Buonomano & Merzenich, 1995) suggest that cortical networks process inherently temporal information, since an input is processed according to the temporal-dependent changes that occur in these networks. In this model all synapses have the same temporal plasticity, unlike spectral models in which neurons are organized in groups. Therefore after an event happens, the network will be different at 50, 100 and 200 ms, so a second event at 100 m will arrive to a different network state. That is, some synapses will be facilitated or depressed and the same event temporal event will activate different populations of neurons depending on the recent history of the network (Mauk & Buonomano, 2004).

However, models most widely reported in the literature on time perception are *clock models* that propose the presence of an internal clock localized in specific brain structures. Within the clock models, the Scalar Expectancy Theory (SET) plays a key role (Gibbon, 1977; Gibbon, Church, & Meck, 1984), and has influenced several neurobiological models such as those proposed by Meck (1996, 2005), Harrington et al. (Harrington & Haaland, 1999), Ivry et al. (Hazeltine, Helmuth, & Ivry, 1997; Ivry & Spencer, 2004) and Lewis and Miall (Lewis & Miall, 2003, 2006).

The Scalar Expectancy Theory

Time perception research has been heavily influenced by the John Gibbon's Scalar Expectancy Theory (Gibbon, 1977; Gibbon et al., 1984). This theory proposes two psychophysical features of the timing process that ensure a reliable and valid time perception. The first feature is the *mean accuracy property,* by which the mean representation of time for several temporal judgements equals real time according to psychophysical law (Eisler, 1975, 1976; Eisler, Eisler, & Hellström, 2008). The second feature is the *scalar property of variance,* by which the variability of temporal estimation increases linearly with standard duration according to Weber's law (Killeen & Weiss, 1987). That is, the longer the interval to be estimated, the greater the variability of the estimation. These psychophysical properties lead to the typical measurement of accuracy and precision (variability) of time perception tasks.

The model also proposes three distinct stages: clock, memory and decision. These stages are supposed to be used in comparison tasks, where individuals need to compare between two temporal intervals (e.g. comparison between a standard interval and an another longer or shorter interval). At the first stage, the model proposes a mechanism that produces

periodic pulses named the *pacemaker*. The perceived subjective time is mediated by attentional processes in the *switch*. The switch can be closed (to allow pulses flowing) or opened (to stop pulses flowing). Thus, the switch is closed when a significant temporal information is detected, and is opened when this information has ended (Meck & Church, 1983). These pulses are stored by an *accumulator* and approximately correspond to objective ('real') time. Some authors (Zakay & Block, 1996) have proposed that the flow of pulses can vary as a function of the amount of attention devoted to time processing by adding an *attentional gate* to the switch (i.e., everyone has felt that time stands still when you are bored, or conversely, that time flies when you give all your attention on a task). At the second stage, this subjective time representation comes into the *working memory* store where it is kept and handled according to current goals. Some of these representations are stored in *long-term memory*. Finally, at the third stage, the present pulses accumulated in the working memory system are compared to those already stored in the reference memory system, resulting in a *decision-making process*, when subjects decide whether the comparison interval is longer or shorter than the standard interval.

Neurobiological models framed in the Scalar Expectancy Theory

The Scalar Expectancy Theory has been an exceptional cognitive framework where neurobiological models have incorporated the neural bases provided by findings on neuropharmacological, neuroimaging and neuropsychological studies. One of the most relevant neurobiological model is the model proposed by Meck (Meck, 1996, 2005). This model focuses on frontal-striatal circuits for time perception and specifies the neural components underlying the five stages of the Scalar Expectancy Theory. That is, the substantia nigra pars compacta (SNc) as the *pacemaker*; the striatum (caudate and putamen nuclei) as the *switch*; the globus pallidus as the *accumulator*; the thalamus as the *attentional gate*; and the prefrontal cortex as the *working memory* and the *comparator* systems. The basal ganglia

(substantia nigra, striatum and globus pallidus) form the internal clock using a dopamine-dependent circuit, while the thalamus and the prefrontal cortex are connected by a cholinergic circuit. A variety of pharmacological and neuropsychological studies support this model in relation to the deficit of the dopaminergic system. Specifically, dopaminergic agonists such as methamphetamine have been related to a faster clock and overestimation, while dopaminergic antagonists such as haloperidol have been related to a decrease in the speed of the internal clock and underestimation. Patients with dopaminergic deficit such as in the Parkinson Disease or the Attentional-Deficit Hyperactivity Disorder also replicate this pattern of results (for reviews see Meck, 1996; 2005).

In the same vein, Harrington et al. (Harrington & Haaland, 1999) consider five neural structures mainly right lateralized: basal ganglia (caudate and putamen nuclei) as the *pacemaker*; the thalamus and the parietal cortex interaction as the *switch* and *accumulator*; the premotor cortex as the *working memory*; and the dorsolateral prefrontal cortex as the *comparator*.

Ivry and colleagues (Hazeltine et al., 1997; Ivry & Spencer, 2004) have also proposed a cortical-subcortical network for time perception. This network is formed by the basal ganglia and the prefrontal cortex, as well as the cerebellum. In this model, the cerebellum plays a key role generating temporal representations in the range of milliseconds (*pacemaker*), which are maintained and manipulated in the prefrontal cortex (*working memory*). The representations accumulated in working memory are updated via basal ganglia, which control the number of updates through a threshold mechanism (*switch* and *accumulator*). Thus, dopamine agonists decrease the basal ganglia's threshold leading to a more frequently updating and a subsequent overestimation, while dopamine antagonists increase the threshold, reducing the updating and leading to the subsequent underestimation.

The model by Lewis and Miall (2003, 2006) considers the existence of an automatic timing related to a motor circuit, specifically the supplementary motor area, the premotor cortex, the cerebellum and the basal ganglia (*internal clock*). With regard to the cognitive-controlled timing, they propose the anterior cingulate cortex and the posterior parietal cortex (*attentional gate*), the dorsolateral prefrontal cortex (*working memory*) and the ventrolateral prefrontal cortex (*reference memory* and *comparison*).

In conclusion, it seems to be a consensus among the neurobiological models to consider that subcortical structures, such as basal ganglia and cerebellum, are related to the internal clock functions, playing a key role in automatic timing. In addition, these models propose that the connection between the subcortical and cortical structures is related to more controlled processes (attention, working memory and decision-making).

Dysfunctions of the clock: when perception of time changes

According to the Scalar Expectancy Theory and the models described above, each stage is independent and its alterations will lead to specific patterns of accuracy and precision, described above, in duration estimations (Meck, 1996; Nichelli, 1993, 1996). Table 1.2 presents the predictions of the model, as well as the components, the structures related and the possible impairments. In particular, alterations of the *pacemaker* can cause temporary overestimation or underestimation depending on whether the mechanism of pulse generation is accelerated or slowed, respectively. Whether an increase or decrease in the rate pulses, the accuracy of time estimation should be impaired, although the precision (or variability) should be relatively unaffected.

The *switch* closes when a relevant event happens allowing the pulses to flow, and then is opened when the event finishes stopping the pulses flowing. There is a variability caused by the latency at both the onset and offset stages, so a disruption in this mechanism will increase the latency affecting the precision (or variability) of the subjects. The counter regularly transfers the information about pulses accumulated to memory systems, so it always works with short intervals (within the perceptual range in milliseconds). As a result, a source of error in the *accumulator* will produce imprecise performances in all tasks involving short intervals.

Table 1.2. Predictions of the Scalar Expectancy Theory.

Component of the model	Structures related	Impairment	Prediction
Pacemaker	Substantia Nigra pars compacta (Meck, 1996; 2005) Striatum (Harrington et al., 1999) Cerebellum (Hazeltine et al., 1997; Ivry & Spencer, 2004) Cerebellum & Basal ganglia (Miall & Lewis, 2003; 2006)	Acceleration or slowing of the clock	- Accuracy impaired: overestimation or underestimation depending on the mechanism is accelerated o slowed. - Precision (variability) unaffected.
Switch & Attentional gate	Striatum (Meck, 1996; 2005) Parietal cortex (Harrington et al., 1999) Basal ganglia (Hazeltine et al., 1997; Ivry & Spencer, 2004) Anterior cingulate and posterior parietal cortex (Miall & Lewis, 2003; 2006)	Latency increased at both the onset and offset stage of the switch	- Accuracy unaffected. - Precision (variability) impaired: inconsistency in responses.
Accumulator	Globus palidus (Meck, 1996; 2005) Thalamus and parietal cortex interaction (Harrington et al., 1999) Basal ganglia (Hazeltine et al., 1997; Ivry & Spencer, 2004) Supplementary Motor Area (SMA) and premotor cortex (Miall & Lewis, 2003; 2006)	Random error when transferring information of short intervals (milliseconds) to memory systems	- Accuracy unaffected. - Precision (variability) impaired: inconsistency at short intervals (milliseconds).
Working memory	Prefrontal cortex (Meck, 1996; 2005; Hazeltine et al., 1997; Ivry & Spencer, 2004) Premotor cortex (Harrington et al., 1999) Dorsolateral prefrontal cortex (Miall & Lewis, 2003; 2006)	Any leakage in the mechanism that register the passage of time	- Accuracy impaired: underestimation regardless the task used. - Precision (variability) unaffected.
Reference memory	Ventrolateral prefrontal cortex (Miall & Lewis, 2003; 2006)	Any leakage of information in the temporal representations stored in memory	- Accuracy impaired: overestimation regardless the task used. - Precision (variability) unaffected.
Comparator	Prefrontal cortex (Meck, 1996; 2005; Hazeltine et al., 1997; Ivry & Spencer, 2004) Dorsolateral prefrontal cortex (Harrington et al., 1999) Ventrolateral prefrontal cortex (Miall & Lewis, 2003; 2006)	Discrepancy between the two values compared (working memory vs. reference memory)	- Accuracy unaffected. - Precision (variability) impaired: inconsistency at both short and long intervals (milliseconds to minutes).

All these components have been mainly related to subcortical structures such as cerebellum and basal ganglia, although the attention and accumulation processes have also been related

to parietal cortex, thalamus, supplementary motor area, premotor cortex and anterior cingulate cortex. Thus, the clock mechanism is expected to be altered after damage or dysfunction of these structures.

Regarding the *working memory* as a mechanism that register the passage of time, any defect will result in underestimation independently of the method used to measure time (i.e. subjects will underestimate in either estimation, production and reproduction tasks). Deficit in this mechanism will affect the accuracy with this temporal bias, but will leave the precision intact. With regard to *reference memory*, any failure in this system will produce overestimation regardless the task used without deficit in precision.

Finally, there must be a decision process after the *comparison* between both the intervals in working memory and reference memory system. This decision process depends on the existence of a rate of discrepancy between the two values compared. Therefore an alteration in the mechanism of comparison will decrease this rate. As a result, different intervals will be judged as similar, which will lead to greater imprecision in all tasks and in both short and long intervals. All these components are related to frontal structures with a key role of prefrontal cortex, so prefrontal damage will produce the impairments predicted.

CHAPTER 2

OVERESTIMATION AFTER FRONTAL DAMAGE: THE NEUROPSYCHOLOGY OF TIME PERCEPTION

Clock models and specifically the Scalar Expectancy Theory have generated many neuropsychological studies with clinical and subclinical populations on time perception. As discussed in chapter 1, this theory predicts different deficits in accuracy and precision of time estimation when the different components proposed by the model are impaired. Specifically, most of the neurobiological models regarding time perception have associated prefrontal structures with the working memory, reference memory and comparator components of the Scalar Expectancy Theory (Meck, 1996, Meck, 2005; Hazeline et al., 1997; Yvry & Spencer, 2004; Miall & Lewis, 2003, 2006, Harrington et al., 1999). Therefore, neuropsychological studies with frontal patients are of great interest to establish correlations between brain regions underlying these cognitive functions related to the ability to estimate time.

To do this, we conducted a review of the main studies about time estimation in patients with lesions in the cerebral cortex, mainly in the prefrontal cortex. The reviewed studies have been organized on one side, according to focal lesions (i.e. strokes, traumatic brain injury or tumor) and on the other side, according to neuropsychological syndromes (neglect, aphasia and amnesia). Neuropsychological syndromes can provide us additional information about the role of cognitive functions such as attention, language and memory. Secondly, the studies have been organized depending on the type of time estimation task (see table 1.1 in previous chapter). That is, estimation, production, reproduction and comparison tasks (i.e., temporal comparison, temporal bisection, temporal resolution, and

temporal order). Estimation and comparison tasks are considered as *perceptual timing*, while production and reproduction tasks are considered as *motor timing*. Estimation, production and reproduction temporal tasks are the most widely used, and they employ intervals mainly in the range of seconds (from 1s to 120s). However, comparison tasks typically employ intervals in the range of milliseconds (from 50ms to 1200ms). These tasks provide measurements of accuracy (overestimation vs. underestimation) and precision (or variability/consistency).

Although the results vary along the articles, there was a main result that deserve to be discussed deeply: overestimation.

OVERESTIMATION: WHEN TIME SEEMS SHORTER

Overestimation refers to a person's belief that an actual time interval is longer than it has really been. That person will have the subjective feeling of time passing faster. This distortion is reflected in behavioral performance either as overestimation in perceptual timing tasks or as underproduction in motor timing tasks. See Figure 2.1.

The reviewed studies presented in the Table 2.1 included patients with lesions in frontal, parietal or temporal lobes of diverse aetiology as Anterior Communicating Artery (ACoA) aneurysm, Traumatic Brain Injury (TBI), seizure focus, tumors, strokes or frontotemporal dementia. Six studies included neuroimaging (MRI or CT) with a description of the lesions location and extension (Berlin, Rolls, & Kischka, 2004; Coslett, Shenton, Dyer, & Wiener, 2009; Danckert et al., 2007; Harrington, Haaland, & Knight, 1998; Picton, Stuss, Shallice, Alexander, & Gillingham, 2006; Wittmann, Burtscher, Fries, & Von Steinbüchel, 2004). Six studies included an extensive neuropsychological assessment beyond the tests used only for patient inclusion (Berlin, Rolls, & Iversen, 2005; Berlin et al., 2004; Danckert et al., 2007;

Harrington, Haaland, & Knight, 1998; Mimura, Kinsbourne, & O'Connor, 2000; Picton et al., 2006).

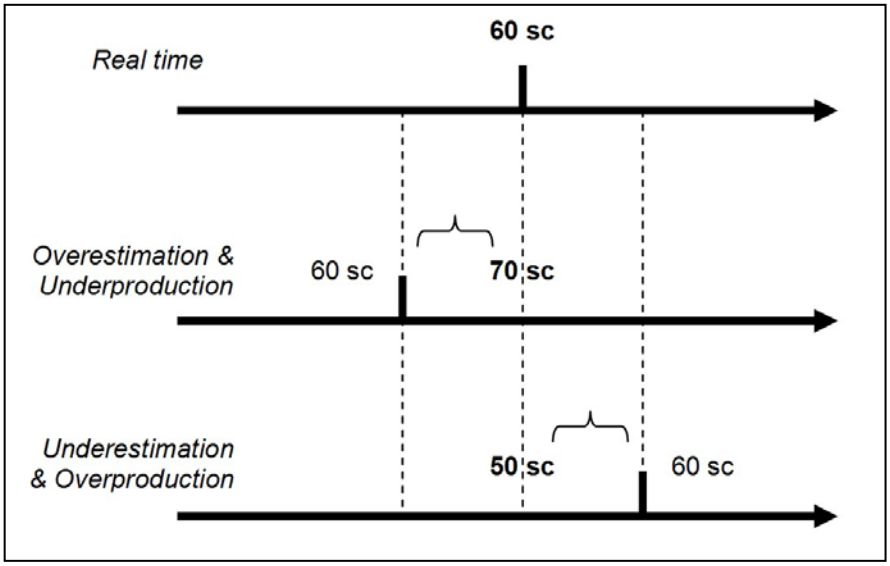


Figure 2.1. Accuracy deficit representation. The top line depicts a specific standard interval (60s) in real time. The middle line represents the deficit of a person with overestimation. That is, estimation of the standard interval as longer (e.g. 70s) and production of the interval earlier when it has thought that 60s have passed (e.g. at 50s). The bottom line represents an underestimation deficit. That is, estimation of the standard interval as shorter (e.g. 50 s) and production of the interval later (e.g. at 70 s).

Behavioral and neuroimaging results

Regarding the *behavioral results*, it is noteworthy that they are somewhat contradictory. That is, overestimation and underproduction in the range of seconds (10-90s) have been related to the orbitofrontal damage compared to patients with lesions in dorsolateral or medial frontal cortex (Berlin et al., 2005; Berlin et al., 2004). However, other studies show that patients with dorsolateral damage tended to overestimate at shorter intervals of seconds (10-30s) and at intervals of milliseconds (300-1500ms) in estimation, reproduction and comparison tasks (Mimura et al., 2000; Nichelli, Clark, Hollnagel, & Grafman, 1995). Other studies do not show differences between prefrontal and control groups (Ivry & Keele, 1989; Mimura et al., 2000), although these patients tended to show higher variability (inconsistency) in pacing tasks (Ivry & Keele, 1989). No other studies show differences

between patients with frontal lesion (orbital or dorsolateral) and controls on tapping, pacing, spatial bisection or frequency discrimination tasks (Berlin et al., 2004; Ivry & Keele, 1989; Mimura et al., 2000; Nichelli et al., 1995; Wiener & Coslett, 2008).

Table 2.1. Main studies regarding temporal estimation tasks.

Group	Estimation tasks	Production tasks	Reproduction tasks	Comparison tasks		
				Temporal Comparison	Temporal Bisection	Order
Frontal lesion	Overestimation at shorter intervals (Berlin et al., 2004; Berlin et al. 2005 ; Mimura et al., 2000)	Underproduction (Berlin et al., 2004; Berlin et al. 2005) No differences with controls (Mimura et al., 2000)	Increased variability in right lateral and superior medial lesions (Picton et al., 2006)	Overestimation in right anterior lesions Harrington et al., 1998) No differences with controls (Ivry & Keele, 1989)	Overestimation (Nichelli et al., 1995)	Increased threshold in right anterior lesions (Wittman et al., 2004)
Parietal lesion	Overestimation (Desai, 2007) at longer intervals (Coslett et al., 2009; Danckert et al., 2007)	Underproduction (Coslett et al., 2009; Desai, 2007)	Accuracy, but inconsistency (Coslett et al., 2009)			
Neglect syndrome	Overestimation (Danckert et al., 2007)	Underproduction on left side (Basso et al., 1996)		Overestimation on left side (Basso et al., 1996)		
Aphasia	No differences between aphasics and non-aphasics (Coslett et al., 2009)	No differences between aphasics and non-aphasics (Coslett et al., 2009)	No differences between aphasics and non-aphasics (Coslett et al., 2009)			Increased threshold in left posterior lesions (Wittman et al., 2004)
Amnesia	No differences with controls (Shaw & Aggleton, 1994)		No differences with controls (Shaw & Aggleton, 1994)	No differences with controls (Ivry & Keele, 1989)		

This inconsistency in the results may be related to the variety of aetiologies included, but especially to the absence of neuroimaging with the location and extent of the lesions. Therefore taking into account the *neuroimaging results,* we found that Berlin et al. (2004) included the CT of the patients, but 20 of their 23 patients in the orbital group had also damage in the dorsolateral and/or medial frontal cortex (only 3 patients had lesions exclusively in orbitofrontal cortex). While in the non-orbital group, 13 of 20 patients had lesions exclusively in the dorsolateral or medial frontal cortex. In addition, it is worth saying that the non-orbital group also showed an overestimation and underproduction profile, but failed to be significant compared with controls. Therefore, the deficit in time

perception may be due to a greater extension of the damage in the orbital group compared to the non-orbital group and, therefore, to the impairment in many cognitive functions.

Of great interest is the study of Harrington and colleagues (1998) in which they used a comparison task in range of milliseconds (300 & 600ms) and studied the MRI of 37 patients after a stroke. They established four groups depending on the location of the lesions: right anterior, left anterior, right posterior and left posterior. The deficits in the duration judgements were only associated with right anterior damage. Specifically, subjects showing these deficits had common injuries in lateral premotor area including the frontal eye field (FEF), as well as the middle and superior gyri of dorsolateral prefrontal cortex (BA8, BA9 and BA46). However, subjects in this group who did not show deficit in duration judgements had lesions located in different areas such as supplementary motor area (SMA), caudal premotor area and somatosensory cortex. Moreover, none of the patients with left anterior damage showed deficits in the duration judgements despite showing lesions in the same areas as those in the right anterior group.

Likewise, Wittman et al. (2004) divided 30 patients after stroke in the same four groups: right anterior, left anterior, right posterior and left posterior. Using a milliseconds temporal order task, a threshold increase was found in the left posterior group, but in the analysis of the location of the lesion only the right anterior group showed a significant correlation. This group showed lesions in right premotor area and adjacent white matter.

More specifically, Picton et al. (2006) studied a group of 39 frontal patients after TBI or tumors and they were classified into four groups according to MRI and CT: right lateral, left lateral, inferior medial and superior medial. In this case a reproduction task in a range of 1500ms was used. Impairment in temporal perception was observed again in the right frontal group. In particular, an increased variability in the right lateral group (BA 45 and underlying regions of the basal ganglia) and an increased variability as time passes in the superior medial group (BA10 and BA32).

Furthermore, some studies have shown an involvement of parietal cortex in the temporal perception. Specifically, overestimation and underproduction have been reported in the range of seconds (4-60s) (Coslett et al., 2009; Danckert et al., 2007; Desai, 2007), although these results have mainly been related to a single case with neglect syndrome (Basso, Nichelli, Frassinetti, & di Pellegrino, 1996) or to a single case with bilateral parieto-occipital lesions (Desai, 2007). Meanwhile, Danckert et al. (2007) found an overestimation pattern in patients with right parietal damage with and without neglect syndrome using an estimation task in the range of seconds (5-60s). Specifically, patients with neglect showed a dramatic overestimation at every interval compared to controls and they had lesions in right insula, supramarginal gyrus, caudate and putamen nuclei, and superior temporal gyrus. However, patients with right parietal damage without neglect, showed an overestimation as the intervals were longer (30-60s) and had lesions in right basal ganglia including the lenticular nucleus and the thalamus.

Also noteworthy is the study of Coslett et al. (2009) with MRI in 31 patients after stroke organized into four groups: lateral frontal lobe, middle temporal gyrus, inferior parietal lobe and superior parietal lobe. Using estimation, production and reproduction tasks in the range of seconds (2-12s), they found that patients with superior parietal damage (in both hemispheres) showed overestimation, underproduction as well as an increased variability in reproduction tasks as intervals were longer (8-12s) as compared to the other groups.

Neuropsychological results

In relation to the *cognitive interpretation and neuropsychological results*, most of the results mentioned above have been interpreted according to the Gibbon's Scalar Expectancy Theory. First, as the result of a faster internal clock (Berlin et al., 2005; Berlin et al., 2004; Coslett et al., 2009; Desai, 2007; Wiener & Coslett, 2008). Second, as a failure in working

memory or reference memory system leading to an overestimation in intervals of milliseconds or few seconds (Coslett et al., 2009; Harrington, Haaland, & Knight, 1998; Mimura et al., 2000; Nichelli et al., 1995; Picton et al., 2006; Wiener & Coslett, 2008). And third, as a failure in sustained attention or in keeping the same decision criteria leading to an overestimation in intervals of seconds (Nichelli et al., 1995; Picton et al., 2006).

Some studies have attempted to specify the memory mechanisms involved. Thus, subvocal counting has been suggested as a mechanism through which people estimate time explicitly (Hinton & Rao, 2004). Therefore, the failure of working memory mechanisms that allow such counting will produce an estimation impairment. Studies with aphasic patients do not show significant differences in left hemisphere patients with and without aphasia neither in estimation, production or reproduction tasks in the range of seconds (Coslett et al., 2009). Although in temporal order tasks in the range of milliseconds, there is an increased threshold in aphasic patients as compared to patients with right hemisphere damage (Wittmann et al., 2004), which has been associated with the impaired ability to discriminate the stimuli in the range of milliseconds needed for phonological discrimination (Mates, Von Steinbüchel, Wittmann, & Treutwein, 2001). Another common proposal is the failure of the reference memory system. However, postencephalitis amnesics and epileptic patients after temporal lobe resection did not show differences compared to controls in estimation, comparison, reproduction or pacing tasks, despite the anterograde amnesia and the deficit in neuropsychological memory tests (Ivry & Keele, 1989; Shaw & Aggleton, 1994).

Related to the attentional mechanisms proposed, hemineglect patients show a dramatic overestimation and underproduction in the stimuli presented at the unattended left side (Basso et al., 1996; Danckert et al., 2007). These authors propose a severe disruption in the mechanisms of orienting of attention as a primary deficit. That is, an alteration in the

attentional switch leads to an impairment in the accumulation of pulses. Thus, durations of unattended stimuli due to their broader temporal profile, would appear to be longer, whereas duration of stimuli appearing at the attended locations would appear to be shorter. However, Harrington et al. (1998) suggest a dissociation between attention deficit and time perception. In their study, right prefrontal patients showed an overestimation in a temporal comparison task, while both right and left prefrontal patients failed in a non-temporal attention task.

Finally, an alternative explanation comes from Berlin et al. (Berlin et al., 2005; 2004), who propose that orbitofrontal patients are more impulsive as they become frustrated while waiting for the time interval to finish. The possibility that impulsivity is on the basis of the overestimation is also provided by Weiner and Coslett (2008) and Coslett (2009).

CONCLUSIONS

The present review suggests that the right prefrontal and the superior parietal cortex (pointing also to a right location) are the areas related to deficit in time perception leading to an overestimation, underproduction and an increased variability. Moreover, this temporal profile of overestimation has been related to other conditions that usually show a prefrontal dysfunction, such as frontotemporal dementia, schizophrenia, borderline personality disorder, antisocial personality disorder or conduct disorder (e.g., Bauer, 2001; Berlin et al., 2005; Berlin & Rolls, 2004; Carroll, O'Donnell, Shekhar, & Hetrick, 2009; Davalos, Kisley, & Ross, 2002; Davalos, Kisley, & Ross, 2003; Dougherty et al., 2007; Elvevag et al., 2003; Lee et al., 2009; Wiener & Coslett, 2008).

Mechanisms underlying this temporal deficit profile are still unclear, although most of the neuropsychological results point to a deficit in working memory that prevents the updating

and maintenance of temporal information. It is remarkable that all the studies using the millisecond range (100-1500ms) show a right lateral frontal involvement (Harrington, Haaland, & Knight, 1998; Picton et al., 2006; Wittmann et al., 2004) compared to groups of patients with posterior lesions, while the studies using seconds range (6-60s) show a superior parietal involvement compared to lateral prefrontal lesions (Coslett et al., 2009). This could be interpreted as the result of different cognitive mechanisms to process the time as it passes. In fact, working memory has been proposed as necessary to update the passage of time in the range of milliseconds and few seconds, while sustained attention would be necessary to maintain the representation of time at longer intervals (Nichelli et al., 1995). The working-memory recruits dorsolateral prefrontal cortex (Stuss & Levine, 2002), while the mechanisms of orienting of attention have been associated with superior parietal cortex (Corbetta & Shulman, 2002). However, this can also be interpreted as a fortuitous coincidence in relation to the tasks and temporal ranges used in these studies, so more research is needed. It would be interesting to conduct more neuropsychological studies with frontal and parietal patients, including neuroimaging and using perceptual (i.e. estimation and comparison tasks) and motor (i.e. production and reproduction) timing tasks in different ranges from milliseconds to seconds.

Finally, the fact that patients with right prefrontal damage show a clear deficit in time perception (ie, overestimation) makes them an interesting group for analyzing temporal processes. Moreover, as we will propose later in the thesis, is of particular interest to consider the existence of these deficits in time perception because they might be interacting with temporal preparation processes.

CHAPTER 3

BEING PREPARED ON TIME

When an athlete is ready to beat the 100 meters at the starting line of his lane, he begins to run immediately after the starting gun fires according to his anticipation of the time the shot will happen. His success in the race depends on his ability to react quickly at the right moment. This is just one example of how humans use temporal information to optimize their responses. This ability is necessary in many everyday situations such as crossing a street, driving a car, setting turns in a conversation, playing sports, playing and listening music, etc. This ability was also crucial for the survival of the species to escape from predators or hunt elusive animals.

As mentioned in Chapter 1, temporal preparation processes have been classified based on more controlled or more automatic mechanisms for using temporal information provided by external cues.

Controlled Temporal Preparation

In relation to the controlled mechanisms of temporal preparation, there are two well-described effects in the experimental literature. On the one hand, the *temporal orienting effect* that reflects the ability to direct the attention strategically and voluntary to a point in time, based on the expectation about the moment that an event will happen (Correa, Lupiáñez, Milliken, & Tudela, 2004; Coull & Nobre, 1998; Nobre, 2001). This effect has been studied experimentally by adapting the cost-benefit spatial-orienting paradigm (Posner, Snyder, & Davidson, 1980) to the temporal dimension. Typically two time intervals are used, one short (e.g., 400 ms) and one long (1400 ms). A predictive cue providing temporal information about when the target will appear (early or late) is presented, and the predictive value of this cue is manipulated. That is, in most trials (e.g., 75%), the cue is valid and the

expectation generated by the subject is fulfilled (the cue indicates "early" and the stimulus appears early, or the cue indicates "later" and the stimulus appears later). But in a smaller percentage of trials (25%), the cue is invalid and the subject generates a temporal expectation that is not fulfilled (the cue indicates "early" but the stimulus appears late, and vice versa). Therefore, the effect is typically observed as smaller reaction time in valid than in invalid trials. Somehow, the subjects use the information provided by the cue in a controlled manner, since there is a cost in their responses (increased reaction time) when the information is invalid. This effect (decreased reaction time on valid trials) is usually found in the short interval, but not in the long one (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Coull, 2004; Coull, Frith, Buchel, & Nobre, 2000; Coull & Nobre, 1998). The absence of effect in the long interval is attributed to a process, also strategic, of *reorientation*. That is, if the cue indicates that one stimulus will appear early and does not appear, subjects may infer that, then, it will appear later and they will prepare for that moment (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Coull et al., 2000; Coull & Nobre, 1998; Karlin, 1959). However, when introducing *catch trials* (i.e. trials where the stimulus does not appear), subjects are prevented from using the reorientation strategy, so that the effect of temporal orientating can be seen at both short and long intervals (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006). Functional neuroimaging studies have related temporal orienting to a left fronto-parietal network. In particular, valid trials have been associated with activation of the supplementary motor area and the right frontal operculum (Coull, Vidal, Nazarian, & Macar, 2004), whereas invalid trials have been associated with the activity of the left fronto-parietal cortex and the bilateral orbitofrontal cortex (Coull et al., 2000).

On the other hand, another effect described within the controlled temporal preparation, is the *Foreperiod effect* or *preparatory interval effect* (note that in the literature on temporal

preparation, the interval of preparation is called foreperiod, hence the name given to the effect). At the experimental level, the effect is observed because the subjects are faster in the long foreperiod than in the short foreperiod. The foreperiod effect has been interpreted as a strategic preparation as time passes according to a computation of probabilities (Karlin, 1959; Niemi & Näätänen, 1981). That is, the longer it takes the traffic light in red, the more likely it is that turns to green soon, so as time passes the driver will be prepared to speed up at the right time. Previous research relates this effect to the right dorsolateral prefrontal cortex (Stuss et al., 2005; Vallesi, Mussoni et al., 2007; Vallesi, Shallice, & Walsh, 2007).

Automatic Temporal Preparation

Within the automatic mechanisms of temporal preparation are the *sequential effects*. According to these effects, the person is influenced by previous experiences of preparation during the preparation of the next response (Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001). Just imagine an expert in *skeet shooting*, where the pace at which the disks are flung changes from trial to trial. The shooter will tend, automatically, to be more prepared to take the shot when it has passed the same time as the last disk was flung. Experimentally, these effects are found when we consider the duration of the previous trial (previous foreperiod or FP_{n-1}), so that individuals are faster when the previous foreperiod was equal or shorter than the current foreperiod, but are slower when the previous foreperiod was longer. This effect has been attributed to an exogenous preparation process, automatically guided by external stimuli rather than by internal expectations. Specifically, Los and colleagues have proposed that sequential effects would result from a learning process of trace conditioning (Los, 1996; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001). Alternately, Vallesi and colleagues have explained these effects in terms of different residual alertness after short vs. long intervals (Vallesi & Shallice, 2007; Vallesi, Shallice et

al., 2007). The authors suggest that arousal is increased after short intervals, but decreased after long intervals because preparing for long intervals is exhausting. The sequential effects have not systematically been related to any brain structure and seem not to depend on prefrontal lobe, although some research suggests that the effects is decreased after damage on left premotor cortex (Vallesi, Mussoni et al., 2007).

Controlled vs. Automatic temporal preparation

Controlled and automatic mechanisms of temporal preparation have been dissociated experimentally. Specifically, the temporal orienting effect and the sequential effects have been dissociated with behavioral and electrophysiological studies (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001). Los and colleagues proposed that subjects use the temporal information endogenously when the expectancy of occurrence of a stimulus is highly predictable, that is, when the cue is valid. They found that the valid condition was related to a higher electrophysiological CNV component, which has been associated with temporal preparation. However, subjects are guided exogenously by the duration of the previous trial when the expectancy of occurrence of a stimulus is unpredictable, as in invalid trials or when the cue is neutral. Moreover, Correa and colleagues found significant cuing validity effects regardless of the duration of the previous foreperiod, which confirms that temporal orienting is independent of sequential effects.

On the other hand, the foreperiod and sequential effects have been dissociated with behavioral, electroencephalography and neuropsychological studies (Karlin, 1959; Niemi & Näätänen, 1981; Stuss et al., 2005; Vallesi, Mussoni et al., 2007; Vallesi, Shallice et al., 2007). Behavioral data show that the foreperiod effect was influenced by the magnitude of the previous foreperiod, since subjects were faster when the previous foreperiod was

shorter than the current foreperiod. Moreover, the foreperiod effect was impaired after both applying TMS and lesions in the right dorsolateral prefrontal cortex. However, the sequential effects were preserved after the application of TMS, although they were somewhat reduced after lesions in the left premotor cortex.

Table 3.1. Main studies regarding temporal preparation effects.

Reference	Type of study	Effects studied			Main Results
		Temporal Orienting	Foreperiod	Sequential effects	
Coull & Nobre, 1998	Neuroimaging (PET y fMRI)	x			The RT is smaller in valid trials. Spatial orienting is associated with activation of right parietal lobe, while temporal orienting is related to the left parietal lobe.
Miniussi et al., (1999)	Electrophysio-logical (ERPs)	x			The RT is smaller in valid trials. The amplitude and latency of P300 was higher in the valid trials.
Coull et al., 2000	Neuroimaging (fMRI)	x			The RT is smaller in valid trials, but subjects reorient when the invalid trial is in the short foreperiod (cue predicts early, but stimulus appears later). Invalid trials are related to the activation of left fronto-parietal cortex and bilateral orbitofrontal cortex.
Griffin et al., (2002)	Electrophysio-logical (ERPs)	x			The RT is smaller in valid trials. Temporal orienting starts late and affects the decision and response components.
Coull et al., 2004	Neuroimaging (fMRI)	x			The RT is smaller in valid trials. Valid trials are related to the activation of the supplementary motor area and the right frontal operculum.
Los, 1996	Behavioral	x		x	If the expectancy is manipulated between blocks (pure blocks), subjects used the temporal information endogenously. But if the expectancy is manipulated trial by trial (mixed blocks), subjects are guided by the duration of previous trial.
Los & Van den Heuvel, 2001	Behavioral	x		x	There is a dissociation between temporal orienting and sequential effects. The latter are used mainly on the condition of invalid trials or when the cue is neutral.
Los & Heslenfeld, 2005	Electrophysio-logical (ERPs)	x		x	There is a dissociation between temporal orienting and sequential effects. The CNV component is related to temporal preparation and is higher when the cue is valid.
Stuss et al., 2005	Neuropsycho-logical		x		The right lateral frontal damage produces a deficit in the foreperiod effect.
Karlin, 1959	Behavioral		x	x	The RT is smaller in the long foreperiod. The foreperiod effect is influenced by the magnitude of the previous foreperiod.
Niemi & Näätänen, 1981	Behavioral		x	x	The RT is smaller in the long foreperiod. The foreperiod effect is influenced by the magnitude of the previous foreperiod.
Vallesi et al., 2007	Magnetoence-phalography (TMS)		x	x	The foreperiod effect was reduced after applying TMS over the right dorsolateral prefrontal cortex. The sequential effects were not affected by TMS.
Vallesi et al., 2007	Neuropsycho-logical		x	x	The foreperiod effect was impaired after damage to the right prefrontal cortex. The sequential effects were reduced after damage to the left premotor cortex.
Correa & Nobre, (2008)	Electrophysio-logical	x	x		There is a strong interaction between the temporal orienting and foreperiod effects, existing an overlap in the modulation of the N1, N2 and P3 components.
Correa et al., 2004	Behavioral	x	x	x	The RT is smaller in valid trials. The introduction of catch trials (trials without stimulus) prevents the reorientation in the long foreperiod. There is a dissociation between the temporal orienting and sequential effects.
Correa et al., 2006	Behavioral	x	x	x	The three effects are observed. There is a dissociation between the effect of temporal orientation and sequential effects.

PET: Positron Emission Tomography; fMRI: functional Magnetic Resonance Imaging; ERP: Event-Related Potencial; TMS: Transcranial Magnetic Stimulation; RT: reaction time.

Finally, the temporal orienting and the foreperiod effects have been associated in behavioral and electrophysiological studies (Correa, Lupiáñez, & Tudela, 2006; Correa & Nobre, 2008). Behaviorally, temporal orienting effect was only observed in the absence of

foreperiod effect (at short foreperiods), while foreperiod effect was only observed in the absence of temporal orienting (on invalid conditions). Moreover, these two effects showed an overlap in the modulation of the N1, N2 and P3 components. These interactions suggest a common mechanism for both types of effects which have been framed within the controlled processes. See Table 3.1 for a review of the most relevant research in temporal preparation.

CONCLUSIONS

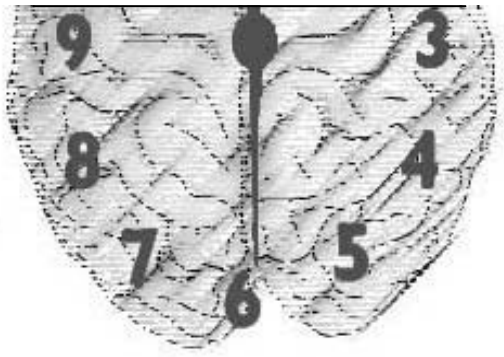
The results from all these studies seem to support the hypothesis of Correa et al. (2006) on the existence of a dual mechanism of temporal orienting of attention, flexible and strategic. By this flexible mechanism, subjects use the expectations provided by the environment, as well as other less explicit contingencies, to respond at the optimal time according to the demands of the task and the temporal information available. This type of mechanism can account for the different strategies that humans use in an environment whose temporal predictability is distributed on a continuum from completely predictable to completely unpredictable.

The still brief literature on temporal preparation has provided results of great relevance for the understanding of these processes and their characteristics and attributes. However, more research is still required, since most studies are behavioral, electrophysiological or use functional neuroimaging. It is essential to advance knowledge through neuropsychological studies with patients having suffered brain injury. Neuropsychological studies provide evidence of the casual role of the injured brain structures beyond the neural correlate provided by functional neuroimaging. As far as we know, there are only few neuropsychological studies regarding the foreperiod effect (Stuss et al., 2005; Vallesi,

Mussoni et al., 2007) and there are no neuropsychological studies exploring the neural basis of *temporal orienting effect* nor considering all the effects and their interactions.

Therefore, we consider that neuropsychological studies could expand our knowledge about temporal preparation, allowing a greater insight into controlled and automatic processes. More specifically, this would provide us for the first time the neural basis of the temporal orienting effect.

EXPERIMENTAL RESEARCH



CHAPTER 4

AIMS OF THE RESEARCH

The use of time is essential to respond in a timely manner. We use time explicitly to estimate the duration of events in the range of milliseconds, seconds or minutes. We also use time implicitly, mainly to prepare our response at the right time. The main aim of the present thesis is to study the neural basis of temporal preparation processes framed within the so-called *implicit timing*. More specifically, our interest is to study the neural basis of the *Temporal Orienting effect*.

In the introductory section of this thesis, we have outlined a broad view of time processing by reviewing the main theoretical frameworks and neurobiological models on time perception. This allowed us to move from the general concept of *timing* to the specific concepts of *time perception* and *temporal preparation*. Specifically, in time perception tasks participants have to estimate the duration of one interval or to discriminate between the duration of two events (*perceptual timing*); or have to produce or reproduce intervals in a sustained, delayed or periodic motor act (*motor timing*). By contrast, temporal preparation requires subjects to use the time information provided more or less explicitly in order to achieve the task goal. In these temporal preparation tasks time information can be used in a *controlled* manner (endogenous) or *automatically* (exogenous). Finally, we focused on the controlled temporal preparation processes by studying the *Temporal Orienting effect*, which is based on expectations about when a stimulus is going to happen induced by explicit and predictive temporal cues (Correa et al., 2004; Coull & Nobre, 1998; Nobre, 2001), and the *Foreperiod effect*, which is ascribed to temporal expectations induced by the passage of time (Karlin, 1959; Niemi & Näätänen, 1981). In contrast, automatic temporal preparation processes are mainly represented by *sequential effects*, which are proposed as the result of a

mechanism of trace conditioning based on the duration of the previous interval (Los, 1996; Los & Van den Heuvel, 2001; Los & Heslenfeld, 2005) or as the result of a decreased arousal after long intervals (Vallesi & Shallice, 2007; Vallesi, Shallice et al., 2007).

Research on these temporal preparation phenomena has experienced a great boost since 1998 (see Table 3.1 in chapter 3), but only recently they have been studied jointly since the temporal preparation is not a unitary concept (Nobre, Correa, & Coull, 2007). In addition, there are few data about the neural basis of these processes, and mainly focusing on fMRI and EEG. There are only few neuropsychological studies but focus on the foreperiod and sequential effects. And, as far as we know, there are no neuropsychological studies exploring the neural basis of the temporal orienting effect nor studying all the effects and their interactions. Therefore, we consider it is essential to advance knowledge through neuropsychological studies in order to deepen in temporal preparation processes.

To do this, we set up our hypotheses about brain areas involved in temporal preparation processes. The first aim of the thesis was to study, for the first time, the neural basis of the temporal orienting effect and its relation with other effects described in the temporal preparation literature. The following hypotheses were tested:

1. Neuroanatomical correlates of temporal orienting have been related to prefrontal structures, mainly left lateralized (Coull, 2009; Coull et al., 2000; Coull & Nobre, 1998; Coull et al., 2004; Hackley et al., 2009; Nobre, 2001). Therefore, **we expected to observe a deficit in the temporal orienting effect after prefrontal damage**.
2. The *foreperiod effect* has been shown to be impaired after both neural damage in the right dorsolateral prefrontal cortex (Stuss et al., 2005; Vallesi, Mussoni et al., 2007) and virtual lesions with TMS in this region (Vallesi, Shallice et al., 2007). Therefore, **we**

expected to replicate the impairment of this effect in a group of patients with right prefrontal damage.

3. *Sequential effects* have not been related systematically with any brain area, although several studies suggest that it does not depend on prefrontal structures (Vallesi, Mussoni et al., 2007; Vallesi & Shallice, 2007; Vallesi, Shallice et al., 2007). **We expected to verify that automatic temporal preparation processes, i.e. sequential effects, were preserved after prefrontal damage** and, therefore, depend on phylogenetically older subcortical structures. Specifically, for this aim, basal ganglia were considered a candidate for study because it has been one of the structures most consistently related to temporal processes. In particular, its dysfunction in Parkinson's disease has been largely related to an impairment in time estimation processes (e.g., Artieda, Pastor, Lacruz, & Obeso, 1992; Pastor, Jahanshahi, Artieda, & Obeso, 1992), and also to a deficit in temporal preparation (Praamstra & Pope, 2007).

A second important goal of the thesis was to study the relation between automatic and controlled temporal preparation processes, as well as the relation between time perception and temporal preparation processes. With this goal in mind we set two further hypotheses intending to deepen the knowledge of temporal preparation processes, as well as to suggest novel strategies for rehabilitation, optimizing the responses of prefrontal patients in their daily lives:

4. Since the automatic mechanisms of temporal preparation were preserved in prefrontal patients (i.e. sequential effects), we thought that patients with deficit in temporal orienting could prepare in time automatically. In fact, rhythmic patterns can induce temporal preparation automatically (M. R. Jones, Moynihan, MacKenzie, & Puente, 2002; Large & Jones, 1999; Rohenkohl, Coull, & Nobre, 2011; Sanabria, Capizzi, & Correa, 2011), so **we expected to observe an improvement in the temporal**

preparation deficit after prefrontal damage by introducing regular rhythms as cues.

5. According to the literature on time estimation, which points to an overestimation of time after right prefrontal damage (Harrington, Haaland, & Knight, 1998; Picton et al., 2006; Wittmann et al., 2004), we wanted to study the role of this function in the temporal preparation performance of our patients. If time estimation is relevant for temporal orienting (e.g., Correa et al., 2004; Coull & Nobre, 1998), we should observe that right frontal patients are impaired in both temporal preparation and time estimation tasks. In contrast, if temporal preparation and time estimation involve different processes (Coull & Nobre, 2008; Lewis & Miall, 2003; Zelaznik et al., 2002), the presence of a deficit in right frontal patients to estimate time can occur simultaneously with intact ability to prepare in time. That is, **right frontal patients could develop automatic temporal preparation based on rhythms despite their deficit in time estimation tasks**.

We conducted two studies with brain-lesion patients to test these hypotheses. Patients were evaluated on several tasks measuring different aspects of temporal preparation and time estimation. The general experimental procedure of the present thesis consisted of a temporal analogue of the costs and benefits paradigm developed by Posner and colleagues to study the spatial orienting of attention (Posner, Nissen, & Ogden, 1978). In this procedure, temporal information is provided by a predictive cue indicating when a visual target will appear (i.e., the cue indicates *early* and the target probably appears after a short interval of 400ms; or the cue indicates *late* and the target appears after a long interval of 1400ms). However, in some trials (25%), the cue may be invalid and the target appears at the non-predicted moment (i.e., the cue indicates *early* but the target appears late; or the cue indicates *late* but the target appears early). Therefore, the temporal orienting effect was

measured as the relative benefit given by a decreased reaction time in trials where the stimulus appears at the expected moment (valid) as compared to trials where it appears at the unexpected moment (invalid).

In the second study, we also included two temporal estimation tasks in the range of milliseconds: a *duration discrimination task* in which participants should decide which of two stimuli had been longer; and a *temporal order judgement task* in which participants should decide which of two stimuli had appeared first.

Study 1. Temporal orienting deficit after prefrontal damage

This study was conducted to test our first set of hypotheses in order to study the neural bases of temporal preparation and, more specifically, the *temporal orienting effect*. We obtained novel results about the neural basis and the lateralization of temporal orienting effect, which was abolished only after right prefrontal damage. Regarding the foreperiod effect, the study also provided novel results, since this effect was impaired after either left or right prefrontal damage. In relation to the neural basis of sequential effects, these effects were effectively preserved after prefrontal damage or after focal and unilateral basal ganglia lesions. Thus, considering all these results, this study provided evidence for the existence of a dual mechanism of *controlled* vs. *automatic* temporal preparation, being damaged the controlled component after prefrontal lesions but preserved the automatic component.

Study 2. Rhythms can overcome temporal orienting deficit after right frontal damage

The goal of this study was to test our second set of hypotheses about the relation between automatic and controlled temporal preparation by introducing a predictive rhythm as a cue. We compared performance in a task presenting a *symbolic cue* identical to that used in our previous study (i.e., a short line meaning early and a long line meaning late target onsets) to

performance in the same task but presenting a *rhythm cue* (i.e., a fast rhythm meaning early and a slow rhythm meaning late). The results with the symbolic cue showed a replica of our previous study. That is, the temporal orienting effect was impaired only in the right frontal group, while the foreperiod effect was impaired again in either left or right frontal groups**.** The most relevant result was the improvement in the right frontal group of the temporal orienting and foreperiod effects after the introduction of predictive rhythms. Moreover, this improvement occurred even though the right frontal group showed a deficit in the ability of estimate time (overestimation) in the range of milliseconds. Another relevant result was the impairment in the temporal orienting effect after the introduction of the rhythms in the left frontal group. Although this result must be interpreted with caution due to the sample size of the left frontal group (5 patients), it suggests a double dissociation with controlled temporal preparation being lateralized at right frontal lobe and automatic temporal preparation being lateralized at left frontal lobe.

In sum, these two studies with patients deepen into the neural basis of temporal preparation effects. The findings confirm different neural basis for controlled and automatic processes and prove that using automatic cuing, as rhythms, the deficit in controlled temporal preparation and, more specifically, in the temporal orienting effect after right frontal damage, can be overcome.

These results are summarized and discussed in the General Discussion of the thesis, where a more thorough reflection on the temporal preparation processes is presented, as well as the mechanisms and functions underlying them are discussed.

PUBLICATIONS BASED ON THE THESIS

Chapters 1 y 2.

Triviño, M., Lupiáñez, J., Arnedo, M., Correa, A. (in preparation). Reviewing the neuropsychology of time perception.

Chapter 5.

Triviño, M., Correa, A., Arnedo, M., Lupiáñez, J. (2010). Temporal orienting deficit after prefrontal damage. *Brain,* 133:1173-1185.

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Chapter 6.

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CHAPTER 5

TEMPORAL ORIENTING DEFICIT AFTER PREFRONTAL DAMAGE

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Abstract

The aim of this study was to explore, for the first time in patients, the neural bases of temporal orienting of attention as well as the interrelations with two other effects of temporal preparation: the foreperiod effect and sequential effects. We administered an experimental task to a group of 14 patients with prefrontal lesion, a group of 15 control subjects, and a group of 7 patients with a basal ganglia lesion. In the task, a cue was presented (a short vs. long line) to inform participants about the time of appearance (early vs. late) of a target stimulus, and the duration of the cue-target time intervals (400 vs. 1400 ms) was manipulated. In contrast to the control group, patients with right prefrontal lesion showed a clear deficit in the temporal orienting effect. The foreperiod effect was also affected in the group of patients with prefrontal lesion (without lateralization of the deficit), whereas sequential effects were preserved. The group of basal ganglia patients did not show deficits in any of the effects. These findings support the voluntary and strategic nature of the temporal orienting and foreperiod effects, which depend on the prefrontal cortex, as well as the more automatic nature of sequential effects, which does not depend on either prefrontal cortex or frontobasal circuits.

Keywords: Attention, foreperiod, sequential effects, prefrontal cortex, basal ganglia.

INTRODUCTION

The main aim of the research described in this paper was to investigate the neural bases of temporal orienting of attention as well as the interrelations with two other well known effects of temporal preparation: the foreperiod effect and sequential effects. This is the first study, as far as we know, in which a neuropsychological approach is taken to investigate temporal orienting.

When we expect a stimulus to occur at a given moment, we get prepared for it, which makes our response to the stimulus faster. This effect relates to temporal orienting, that is, the capacity to voluntarily and strategically direct attention to a point in time based on the subject's expectations of the time when an event will take place (Correa et al., 2004; Coull, 2009; Coull & Nobre, 1998; Nobre, 2001). This effect has been studied experimentally using a cost-benefit paradigm (Posner et al., 1980). This is done by presenting a cue that provides information about the time of appearance (i.e. early vs. late) of the target or stimulus the subject must respond to. Moreover, the foreperiod duration and the validity of the cue are manipulated. The foreperiod is the time interval between the cue and the target. The cue may be valid in indicating the exact time when the target will appear (e.g., early cue–short foreperiod or late cue–long foreperiod) or invalid by indicating a time that will not match the appearance of the target (e.g., early cue–long foreperiod or late cue–short foreperiod). The temporal orienting effect is observed as a shorter reaction time (RT) in valid trials as compared to invalid ones (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Correa & Nobre, 2008; Coull, 2004; Coull et al., 2000; Coull & Nobre, 1998).

The temporal orienting effect is typically observed just in the short foreperiod; the lack of effect in the long foreperiod is attributed to a reorientation process (Correa et al., 2004; Coull & Nobre, 1998; Karlin, 1959), such that no RT cost is observed in an invalid trial in which an early cue is presented but the target appears at the long foreperiod. According to

the reorienting account, individuals are able to reorient themselves from short to long intervals, given that "if the target has not appeared early, it will necessarily appear late". Therefore, subjects will always be prepared in the long foreperiod. However, if the target does not appear in some trials (i.e., some catch trials are included), subjects cannot use the reorientation strategy, as they no longer have the certainty that the target will appear in the long foreperiod. As a consequence of including catch trials, RTs are increased in long foreperiods and, more interestingly, the temporal orienting effect is found both in the short and the long foreperiod (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006).

Neuroanatomical correlates of the temporal orienting have been related to prefrontal structures (Coull, 2009; Coull et al., 2000; Coull & Nobre, 1998; Coull et al., 2004; Hackley et al., 2009; Nobre, 2001). In these studies, temporal orienting is mainly associated with bilateral activation of the orbitofrontal, prefrontal and premotor cortices, and activation of areas of the left hemisphere such as the frontal operculum, inferior parietal cortex and insula. This systematic activation of prefrontal structures in temporal orienting tasks supports the proposal of a strategic process that depends on evolved brain circuits.

Besides the prefrontal cortex, the timing functions of basal ganglia (e.g., see Meck, 2005 for a review) may also play a relevant role in temporal orienting. First, neuropsychological studies with Parkinson's disease patients (Artieda et al., 1992; Harrington, Haaland, & Hermanowicz, 1998; C. R. Jones, Malone, Dirnberger, Edwards, & Jahanshahi, 2008) and functional magnetic resonance imaging (fMRI) research have shown the involvement of the striatum (caudate nucleus and putamen) and substantia nigra in temporal estimation tasks (Coull et al., 2004; Jahanshahi, Jones, Dirnberger, & Frith, 2006; Rao, Mayer, & Harrington, 2001). Obviously, time perception is necessary to be able to orient attention to specific time intervals. Moreover, basal ganglia and the dopaminergic system have been

related to temporal preparation processes in neuropsychological (Jurkowski, Stepp, & Hackley, 2005) and electrophysiological studies (Praamstra & Pope, 2007) carried out with Parkinson's disease patients, who show deficit in temporal preparation based on rhythmic tasks. Therefore, given the role of basal ganglia in timekeeping and temporal preparation tasks, a lesion in this structure can be expected to alter subjects' ability to estimate the passage of time properly and therefore led to a deficit in the temporal orienting effect.

So far, studies carried out on the neuroanatomical correlate of the temporal orienting effect can only provide correlational data suggesting that the highlighted structures are involved. Yet, we do not know whether they are necessary for temporal orienting. Therefore, it is highly interesting to study the neural bases of temporal orienting with data allowing causal inferences through lesion studies with neuropsychological patients. If the prefrontal cortex is necessary for temporal orienting, as suggested by the studies mentioned earlier, we should find impaired temporal orienting in patients with prefrontal injuries.

To test this hypothesis, we carried out an experiment combining the temporal orienting task used by Correa et al. (2004) and the neuropsychological and structural neuroimaging study of a group of patients with lesions in the prefrontal lobe. Task performance of these subjects was compared to that of a matched control group. Groups with right versus left prefrontal lesions were compared to test whether there is lateralisation of the temporal orienting effect, to the left hemisphere (Coull, 2004; Coull & Nobre, 1998; Miniussi et al., 1999), or it is bilaterally distributed instead (Coull et al., 2000). We also tested a group of patients with basal ganglia lesions, because if the time-keeping functions of this structure play a role in the temporal orienting capacity, a similar deficit to that expected in frontal patients should then be observed.

The current task enabled us to simultaneously explore other related ways of getting prepared in time, such as those underlying the foreperiod effect and sequential effects (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006). Exploring the potential interrelations between the three effects related to temporal preparation is an important objective, since they have been usually studied from separate traditions of research (Nobre et al., 2007). The *foreperiod effect* implies that RT decreases as the foreperiod is longer in conditions in which the foreperiod duration is randomly manipulated in a block of trials without catch trials. This effect has been classically interpreted as the result of an endogenous process in which subjects use the conditional probabilities associated with the passage of time to anticipate the next stimulus (e.g., Karlin, 1959; but see Los, 1996; Los & Heslenfeld, 2005; Los, Knol, & Boers, 2001; Los & Schut, 2008, for an alternative -automatic- account based on a mechanism of trace conditioning). The foreperiod effect has been related to the activity of the right dorsolateral prefrontal cortex both in studies with transcranial magnetic stimulation (TMS) and fMRI (Vallesi, McIntosh, Shallice, & Stuss, 2009; Vallesi, Shallice et al., 2007), and in neurological studies with patients (Stuss et al., 2005; Vallesi, Mussoni et al., 2007).

Sequential effects depend on the duration of the previous foreperiod. This effect consists of an increase in RT when the previous foreperiod was longer than the current foreperiod, or a decrease in RT if the previous foreperiod was shorter or of the same duration as the current foreperiod (Woodrow, 1914). Sequential effects have been attributed to an exogenous preparation process, automatically guided by external stimuli rather than by the internal expectations of individuals. In fact, according to Los and colleagues, sequential effects are the result of a learning process based on trace conditioning (Los, 1996; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001; see also Steinborn, Rolke, Bratzke, & Ulrich, 2008). Sequential effects have not been related systematically with any brain area,

although several studies suggest that it does not depend on prefrontal structures (Vallesi, Mussoni et al., 2007; Vallesi & Shallice, 2007; Vallesi, Shallice et al., 2007). Moreover, other studies show dissociations between sequential effects and temporal orienting (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001). In general, these studies suggest that temporal orienting and foreperiod effects involve prefrontal structures and probably imply controlled orienting of attention, whereas sequential effects tend to be associated to automatic processing that may depend on more ancient subcortical structures from a phylogenetic and ontogenetic point of view (Vallesi & Shallice, 2007). Thus, the group of basal ganglia patients allowed us to explore the role of this structure in the automatic preparation that underlies sequential effects.

However, these three preparation processes and their interrelations have not been studied together. Our experimental task allowed us to carry out a comprehensive study in neurological patients of the main effects described in temporal preparation and their interactions. We expected our group of subjects with prefrontal lesion to show a deficit not only in the temporal orienting effect but also in the foreperiod effect, and the sequential effects to be preserved as in control subjects. Likewise, if basal ganglia are involved in voluntary temporal preparation, we should find a similar deficit to that predicted in our group of frontal patients; however, if basal ganglia are necessary for automatic preparation, we should find the opposite deficit pattern to that predicted for the group of frontal patients, that is, impaired sequential effects while temporal orienting would be unaffected.

METHOD

NEUROLOGICAL EVALUATION

Participants

Our study was carried out with 14 subjects with a brain lesion, mainly in the frontal lobes, 7 subjects with basal ganglia lesion and 15 subjects who were neurologically intact. Out of the 15 control subjects, 7 were chosen as controls for the 7 basal ganglia patients because of their similar ages. The groups were matched in age, sex and years of education (see Table 1). All the patients had suffered an acute lesion leading to a dysfunction. Prior to the lesion, they were functionally independent, had no neurological or psychiatric disorders, and had normal intellectual level.

Table 1. Demographic and neurological data of both frontal and basal ganglia groups in relation to their corresponding control groups. Group averaged data and standard deviation (in parenthesis) are included.

Group	Age in Years	Years of Education	Sex	Etiology	Time elapsed from lesion in months	Lateralization of the lesion
Frontal	37.37 (17.00)	13.36 (3.43)	10 M 4 F	11 TBI 2 Stroke 1 Aneurism	22.42 (22.3)	6 Right 5 Left 3 Bilateral
Control Frontal	39.9 (19.28)	13.53 (2.87)	9 M 6 F			
BG	58.87 (8.97)	9.71 (4.57)	4 M 3 F	6 Stroke 1 Astrocytom	19.86 (18.03)	5 Right 2 Left
Control BG	47.86 (12.3)	12.71 (3.82)	4 M 3 F			

BG: Basal Ganglia; M: male; F: female; TBI: traumatic brain injury

Inclusion criteria for the frontal group to be tested on the temporal orienting task were the presence of acquired damage in the frontal lobes according to the radiological report as well as a significant dysfunction of prefrontal functions observed in the neuropsychological assessment. Exclusion criteria were the lack of dysfunction of prefrontal functions in the neurological assessment in spite of a positive radiological report (two patients were excluded for this reason; they are not included in the 14 patients who were finally tested on the temporal orienting task), or the presence of aphasia, hemispatial neglect and/or dementia (another patient was excluded for this reason). As for the basal ganglia group, the

inclusion criteria were the presence of acquired damage in the basal ganglia according to the radiological report and the absence of prefrontal dysfunction according to the neuropsychological assessment. Exclusion criteria were the same as for the frontal group and led to excluding four patients. By using this criterion we aimed to assure that any deficit shown by basal ganglia patients is not due to prefrontal dysfunction as a result of fronto-striatal circuits disruption.

Table 1 summarizes the data on the aetiology of the lesions. Radiological reports of frontal and basal ganglia patients are reported on the table of the Supplementary material. All patients except four were assessed at the Neuropsychology Unit of San Rafael University Hospital in Granada. The four remaining patients were assessed at the Fydian Neurorehabilitation Center and Aliter Clinical Psychology Center, both in Granada. Medical histories of the patients from the reference hospitals (Virgen de las Nieves University Hospital and San Cecilio University Hospital) were obtained after informed consent from both patients and the Ethics Committee of the hospitals involved, in compliance with national legislation on the protection of personal data, *Ley Orgánica de Protección de Datos de Carácter Personal* (15/1999, 1999). We also obtained the radiological reports and the images of the computerized axial tomography (CT scan) and Magnetic Resonance Imaging (MRI). The experiment was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Neuropsychological Assessment

The results of the neuropsychological assessment were considered to be crucial for the inclusion or exclusion of patients in the study. Therefore, all patients underwent a full neuropsychological evaluation, and only those who fulfilled the inclusion criteria then

performed the experimental task. This evaluation took about 8 hours for each patient. Control subjects underwent the same evaluation. A summary of the functions assessed and the tests used is shown in Table 2.

Neuroimaging

All the CT and MRI images obtained from the medical history of patients were drawn with MRIcron computer software (Rorden & Brett, 2000), which provides MRI slices with 1 mm resolution of a standard brain where the lesion can be drawn.

BEHAVIOURAL TASK

Apparatus and stimuli

The experiment was performed on a 15-inch screen laptop computer. E-prime software (Schneider, Eschman, & Zuccolotto, 2002) was used to program the experiment, run the experimental task, and collect data on RT and accuracy of responses.

All stimuli appeared in the centre of the screen. Each trial included the following stimuli: a fixation point (the "+" symbol), a temporal cue, and a target, using the parameters used by Correa et al. (2004; 2006b). The temporal cue was a short red line (0.38º x 0.95º visual angle from a distance of 60 cm from the screen) or a long red line (0.38º x 2.1º). The short line indicated that the target would appear early (after 400 ms), whereas the long line indicated that the target would appear late (after 1400 ms). The target was either the letter "O" or the letter "X" (0.38º x 0.76º). Subjects had to detect any of the two letters – which appeared with identical probability (p=.5) – by pressing the right button of the mouse with their dominant hand. Although participants were to detect the target letter, two letters were used instead of one in order to be able to compare the results with future studies in which we will use a discrimination task.

Table 2. Summary of cognitive functions and neuropsychological tests used in the clinical assessment, and the results comparing the frontal group to their 15 matched-control subjects and the basal ganglia group compared to their 7 matched-control subjects.

FUNCTION		TEST	RESULTS					
			Frontal vs. Control Group			Basal Ganglia vs. Control Group		
			Frontal mean (sd)	Control mean (sd)		basal ganglia mean (sd)	Control mean (sd)	
Premorbid Intellectual Functioning		Bilbao & Seisdedos (2004) formula	119.7 (16.9)	114.7 (10.2)		112.6 (21.6)	112.7 (12.3)	
Language	Denomination	Boston Naming Test	53.3 (3.6)	55.9 (2.5)		49.0 (8.4)	55.2 (1.5)	
	Comprehension	Token Test	35.1 (0.7)	35.3 (0.5)		33.2 (4.3)	35.0 (0.0)	
Premotor Function	Premotor Functions (Barcelona Test)	Rhythm (errors)	1.4 (2.3)	0.2 (0.7)		2.8 (3.2)	1.0 (1.4)	*
		Bimanual coordination	1.8 (0.5)	2.0 (0.0)		1.7 (0.6)	2.0 (0.0)	*
		Motor alternances	1.6 (0.5)	2.0 (0.0)		1.3 (0.5)	2.0 (0.0)	**
		Graphic alternances	1.5 (0.5)	2.0 (0.0)		1.3 (0.8)	2.0 (0.0)	*
		Reciprocal inhibition (errors)	0.3 (0.5)	0.2 (0.7)		2.0 (2.9)	0.0 (0.0)	
Memory	Verbal Memory (Test Aprendizaje Verbal España Complutense, TAVEC)	Learning	40.9 (11.3)	57.6 (8.3)	***	44.3 (9.0)	53.8 (6.3)	
		Short term free recall	6.8 (3.9)	13.1 (2.6)	***	9.6 (2.5)	12.5 (2.5)	
		Long term free recall	8.1 (3.6)	13.6 (2.6)	***	9.6 (2.5)	13.0 (3.0)	*
		Intrusions (in both free and cued recall)	8.4 (7.9)	2.6 (4.2)	*	5.9 (4.7)	3.9 (5.4)	
		Semantic strategies	3.3 (5.3)	10.0 (10.3)	***	3.8 (3.9)	7.9 (7.4)	
		Serial strategies	1.8 (2.8)	1.7 (2.6)		1.8 (2.7)	1.8 (2.7)	
		Recognition	12.0 (4.5)	15.6 (0.6)	**	14.9 (0.7)	15.7 (0.5)	*
		Discrimination Index	88.9 (6.7)	96.2 (6.5)	**	88.4 (8.5)	93.8 (8.7)	
Working Memory	Phonological loop	Digit Span Subtest of WAIS-III	8.4 (2.4)	11.1 (2.8)	**	10.6 (1.9)	10.6 (1.9)	
	Visuospatial sketchpad	Spatial Span Subtest of WMS-III	8.4 (2.4)	10.9 (4.4)		9.3 (2.1)	10.0 (4.7)	
	Central executive	Letter-Number Sequencing Subtest of WAIS-III	9.0 (2.9)	11.9 (2.2)	**	12.4 (1.1)	12.0 (2.3)	
Attention	Sustained attention	Trail Making Test, A – errors	0.2 (0.6)	0.1 (0.3)		0.4 (1.1)	0.1 (0.4)	
	Selective attention	Picture Completion Subtest of WAIS-III	8.6 (5.6)	13.7 (2.1)	**	10.6 (2.5)	14.0 (2.4)	*
	Divided attention	Trail Making Test, B – errors	3.1 (2.6)	0.5 (0.9)	***	0.0 (0.0)	0.9 (1.2)	
	Interference	Stroop Color and Word Test	50.1 (7.7)	48.9 (9.6)		54.0 (6.1)	49.0 (6.1)	
Executive Functions	Verbal abstraction	Similarities Subtest of WAIS-III	10.1 (3.4)	14.3 (2.3)	**	10.9 (3.8)	14.1 (2.5)	
	Visual abstraction	Matrix Reasoning Subtest of WAIS-III	7.3 (2.6)	11.7 (2.7)	***	9.6 (3.5)	11.6 (2.4)	
	Temporal sequencing	Picture Arrangement Subtest of WAIS-III	7.1 (2.3)	10.9 (2.5)	***	9.0 (3.1)	10.6 (1.7)	
	Constructive praxia	Block Design Subtest of WAIS-III	7.1 (3.5)	10.8 (3.3)	**	8.7 (2.0)	10.1 (3.8)	
	Fluency	FAS fluency test	22.3 (10.1)	39.0 (9.5)	***	26.1 (14.4)	36.4 (9.4)	
		Animal fluency test	15.6 (4.4)	24.0 (4.1)	***	14.0 (3.0)	24.3 (4.1)	***
	Mental flexibility and categorization (Wisconsin Card Sorting Test, WCST)	Errors percentage (PC)	21.5 (24.5)	52.1 (23.6)	**	24.7 (19.2)	42.9 (25.6)	
		Perseverative responses percentage (PC)	23.2 (29.8)	68.9 (26.4)	***	32.1 (24.3)	52.4 (25.2)	
		Perseverative errors percentage (PC)	22.9 (30.9)	70.4 (27.7)	***	33.4 (24.8)	50.3 (26.8)	
		Non-perseverative errors percentage (PC)	34.9 (23.7)	37.4 (22.3)		47.9 (39.3)	33.7 (26.5)	
		Number of categories completed (PC)	3.4 (2.1)	5.8 (0.6)	***	3.6 (1.8)	5.9 (0.4)	**

	Planning	Zoo Map Test (Behaviour Assessment of Disexecutive Syndrome, BADS)		1.4 (1.6)	2.8 (0.8)	*	1.8 (1.0)	2.6 (0.9)	
Personality	Personality and Psychological Disorders (Millon Clinical Multiaxial Inventory, MCMI-II) Classification according to DSM-IV-TR	Mood lability	Histrionic	56.6 (29.2)	47.3 (24.6)		53.4 (14.4)	35.6 (13.8)	*
			Anxiety	67.1 (18.6)	35.1 (24.0)	***	66.9 (25.7)	48.0 (30.3)	
			Dysthymia	62.6 (20.7)	37.7 (25.7)	*	55.4 (17.6)	52.6 (31.6)	
		Behavioural desinhibition	Borderline	53.3 (24.5)	28.4 (27.5)	*	45.0 (25.6)	42.6 (36.1)	
			Hysteriform	63.2 (25.5)	33.3 (21.0)	**	70.3 (24.7)	45.3 (26.0)	
			Alcohol abuse	48.9 (24.1)	19.1 (24.2)	*	43.9 (23.4)	29.0 (32.7)	
		Apathy	Schizoid	70.5 (28.3)	37.3 (28.5)	*	68.1 (25.4)	53.7 (30.2)	
			Major depression	50.9 (26.1)	19.7 (29.8)	*	48.3 (24.2)	35.4 (38.6)	
		Paranoia	Schizotipic	68.4 (20.3)	32.7 (26.7)	**	57.0 (30.8)	48.1 (32.7)	
			Paranoid	86.9 (24.1)	27.9 (26.2)	***	61.9 (35.0)	45.1 (29.7)	
			Psychotic thinking	64.7 (26.5)	22.5 (26.5)	***	54.3 (32.4)	33.1 (34.8)	
			Psychotic delusions	83.7 (24.7)	39.1 (27.5)	***	58.3 (34.6)	43.3 (32.6)	

* p<.05 ; ** p<.01 ; *** p<.001

sd=standard desviation; WAIS-III=Weschler Adult Intelligence Scale 3rd edition; WMS-III=Weschler Memory Scale 3rd edition; PC=percentile; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision.

Procedure

Participants were seated about 60 cm from the screen. They were all instructed to respond as fast as they could without making mistakes and use the temporal cue to get ready for the time of appearance of the target. Whenever they made a mistake, they heard a sound (a 2000 Hz tone for 50 ms) and a feedback message was displayed, telling them whether they had responded before the target appeared or they did not respond before the 2000-ms deadline.

Figure 1 shows the sequence of stimuli presented in a trial. The fixation point ("+") was shown in black on a white background for 1000 ms. After this, the temporal cue was shown for 50 ms, and then the screen remained blank for a time interval of 350 or 1350 ms, depending on the foreperiod. Immediately after the short or long foreperiod, the target letter was shown for 100 ms, after which the screen remained blank again until the subject responded or for 2000 ms. After this sequence, the next trial began.

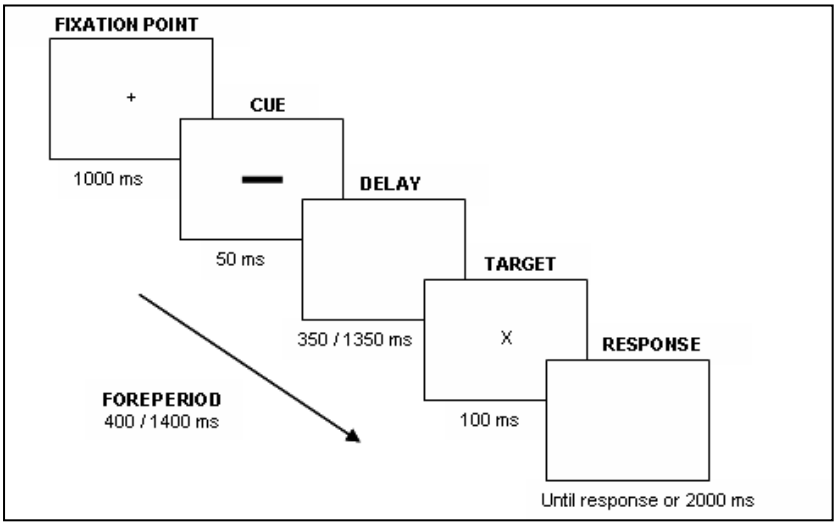

Figure 1. Sequence of events on a trial.

The experiment consisted of one block with 64 practice trials, followed by 4 blocks with 120 experimental trials each. There was a break of at least one minute after each block. An optional break was offered halfway through each block for participants to rest if they wished to. This was aimed at avoiding the effects of fatigue in all subjects, especially those with brain damage.

To study endogenous temporal orienting, temporal expectation was manipulated between different blocks of trials, since it produces more robust temporal orienting effects as compared to trial-by-trial manipulations (Correa, Lupiáñez, & Tudela, 2006). Participants were assigned two blocks with the early cue and two blocks with the late cue. The order of presentation was counterbalanced across participants. The type of temporal cue shown in each trial was kept constant during the whole block; foreperiod matched the duration indicated by the cue in most trials (75% valid trials), whereas temporal expectation was not fulfilled in the remaining trials (25% invalid trials). Note that temporal expectation mainly relied on this validity manipulation rather than on the temporal cue *per se*, which just served to mark the onset of the preparatory interval in this type of blocked design. More specifically, each experimental block comprised 72 valid trials and 24 invalid ones. In the valid trials of early blocks, the cue informed that the target was going to appear *early* and the target appeared after the short foreperiod (that is, 400 ms after the temporal cue was shown). In the valid trials of late blocks, the cue informed that the target was going to appear *late* and it appeared after the long foreperiod (1400 ms after the temporal cue appeared). Invalid trials were correspondingly distributed between the incorrectly cued foreperiods.

The 96 trials of each block in which the target was presented were completed with 24 trials. In one of the experimental sessions, these trials were *catch trials* (session with 20% catch trials); in the other session, however, the target was shown in the 120 trials (session without

catch trials). All the participants performed the task twice in independent sessions (on different days). One session had catch trials and the other one did not. The order of sessions was counterbalanced across participants. The 20% of catch trials was eliminated from the analyses also in the task without catch trials in order to analyze exactly the same dataset.

Design and Analysis of Behavioural Results

Mean RTs were submitted to a 3 (Lesion Group: Frontal, Basal Ganglia, Control) x 2 (Target uncertainty: 0% vs. 20% catch trials) x 2 (Foreperiod: short vs. long) x 2 (Previous foreperiod: short vs. long) x 2 (Validity: valid vs. invalid) mixed analysis of variance (ANOVA), with the first variable as a between participants factor and the other as within participants variables. Temporal orienting effect was indexed as the main effect of validity. Foreperiod effect was indexed as the main effect of foreperiod. Sequential effects were revealed by the main effect of previous foreperiod and mainly by the interaction between previous foreperiod and current foreperiod. Catch trials were included in one condition to maximize the appropriate conditions for finding temporal orienting effects, especially at the long foreperiod. The analyses therefore focused on whether temporal orienting, foreperiod and sequential effects differed as a function of the lesion group. Performance of prefrontal patients was compared to their 15 matched controls, whereas performance of basal ganglia patients was compared to both the 15 controls and their 7 age-matched controls.

RESULTS

NEUROLOGICAL RESULTS

First we analyzed the demographic and neuropsychological differences between patients and control groups to verify that the selection of participants in each group was correct.

We expected to find differences between frontal patients and their control subjects in the neuropsychological variables linked to the frontal deficit. No differences should be found in other variables that were not related to that deficit, such as age, educational level or premorbid intellectual quotient (IQ). The group of patients with basal ganglia lesion should not show differences with their control group in the demographic variables or the frontal neuropsychological profile.

Demographic Results

Frontal Group

Each patient with a lesion was matched to a control subject in age, sex and education. Differences in age and education were analyzed by means of a single-factor ANOVA. No significant differences were found concerning age and years of education (F<1 in both cases). The premorbid IQ of patients was compared to the current IQ of control subjects and no significant differences were found between both groups, F<1.

Basal Ganglia Group

Basal ganglia patients were matched with the 7 oldest healthy controls. The analysis carried out with a single-factor ANOVA did not show significant differences between both groups as regards age, $F(1,12)=3.064$; $p=.105$, years of education, $F(1,12)=1.967$; $p=.186$, or premorbid IQ, F<1.

Neuropsychological Assessment

Frontal Group

Patients and control groups were compared using a single-factor ANOVA for each score in the neuropsychological tests. As we expected, no differences were found between the language and premotor functions of the groups (all ps>.05; see Table 2). As regards the rest

of functions assessed, we observed the typical deficits of prefrontal lesions, such as dysexecutive syndrome with a significant impairment of working memory, selective and divided attention, and the rest of the executive functions assessed, as well as personality disorders. We also observed a characteristic impairment of the memory function, affecting learning, recall and mainly recognition, presenting intrusions and poor use of encoding strategies. For a more detailed analysis of the results and differences between both groups, see the summary provided in Table 2.

No significant differences were found between patients with right and left prefrontal lesion regarding age, education, premorbid IQ, or any of the neuropsychological variables studied (ps>.05).

Basal Ganglia Group

A single-factor ANOVA was also performed for each score, comparing the basal ganglia group and its corresponding controls. Significant differences were found between both groups regarding memory and premotor functions (ps<.05). However, as expected, the basal ganglia group did not show a profile of prefrontal dysfunction or significant personality disorders. Results and differences between groups are shown in Table 2.

Neuroimaging Data

Figure 2 shows the patients neuroimage sections treated with MRIcron, the software used to draw lesions in 7 mm MRI cuts (see Figures A-D in Supplementary material for more specific details about the lesioned areas in each patient of each group). In spite of the heterogeneous size of the lesions, all the frontal patients had their prefrontal lobe impaired, and all the basal ganglia patients had subcortical lesions in the territory of the basal ganglia, internal capsule and/or external capsule.

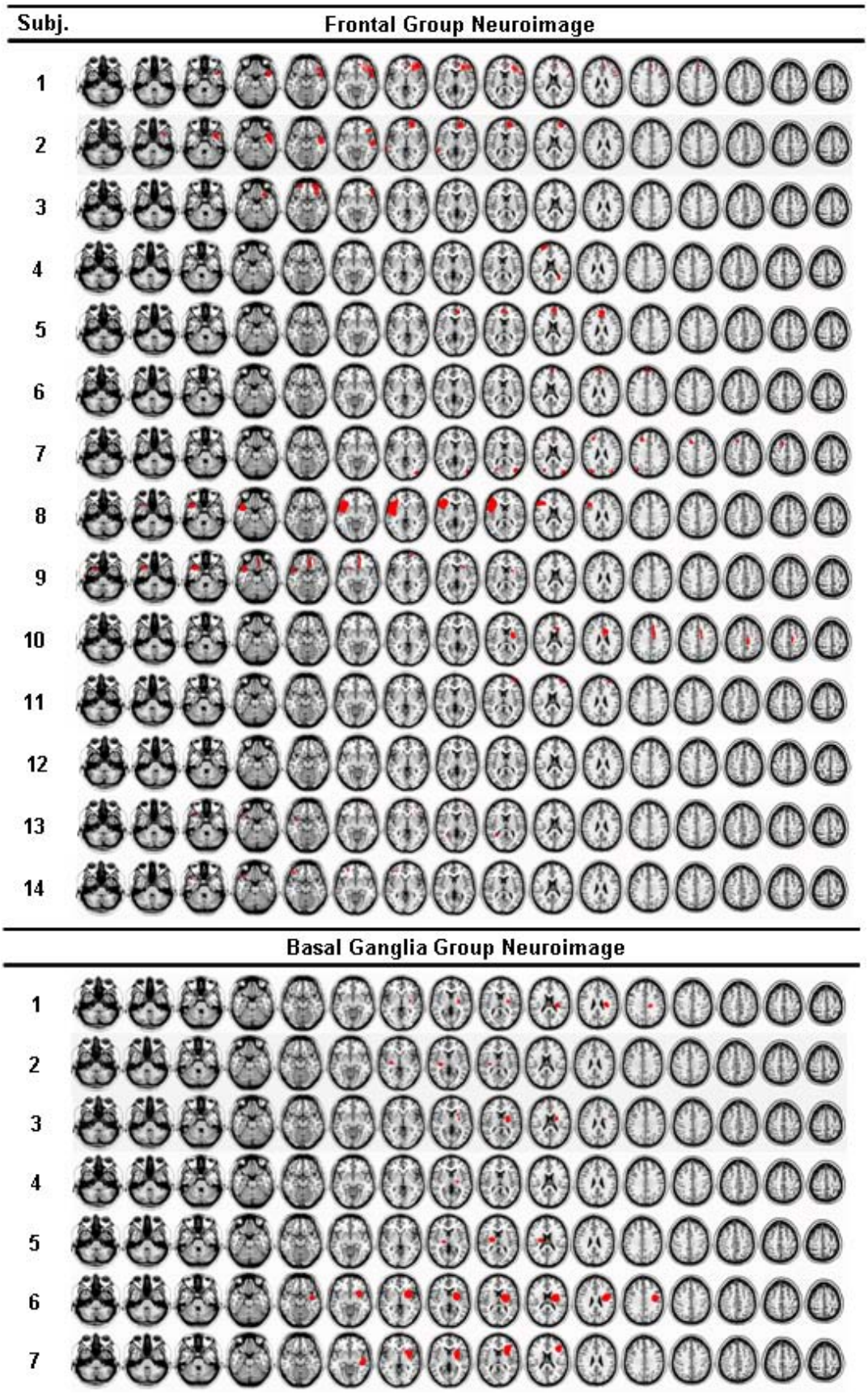

Figure 2. MRI images in 7mm slices with the patients' lesions. All the images were drawn with MRIcroN software. The left hemisphere is represented at the left side of the images and viceversa.

BEHAVIOURAL RESULTS

Catch trials (and the corresponding 20% of target trials in the no catch trial session) were eliminated from the analyses. Practice trials and the first trial of each block were also eliminated, as well as trials in which participants responded before the target appeared (anticipation errors: 2.45%) or did not respond when it appeared (misses: 0.14%). Furthermore, correct response trials with RT 2.5 SD slower or faster than the mean for each participant and session were considered outliers (2.83%) and therefore also eliminated from the analyses. Mean RTs per experimental condition were computed with the remaining observations, which are presented in Table 3.

Table 3. Mean RTs and percentage of errors (i.e. anticipation errors are in parentheses and missing responses between square brackets) per experimental condition from all Lesion groups (Frontal, Basal Ganglia and Control) broken down by Previous Foreperiod (short vs. long Foreperiod$_{n-1}$), Current Foreperiod (short vs. long Foreperiod) and Validity (valid – val vs. invalid – inv). **Top.** Condition of 0% Catch Trials (Target certainty). **Bottom.** Condition of 20% Catch Trials (Target uncertainty).

0% Catch Trials

	Short Foreperiod$_{n-1}$				Long Foreperiod$_{n-1}$			
	Short Foreperiod		Long Foreperiod		Short Foreperiod		Long Foreperiod	
	Val	Inv	Val	Inv	Val	Inv	Val	Inv
Frontal	503 (0.3%) [1.3%]	523 (0%) [3.1%]	524 (0.2%) [3.1%]	517 (0%) [3.1%]	533 (5.9%) [1.8%]	542 (10.9%) [0.9%]	535 (2.5%) [1.5%]	532 (2.1%) [1.1%]
Basal Ganglia	474 (0.8%) [2.2%]	513 (0%) [0%]	457 (0.9%) [2.3%]	455 (0%) [2.8%]	497 (5.1%) [2.9%]	551 (17.5%) [2.2%]	474 (3.2%) [1.8%]	491 (4.2%) [1.4%]
Control	362 (0.7%) [0.3%]	386 (1.1%) [0.6%]	364 (0.4%) [0.5%]	373 (0%) [0.5%]	385 (5.9%) [0.6%]	416 (10.4%) [0.2%]	366 (2.4%) [0.6%]	379 (1.8%) [0.6%]
Total	438 (0.5%) [1.0%]	464 (0.5%) [1.5%]	444 (0.4%) [1.9%]	445 (0%) [1.9%]	465 (5.8%) [1.5%]	491 (11.8%) [0.8%]	453 (2.6%) [1.1%]	460 (2.3%) [0.9%]

20% Catch Trials

	Short Foreperiod$_{n-1}$				Long Foreperiod$_{n-1}$			
	Short Foreperiod		Long Foreperiod		Short Foreperiod		Long Foreperiod	
	Val	Inv	Val	Inv	Val	Inv	Val	Inv
Frontal	576 (0.2%) [2.3%]	569 (0%) [1.0%]	615 (0%) [3.3%]	645 (0%) [3.7%]	586 (3.0%) [1.6%]	593 (5.6%) [1.6%]	617 (2.2%) [2.3%]	644 (3.4%) [2.9%]
Basal Ganglia	505 (0.1%) [2.9%]	523 (1.5%) [9.3%]	527 (0.5%) [2.0%]	534 (0%) [3.3%]	511 (2.9%) [2.9%]	551 (3.0%) [4.0%]	518 (2.1%) [2.7%]	544 (1.3%) [5.1%]
Control	387 (0.7%) [0.5%]	412 (0.6%) [0%]	419 (0.2%) [0.2%]	444 (0.4%) [0%]	402 (1.8%) [0.2%]	435 (3.6%) [0.6%]	414 (1.0%) [0.5%]	442 (2.9%) [0%]
Total	484 (0.4%) [1.7%]	494 (0.5%) [2.1%]	517 (0.2%) [1.9%]	540 (0.2%) [2.2%]	495 (2.5%) [1.3%]	519 (4.4%) [1.6%]	513 (1.7%) [1.6%]	541 (2.8%) [2.1%]

The 3 (Lesion Group: Frontal, Basal Ganglia, Control) x 2 (Target uncertainty: 0% vs. 20% catch trials) x 2 (Foreperiod: short vs. long) x 2 (Previous foreperiod: short vs. long) x 2 (Validity: valid vs. invalid) mixed ANOVA showed a main effect of group, $F(2, 33)=3.82$, $p=.0321$, $\mu p^2 = .19$, showing that the two groups of patients were slower than controls[1]. A significant t**emporal orienting effect** was observed, as shown by the main effect of validity, $F(1, 33)=76.21$, $p<.0001$, $\mu p^2 = .70$. As indexed by the Foreperiod x Validity x Target uncertainty interaction, $F(1, 33)=4.62$, $p=.0389$, $\mu p^2 = .12$, and usually observed in the literature, this temporal orienting effect depended on the foreperiod when no catch trials were included ($F(1, 33)=10.99$, $p=.0022$), so that temporal orienting was only observed at the short foreperiod, $F(1, 33)= 36.21$, $p<.0001$, but not at the long foreperiod, $F<1$. However, in the session with catch trials temporal orienting was independent of foreperiod ($F<1$), and significant temporal orienting effects were observed at both foreperiods (both $p<.01$). More importantly, the validity x group interaction was significant (see Figure 3A), $F(2, 33)=5.96$, $p=.0062$, $\mu p^2 = .26$, showing that frontal patients showed a significantly reduced temporal orienting effect as compared to controls, $F(1, 27)=14.45$, $p=.0007$, $\mu p^2 = .35$, whereas basal ganglia patients showed a temporal orienting effect similar to that shown by controls, $F<1$. Although frontal patients also showed a significant temporal orienting effect, $F(1, 13)=11.47$, $p=.0049$, $\mu p^2 = .47$, the effect they showed (RT-invalid minus RT-valid: 9 ms) was 2.5 times smaller than that shown by controls (23 ms), whereas basal ganglia patients showed fairly the same effect (25 ms).

Regarding the **Foreperiod effect**, no main effect of this factor was observed, $F<1$. This was due to the fact that it was modulated by Target uncertainty, $F(1, 33)=72.16$, $p<.0001$, $\mu p^2 = .69$, so that RT only decreased at the long vs. short foreperiod when no catch trials

[1] In order to account for this main effect of group, all the analyses reported in this paper were repeated taking as dependent variable the proportional RT, i.e., the mean RT for each experimental condition and participant divided by the mean overall RT for that participant. Exactly the same pattern of results was observed with this measure. Therefore, for the sake of simplicity mean RT is reported.

were presented, $F(1, 33)=9.91$, $p=.0035$, $\mu p^2 = .23$, whereas RT increased at the long vs. short foreperiod in the session with catch trials, $F(1, 33)=23.75$, $p<.0001$, $\mu p^2 = .42$. More

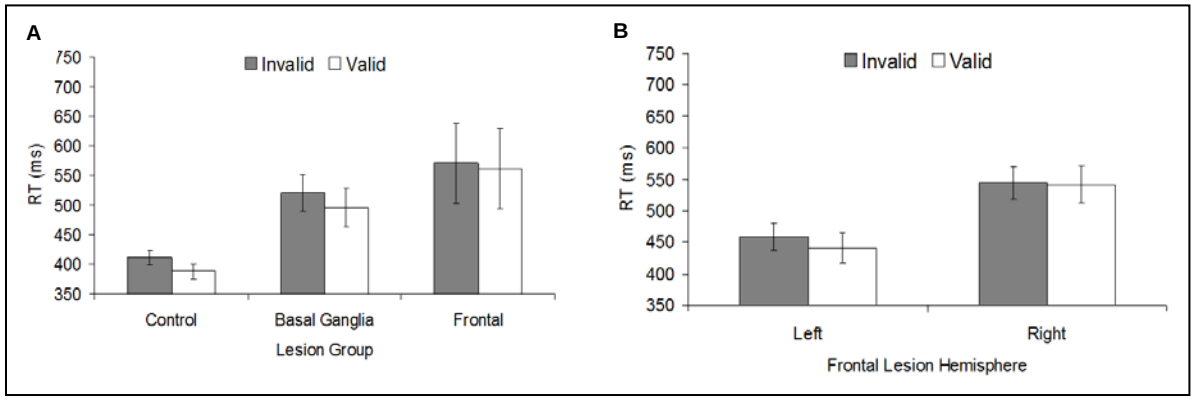

Figure 3. A. Temporal orienting effect in control, basal ganglia and frontal groups. The temporal orienting effect (faster RTs in valid vs. invalid trials) was significantly smaller for the frontal group as compared to both control and basal ganglia groups. **B.** The temporal orienting effect in subgroups of left (n=5) vs. right (n=6) prefrontal patients. Only the left prefrontal group show the temporal orienting effect. Error bars represent the standard error of the mean.

importantly, the foreperiod effect was also different for each group (see Figure 4), $F(2, 33)=5.56$, $p=.0083$, $\mu p^2 = .26$. In the appropriate condition for observing foreperiod effects (i.e., the no catch session), only controls and basal ganglia patients showed main effects of foreperiod, $F(1, 14)= 7.55$, $p=.0157$, $\mu p^2 = .35$, and $F(1, 6)= 5.34$, $p=.0602$, $\mu p^2 = .47$, respectively, whereas frontal patients showed no effect, $F<1$. With catch trials, both frontal and control groups showed a significant increase in RT at the long as compared to the short foreperiod, $F(1, 13)= 30.05$; $p=.0001$, $\mu p^2 = .70$, and $F(1, 14)= 7.39$; $p=.0166$, $\mu p^2 = .35$, respectively, whereas the basal ganglia group showed no effect, $F<1$. As shown in Figure 4, the interactions between Group, Foreperiod and Target uncertainty, and between Target uncertainty and Group were not significant (both $ps<.25$), showing that the general RT slowing down due to the presence of catch trials along the foreperiod was similarly present in the three groups.

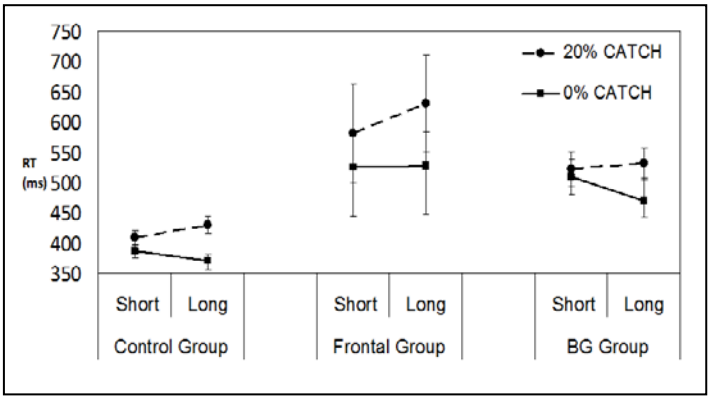

Figure 4. Foreperiod effect in control, basal ganglia and frontal groups. The effect is usually observed as a significant RT decrease in the long foreperiod compared with the short one, when the target always occurred (0% catch). In this condition, both control and basal ganglia groups show the foreperiod effect, whereas the frontal group does not show it. However, in the 20% catch trials condition, a RT increase in the long foreperiod is observed compared with the short one. In this case, all the groups show this RT slowing. Error bars represent the standard error of the mean.

Regarding **sequential effects**, the effect of Previous foreperiod was significant, $F(1, 33)=53.64$, $p<.0001$, $\mu p^2 = .62$, as was the interaction between Previous foreperiod and Target uncertainty, $F(1, 33)=12.83$, $p=.0010$, $\mu p^2 = .28$, showing that the effect of Previous foreperiod (faster RT for previous short vs. long foreperiod) was more pronounced in the session without catch trials. These Previous-foreperiod effects were also independent of group (both Fs <1). The Foreperiod x Previous foreperiod interaction was also significant, $F(1, 33)=20.07$, $p<.0001$, $\mu p^2 = .38$, reflecting the typical asymmetrical sequential effect, as shown in Figure 5. Importantly, this interaction was independent of group, $F(1, 33)=1.06$, $p=.3571$, $\mu p^2 = .06$. The three groups were faster when the previous foreperiod was short vs. long for the current short foreperiod (all ps <.005). For the current long foreperiod controls and frontal patients showed no effect of the previous foreperiod (both ps >.23), whereas the basal ganglia group were faster on previous long foreperiod trials ($F(1, 6)=5.97$, $p=.0502$). In other words, controls and frontal patients clearly showed asymmetrical sequential effects, whereas the basal ganglia group showed a rather symmetrical pattern.

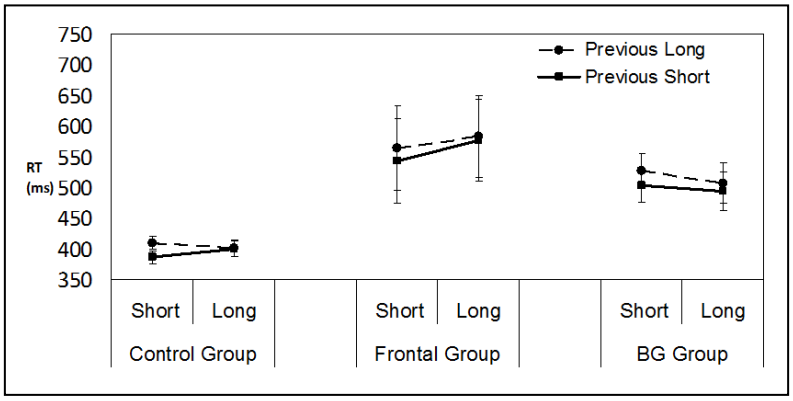

Figure 5. Sequential effects in control, basal ganglia and frontal groups. This effect may be observed as a RT decrease in the current short foreperiod when the previous foreperiod was short instead of long. All the groups show the typical pattern of sequential effects. Error bars represent the standard error of the mean.

To sum up, basal ganglia patients and controls showed similar temporal orienting, the typical foreperiod effect without catch trials and significant Sequential Effects. The only difference was that the basal ganglia group did not show any increase in RT at the long foreperiod with catch trials. This pattern of results was replicated in two analyses using different control groups: when the overall control group (n=15) was taken into account, and when only considering the corresponding 7 age-matched controls. In contrast, the Frontal group showed normal Sequential Effects, with a dramatically reduced temporal orienting effect and a completely absent foreperiod effect.

Analysis of lateralization effects

This analysis specifically tested whether temporal orienting, Foreperiod and Sequential Effects depended on a specific hemisphere. Our sample size enabled us to perform this analysis only on the frontal group, which had 5 patients with left frontal and 6 patients with right frontal lesions (the 3 patients with bilateral lesion were excluded from this analysis, though). Using the same set of RT data as analysed above, mean RTs from the frontal group were submitted to a 2 (Hemisphere lesion: left vs. right) x 2 (Target uncertainty: 0%

vs. 20% catch trials) x 2 (Foreperiod: short vs. long) x 2 (Previous foreperiod: short vs. long) x 2 (Validity: valid vs. invalid) mixed ANOVA, with the first variable as a between participants factor. Only significant effects involving the Hemisphere lesion factor will be reported.

The only significant effect was the interaction between Validity and Hemisphere, $F(1, 9)=8.85$, $p=.0156$, $\mu p^2 = .50$, such that validity effects were only significant for patients with left frontal lesions, $F(1, 4)=33.592$, $p=.004$, $\eta^2=.89$, but not for patients with right frontal lesions, $F<1$ (see figure 3B). Patients with left lesion showed exactly the same temporal orienting effects as controls (i.e., with catch trials they showed a significant temporal orienting effect, p=.0061, independently of foreperiod, F<1, whereas without catch trials they only showed a significant temporal orienting only at the short foreperiod, p=.003, but not at the long foreperiod, F<1). Patients with right lesion showed no temporal orienting effect in any condition. In contrast, both sequential effects (as indexed by both the main effect of Previous foreperiod, and the interaction between Previous foreperiod and Foreperiod) and the Foreperiod effect did not depend on the hemisphere of the lesion (all $Fs<1$).

DISCUSSION

This study provides new insights on the neural bases involved in different strategies for orienting attention in time, particularly as regards voluntary vs. automatic mechanisms. The relevance of this study is that it provides data from neurological patients about the three main effects of temporal preparation and their interrelations, providing causal data on the brain structures involved in such effects.

The current study is the first one to show that the right prefrontal cortex is necessary for the temporal orienting of attention. However, lesions in the basal ganglia did not affect temporal orienting. This finding supports the assumption that temporal orienting is a voluntary process that requires more evolved structures from a phylogenetic and ontogenetic point of view – such as the prefrontal cortex – that are involved in the strategic and voluntary (top-down) regulation of behaviour (Konishi et al., 2008). Our study shows a clear lateralization of the temporal orienting effect in the right prefrontal cortex, which agrees with the involvement of the right frontoparietal network in attentional orienting (Corbetta & Shulman, 2002; Nobre, 2004), both in spatial and temporal dimensions (Coull et al., 2000; Hackley et al., 2009).

However, some fMRI studies have reported an involvement of left prefrontal structures and a systematic activation of the left intraparietal sulcus (Coull, 2004; Coull & Nobre, 1998; Coull, Nobre, & Frith, 2001); these studies suggest that the left frontoparietal network may be specialized in temporal orienting in the same way as the right hemisphere is specialized in spatial orienting. This latter hypothesis was not supported by our results, although Coull and Nobre also considered the possibility that the left-biased activation of such a frontoparietal network might also be related to motor preparation necessary to execute the task with the right hand (Coull and Nobre, 1998). In this respect, our results support the hypothesis of the right frontoparietal involvement in temporal orienting. Another possible explanation may be attributed to the characteristics of the task itself: in our study, temporal expectation remained the same in each block, whereas the expectation changed between trials in the studies mentioned above. A frequent change of expectation is likely to demand a greater involvement of left prefrontal areas in updating and shifting the temporal information provided by the cue (Konishi et al., 2008).

The fact that the basal ganglia lesion did not affect temporal orienting suggests that timekeeping functions attributed to basal ganglia are probably not essential for endogenous temporal preparation, at least when the time intervals involved require timekeeping for one or two seconds (Koch et al., 2008; Lewis & Miall, 2003). However, studies relating basal ganglia lesions with a deficit in temporal preparation tasks use similar time intervals to what we used in our study. The greatest difference between those studies and ours is probably that most of them focus on Parkinson's disease patients (Jahanshahi et al., 2006; C. R. Jones et al., 2008; Jurkowski et al., 2005; Praamstra & Pope, 2007; Wearden et al., 2008); this disease implies bilateral impairment of the substantia nigra and dopamine production that causes a deficit of all the frontobasal circuits and motor programming. In fact, the study carried out by Wearden et al. (2008) shows that when Parkinson's patients do not have to provide motor responses in time estimation tasks, they do not show significant differences with a group of healthy controls. Our 7 basal ganglia patients had suffered a unilateral stroke that mainly affected the striatum (putamen and caudate nucleus); however, the stroke did not affect dopamine production and dopaminergic functioning of the frontobasal circuit or the necessary motor programming for our task. In fact, our basal ganglia patients showed impairment of premotor functions (bimanual coordination, motor rhythms and motor alternances), but not of primary motor functions (none of them had hemiplegia, hemiparesis or difficulty programming or initiating movements). Therefore, unilateral impairment of the striatum does not interfere with the temporal orienting ability. Moreover, this finding allows us to rule out the possibility that frontal patients show a deficit in temporal orienting due to the damage of the frontobasal circuits and the damage of the basal ganglia, which is very frequent after a traumatic brain injury due to diffuse axonal injury. Nevertheless, is it possible that lesion on basal ganglia, might lead to temporal orienting deficits when accompanied by frontal neuropsychological dysfunction. Future research should evaluate this issue.

As for the foreperiod effect, we found a clear deficit in the group of prefrontal patients, as observed in earlier studies (Stuss et al., 2005; Vallesi, Mussoni et al., 2007). Similarly to the temporal orienting effect, the foreperiod effect requires more evolved structures that allow voluntary strategies. In this regard, Vallesi and Shallice (2007) found that children of 4-5 years, who typically lack of a complete maturation of prefrontal cortex, did not show the foreperiod effect. Earlier studies with patients and TMS located this effect in the right prefrontal cortex. In our study, however, we did not find any lateralization, as a deficit in the foreperiod effect was found both in right and left prefrontal patients. A possible explanation might be a lack of statistical power caused by the smaller size of our sample compared to the studies mentioned above[2]. Again, the fact that the foreperiod effect is present in the basal ganglia group suggests that the unilateral lesion of the striatum and the associated frontobasal circuits does not interfere in the use of the strategic processes involved in this effect. Therefore, this result suggests again that the deficit observed in frontal patients is not due to the diffuse axonal injury caused by a traumatic event.

As we expected, sequential effects were preserved in prefrontal patients, which replicates the results by Vallesi et al. (2007). The fact that foreperiod and temporal orienting effects were impaired in frontal patients but sequential effects were preserved supports the hypothesis that they are produced by two different temporal preparation mechanisms (Vallesi, Shallice et al., 2007), in contrast to the single process model defended by Los and colleagues (e.g., Los & Van den Heuvel, 2001). Los' model assumes that the foreperiod effect is the product of sequential effects, and that both foreperiod and sequential effects can be accounted for by a single mechanism of trace conditioning (Los & Heslenfeld, 2005;

[2] This absence of lateralization may also be explained by the presence of catch trials in one of the sessions of our task, which prevents response preparation in both patients and controls, and may affect the typical foreperiod effect. The task with and without catch trials was counterbalanced *a priori* for all groups (control, frontal patients and basal ganglia patients), but not for the subgroups *a posteriori* divided depending on the site of the lesion. By chance, more than half of the patients with left prefrontal lesion first performed the task with catch trials, which may have impaired the foreperiod effect in the session with catch trials (as usually happens). This possibility points out the need to control this variable in future studies.

Los & Van den Heuvel, 2001). If the trace conditioning mechanism was damaged in frontal patients, as it might be induced from the finding of no foreperiod effects, we should have neither found preserved sequential effects in this group of patients. More in agreement with Los' model was our finding of the neuropsychological dissociation between temporal orienting and sequential effects, replicating previous research (Correa et al. 2006; Correa et al, 2004; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001).

The finding of preserved sequential effects in frontal patients strengthens the hypothesis that sequential effects require more automatic mechanisms and therefore depend on brain structures that are less evolved and older from a phylogenetic and ontogenetic (Vallesi & Shallice, 2007) point of view. Although the basal ganglia was a possible candidate of subcortical structure in the current study, the finding that sequential effects were intact in the basal ganglia group rules out this possibility (if any they showed a greater effect of the previous foreperiod). If sequential effects were based on trace conditioning (Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001), their neural bases might involve other subcortical structures such as the hippocampus (Clark & Squire, 1998) or the cerebellum instead (Kalmbach, Ohyama, Kreider, Riusech, & Mauk, 2009). The left motor and premotor cortex is an additional candidate for the substrates of sequential effects, according to Vallesi and colleagues (2007).

The involvement of the prefrontal cortex in voluntary temporal orienting and foreperiod effects has been related to the selective orienting of attention to the relevant stimulus depending on the strategic use of the information provided by the environment. This may involve a temporal cue (Coull & Nobre, 1998) or the monitoring of the conditional probability of stimulus occurrence (Vallesi, Mussoni et al., 2007). In this respect, the right frontoparietal network of attentional orienting may be crucial for both spatial and temporal

stimuli. The function of this network in the temporal domain may be to modulate the temporal course of preparation depending on the expectations on the appearance of such stimuli. Studies have shown that temporal orienting modifies the time course and latency of the contingent negative variation (CNV), an electrophysiological index of temporal preparation that is associated to the activation of central and frontal structures (Correa, Lupiáñez, Madrid, & Tudela, 2006; Miniussi et al., 1999). This suggests an interesting area of research, that is, studying the CNV of frontal patients while they perform temporal orienting tasks, to directly investigate the temporal orienting mechanism rather than its consequences on performance. We expect frontal patients to show a reduced CNV amplitude and/or a reduced synchrony between the CNV peak and the expected moment in time.

In short, the prefrontal cortex seems to be involved in the temporal control of the preparation of responses. This structure is important for functions such as timekeeping (Coull et al., 2004; Harrington & Haaland, 1999; Rao et al., 2001), computing and monitoring probabilities in time (Vallesi, Shallice et al., 2007), and possibly inhibitory control of responses to avoid giving them at inappropriate times (Correa & Nobre, 2008; Davranche et al., 2007; Narayanan, Horst, & Laubach, 2006).

In conclusion, our study shows for the first time in patients a clear dissociation between automatic sequential effects and voluntary mechanisms of temporal preparation (i.e. temporal orienting and foreperiod effects). This finding strengthens the hypothesis of a dual mechanism in temporal preparation and provides an answer to the complexity of our behaviour, which takes place in an environment where stimuli are distributed in a predictable-unpredictable continuum. It would be interesting for future studies to explore what brain circuit underlies the other side of the double dissociation. In other words, it

remains to be discovered what structure, if injured, would lead to a specific deficit in sequential effects but not in temporal orienting.

CHAPTER 6

RHYTHMS CAN OVERCOME TEMPORAL ORIENTING DEFICIT AFTER RIGHT FRONTAL DAMAGE

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Abstract

The main aim of this study was to test whether the use of rhythmic information to induce temporal expectations can overcome the deficit in controlled temporal preparation shown by patients with frontal damage (i.e. temporal orienting and foreperiod effects). Two tasks were administered to a group of 15 patients and a group of 15 matched control subjects: a Symbolic Cued task where the predictive information regarding the time of target appearance was provided by a symbolic cue (short line-early vs. long line-late interval) and a Rhythm Cued task where the predictive temporal information was provided by a rhythm (fast rhythm-early vs. slow rhythm-late interval). The results of the Symbolic Cued task replicated both the temporal orienting deficit in right frontal patients and the absence of foreperiod effects in both right and left frontal patients, reported in our previous study. However, in the Rhythm Cued task, the right frontal group showed normal temporal orienting and foreperiod effects, while the left frontal group showed a significant deficit of both effects. These findings show that automatic temporal preparation, as induced by a rhythm, can help frontal patients to make effective use of implicit temporal information to respond at the optimum time. Our neuropsychological findings also provide a novel suggestion for a neural model, in which automatic temporal preparation is left-lateralized and controlled temporal preparation is right-lateralized in the frontal lobes.

Keywords

Attention; Implicit timing; Temporal orienting; Foreperiod; Rhythms; Time perception; Neuropsychology; Frontal lobe.

INTRODUCTION

The environment provides us with regular temporal information that we use to prepare and respond at the optimal time. This kind of temporal preparation has been considered as *implicit timing* in the literature, which is defined *"as a by-product of non-temporal task goals, when sensory stimuli or motor responses are temporally structured and can be used to predict the duration of future events"* (Coull & Nobre, 2008). The implicit use of temporal information to respond at the appropriate moment in time may depend either on controlled or more automatic processes (Correa, 2010; Rohenkohl et al., 2011).

Controlled temporal preparation

Controlled temporal preparation depends on the expectation about when a stimulus will happen, which is called *Temporal Orienting* (Coull & Nobre, 1998; Nobre, 2001). When predictive information about a stimulus onset is given explicitly to subjects by temporal cues, they prepare themselves to respond at the expected time. Thus, the Temporal Orienting effect is reflected as enhanced performance (faster reaction time and/or higher accuracy) when temporal expectations are fulfilled (i.e. valid trials where the stimulus appears when subjects expect) than when they are not fulfilled (i.e. invalid trials where the stimulus appears when subjects do not expect) (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Coull et al., 2000). In a recent neuropsychological study, we observed that this mechanism of temporal preparation, voluntary in nature, depends on the right frontal cortex (Triviño, Correa, Arnedo, & Lupiañez, 2010).

Another effect related to controlled temporal preparation is the *Foreperiod effect*, which consists of faster reactions at longer intervals after a warning cue. This effect can be explained on the basis of calculation of probabilities (Karlin, 1959; Niemi & Näätänen,

1981). That is, as time passes by and the stimulus has not appeared, subjects increase preparation because of the increasing likelihood of stimulus occurrence. The deficit in the Foreperiod effect has been related to right frontal lesion (Stuss et al., 2005; Vallesi, Mussoni et al., 2007), although in our previous study it was impaired in patients with either right or left frontal lesions (Triviño et al., 2010). The fact that both Temporal Orienting and Foreperiod effects are related to the proper functioning of frontal structures suggests these two effects rely on more evolved mechanisms, voluntary in nature, and based on top-down processing of time information (see Correa, Lupiáñez, & Tudela, 2006, for a explanation of dual-mechanism hypothesis).

Automatic temporal preparation

The finding of *Sequential effects* suggests that there are alternative ways for subjects to prepare on time that are less dependent than temporal orienting on controlled mechanisms. Sequential effects rely on the previous experiences of response preparation. As a result, subjects are faster when the previous foreperiod had the same duration or was shorter than the current foreperiod, even when the sequence of short and long preparatory intervals is completely unpredictable (Woodrow, 1914). These have been associated with automatic mechanisms of implicit timing based on trace conditioning (Los, 1996; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001).

Sequential effects have been dissociated from Temporal Orienting and Foreperiod effects in behavioral and electrophysiological studies (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001), as well as in neuropsychological studies, where Sequential effects were not impaired after frontal damage (Triviño et al., 2010; Vallesi, Mussoni et al., 2007; Vallesi, Shallice et al., 2007). Sequential effects have not been related to a specific brain structure, although classical

conditioning has been associated with more ancient structures like hippocampus (Clark & Squire, 1998) or cerebellum (Kalmbach et al., 2009).

The fact that automatic mechanisms for temporal preparation are preserved after frontal damage is of special interest here, when considering the possibility of using this form of preparation to improve the performance of patients. In fact, rhythmic patterns can induce temporal preparation automatically (M. R. Jones et al., 2002; Large & Jones, 1999; Rohenkohl et al., 2011; Sanabria et al., 2011). Rhythmic contexts have been related to an enhancement in temporal discrimination tasks when the standard duration ended on predicted time compared to durations that ended earlier or later (McAuley & Jones, 2003). This pattern of improvement has been named an *expectancy profile* (Barnes & Jones, 2000), which resembles the expectation effects observed in the Temporal Orienting paradigm (Correa & Nobre, 2008; Griffin, Miniussi, & Nobre, 2001).

Therefore, cueing time by means of rhythmic patterns seems to enhance implicit timing, which benefits performance in temporal preparation tasks. Given that automatic implicit timing mechanisms are presumably preserved after frontal damage, we should expect an improvement in temporal preparation in these patients when a rhythm is used as temporal cue. However, to our knowledge there are no studies about temporal preparation guided by rhythms in frontal patients (but see Praamstra & Pope, 2007, for a study in Parkinson Disease). Thus, the main aim of this study was to test the effectiveness of regular rhythms to induce temporal preparation in right frontal patients, who show deficit in temporal orienting.

We designed a simple and short task, based on our previous studies (Correa, Miró, Martínez, Sánchez, & Lupiáñez, 2011; Correa, Triviño, Pérez-Dueñas, Acosta, & Lupiañez, 2010; Triviño et al., 2010), that was administered to both control subjects and frontal

patients groups. Two versions of the task were administered to each participant. In the Symbolic Cued Task, the usual symbolic cue (short vs. long static line) identical to that used in our previous studies was used as temporal cue; while in the Rhythm Cued Task a regular rhythm was used as temporal cue (fast vs. slow pace of a intermittent line). The Symbolic Cued task allowed us to replicate the results obtained in our previous study in patients. Specifically, we expected to observe that the Temporal Orienting effect was again abolished by prefrontal lesion only in the group of patients with right frontal damage; similarly, we would be able to test whether the Foreperiod effect was only associated to the right frontal cortex (Vallesi, Mussoni et al., 2007) or was rather not lateralized (Triviño et al., 2010). In the Rhythm Cued task, a fast rhythmic pattern was associated in 75% of trials to an early onset of the target (fast-early) and a slow rhythmic pattern was associated in 75% of trials to a delayed onset of the target (slow-late). With this new version we expected an improvement in temporal preparation in frontal groups. Finally, from a more practical point of view, the brief version of the temporal orienting task (less than 10 minutes) would approach the future design of a clinical tool to assess temporal preparation processes, whereas the rhythm task might be used with training purposes in neuropsychological rehabilitation.

Implicit vs. Explicit timing

Furthermore, we must take into account that there are several studies showing an impaired ability to estimate time explicitly in patients with frontal damage. This impairment has been described in temporal estimation tasks, as well as in production and reproduction tasks. Specifically, these patients show a time overestimation in the range of seconds and milliseconds (Berlin et al., 2005; Berlin et al., 2004; Mimura et al., 2000; Nichelli et al., 1995) as well as a subproduction and an accelerated interval reproduction in the range of seconds (Berlin et al., 2005; Berlin et al., 2004; Mimura et al., 2000). Therefore, if a patient with

frontal damage tends to overestimate the passage of time and believes that a given interval (e.g. 1000 ms) would end before (e.g. at 800 ms) it really ends, we could expect that this patient uses that distorted information implicitly in the task of temporal preparation. That is, time overestimation will lead to premature preparation and responses.

Alternatively, one can expect no influence of distortions of explicit time estimation upon the performance during implicit temporal preparation tasks, according to the literature considering explicit and implicit timing to be independent processes (Coull & Nobre, 2008; Lewis & Miall, 2003; Zelaznik et al., 2002). However, although it is generally agreed that time perception is fundamental for temporal orienting (e.g., Coull & Nobre, 1998), there are no studies, to our knowledge, testing directly the role of time perception accuracy in temporal orienting.

Therefore, we measured explicit timing in the range of milliseconds and minutes with a duration discrimination task and a temporal order judgment task. We expected frontal patients to show abnormal temporal estimation as has been described in the literature, i.e. time overestimation. The analysis of correlations between the performances in explicit and implicit timing tasks should inform us about the relationship between these two processes.

METHOD

PARTICIPANTS

Fifteen subjects with a frontal brain lesion and 15 neurologically intact subjects participated in the study. All the patients had suffered an acute lesion leading to cognitive dysfunction (14 due to a traumatic brain injury and 1 due to an anterior cerebral artery stroke). Prior to the lesion, they were functionally independent, had no neurological or psychiatric disorders, and had normal intellectual level. They were divided into two different groups according to

the lesion lateralization, so that there was a group of 10 patients with right frontal lesion and another group of 5 patients with left frontal lesion. Unfortunately, the Rhythm Cued task could not be administered to a right frontal subject. Each patient was matched in age, sex and years of education with a control subject. See Table 1.

Table 1. Demographic data of both frontal and control groups with the right and left division. Group averaged data and standard deviation (in parenthesis) are included.

Frontal Group		Age in Years	Years of Education	Sex	Etiology	Total
Right Frontal	mean (s.d)	33.7 (15.2)	10.5 (4.9)	7 M 3 F	9 TBI 1 Stroke	10
Left Frontal	mean (s.d)	33.6 (10.3)	12.2 (2.7)	5 M 0 F	5 TBI	5
Total Frontal	mean (s.d)	33.7 (13.4)	11.1 (4.2)	12M 3F	14 TBI 1 Stroke	15

Control Group	Age in Years	Years of Education	Sex	Total
Right Control	33.6 (14.8)	22 (31.8)	5 M 5 F	10
Left Control	32.8 (9.9)	13.6 (4.7)	4 M 1 F	5
Total Control	33.33 (13.0)	13.0 (4.3)	9 M 6 F	15

F: female; M: male; TBI: traumatic brain injury

Following our previous study (Triviño et al., 2010), inclusion criteria for the frontal group to be tested on the temporal tasks were the presence of acquired damage in either left or right frontal lobes according to the radiological report as well as a significant dysfunction of frontal functions observed in the neuropsychological assessment. Exclusion criteria were the presence of bilateral frontal damage (for this reason 5 patients were not included in the study) as well as the presence of aphasia, hemispatial neglect and/or dementia.

Nine patients were assessed at the Neuropsychology Unit of different hospitals in Valencia, Spain (*Valencia al Mar Nisa Hospital*, *Aguas Vivas Nisa Hospital* and *Nuestra Señora del Carmen Hospital*), whereas the 6 remaining patients and the 15 controls were assessed at the Neuropsychology Unit of *San Rafael University Hospital* in Granada, Spain. The experiment was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

NEUROPSYCHOLOGICAL ASSESSMENT

The neuropsychological assessment was crucial to confirm frontal dysfunction in the frontal group (for their inclusion in the study). Therefore, all patients and controls subjects underwent a full neuropsychological evaluation. This evaluation took about 6 hours for each subject distributed in about 3 to 4 sessions. A summary of the functions assessed and the tests used is shown in Table 2.

BEHAVIOURAL TASKS

Temporal Preparation Tasks: Symbolic and Rhythm Cued Tasks

We used E-prime software (Schneider et al., 2002) to program and run the experimental tasks and collect behavioural data. The tasks were administered on a 15-inch screen PC laptop computer. Participants performed two temporal-preparation tasks, one with symbolic cue and the other with a rhythm cue, administered in counterbalanced order across participants. Each task lasted about 10 to 15 minutes.

Stimuli

We used the same stimuli and procedure as used in a recent study (Correa et al., 2010), which validated a shorter version of the task with clinical purposes. Both *Symbolic* and *Rhythm* cued tasks shared the following characteristics. The stimuli were presented at the centre of the screen over a black background. Each trial included a fixation point, a temporal cue, and a target. The fixation point consisted of a dark gray square (0.25º x 0.25º of visual angle at a viewing distance of 60 cm). In the *Symbolic* cued task, the temporal cue was either a short red line (0.38º x 0.95º) or a long red line (0.38º x 2.1º). The short line indicated that the target would appear early (after 400 ms), whereas the long one indicated that the target would appear late (after 1400 ms). In the *Rhythm* cued task, the temporal cue consisted of two horizontal red lines of the same length (1.05º), which appeared and

disappeared 5 times at either a short (400 ms) or long (1400) pace (see figure 1). In both tasks, the target involved either go or no-go responses. The go target was either the letter 'O' or the letter 'X', whereas the no-go target was the digit '8' which shares features with both go targets (all stimuli subtending 0.38º x 0.76º). In the go condition, subjects had to detect any of the two letters – which appeared with identical probability (p=.5) – by pressing the 'B' key. Two letters were used instead of just one in order to be able to compare the results with our previous studies and with future studies in which we will use a discrimination task. In the no-go condition, subjects should inhibit responding. Otherwise they were provided with feedback including the word "Incorrect" and a 2000-Hz auditory tone of 50 ms. The trial proportion was of .75 for the go condition (.375 for each go target) and .25 for the no-go condition.

Procedure

Participants seated about 60 cm from the computer screen. In both tasks the subjects were instructed to respond as quickly as possible but only to the go targets ('X' or 'O' letters), and therefore avoid responding to the no-go target ('8' digit). Each trial began with the fixation point presented for a random interval ranging between 500 and 1500 ms. In the *Symbolic* cued task, the temporal cue (short or long red line) was presented for 50 ms, and then the screen remained blank for a time interval of 350 or 1350 ms, depending on the foreperiod of that trial. However, in the *Rhythm* cued task the temporal cue appeared for 50 ms and disappeared five times every 350 or 1350 ms (depending on the foreperiod condition; see figure 1). The final cue in each trial (the fifth one) turned thicker to warn about the impending target (see Sanabria et al., 2011, for a similar procedure). After the last thicker cue of these rhythm cues, the screen remained blank for 350 or 1350 ms, as in the *Symbolic* cued task, depending on the foreperiod (Figure 1). The target was displayed for 100

ms and was then replaced by a blank screen until the participant made a response or for a maximum duration of 2000 ms. A final pause of 500 ms preceded the next trial.

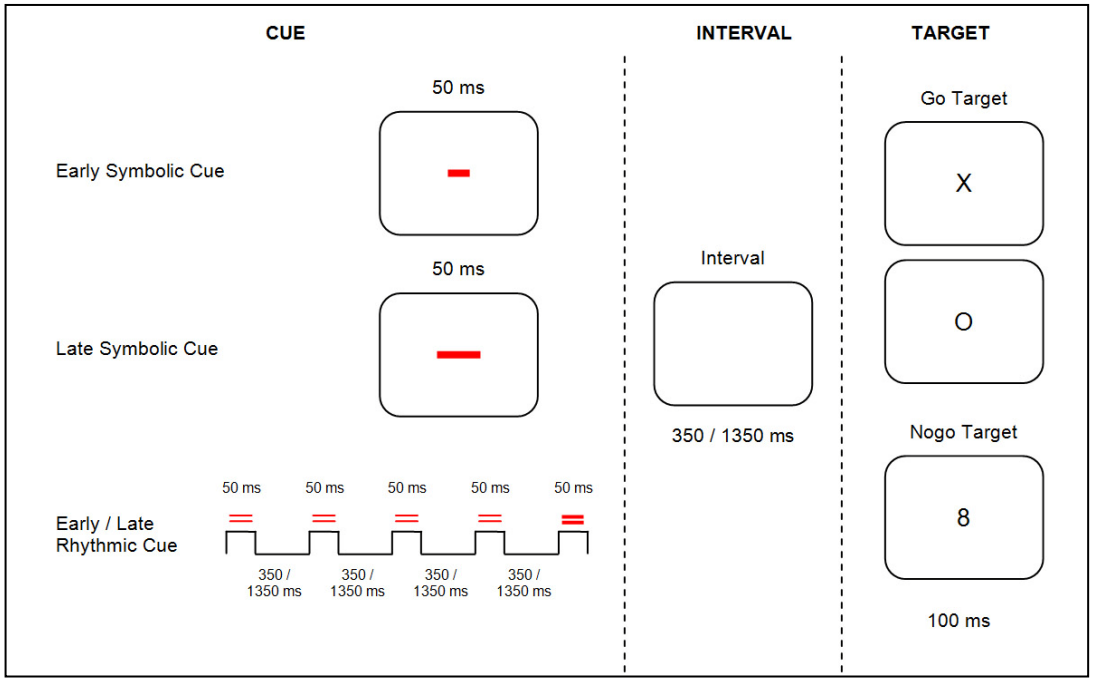

Figure 1. Sketch of the main experimental conditions and events in Symbolic and Rhythm Cued Tasks.

Both *Symbolic* and *Rhythm* cued tasks included one practice block and 4 experimental blocks. The practice block included 32 trials with 16 early cues followed by 16 late cues (in practice trials cues were 100% valid in order to encourage participants to use their predictive value). The experimental blocks were divided into 2 'early' blocks, in which the cue indicated that the target would probably appear after 400 ms, and 2 'late' blocks, in which the cue indicated that the target would probably appear after 1400 ms (cue validity: 75%). Temporal expectancy was manipulated between blocks to optimise temporal orienting effects (Correa, Lupiáñez, & Tudela, 2006). Blocks of early and late cues were presented in alternating runs, and the order of presentation was counterbalanced across participants. Each experimental block included 32 trials that were randomly presented. They were divided according to cue validity (24 valid and 8 invalid). In the valid condition, when the cue was early the target appeared after a short foreperiod of 400 ms, but when the cue was

late the target appeared after a long foreperiod of 1400 ms. In the invalid condition, when the cue was early the target appeared after a long foreperiod of 1400 ms. Likewise, when the cue was late the target appeared after a short foreperiod of 350 ms. Eight of the 32 trials were nogo trials, in which the digit "8" was presented, so that the participant had to withhold responding (25% of nogo trials).

Design and Analyses of Behavioural Results

Based on our previous studies, the analyses were simplified by computing an index for each temporal preparation effect[1], temporal orienting and the foreperiod effect (Correa, Lupiáñez, & Tudela, 2006; Triviño et al., 2010). Specifically, the **Temporal Orienting effect** was indexed as the main effect of Validity in the short foreperiod experimental condition, subtracting the valid from the invalid condition. This index was calculated since the temporal orienting effect depend on the foreperiod, so that Temporal Orienting effect is only observed at the short foreperiod, unless catch trials are included (Correa et al., 2004). The **Foreperiod effect** was indexed as the main effect of Foreperiod in the invalid experimental condition, subtracting the long foreperiod from the short foreperiod condition. In this case, valid trials were excluded since the literature show that the foreperiod effect is not observed when there is a strong expectancy for the target to appear at the short interval, so that when trials are valid subjects are equally fast on both short and long foreperiods (e.g., Correa et al., 2004; Correa & Nobre, 2008). However, when trials are invalid, subjects are usually slower in short vs. long foreperiods showing a robust foreperiod effect.

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[1] These indices have shown to be more specific and sensitive measures of our two main effects of interest. In any case, they were validated by an analysis similar to our previous studies, in which mean RTs were submitted to a 3 (Group: Right frontal, Left frontal, Control) x 2 (Foreperiod: short vs. long) x 2 (Validity: valid vs. invalid) mixed analyses of variance (ANOVA). The Foreperiod x Validity interaction was significant, $F(1,27)=5.69$, $p=0.024$, $\mu p^2 =0.17$, with the effect of validity in the short foreperiod being significant, $F(1,27)=8.47$, $p=0.007$, but not in the long foreperiod, $F<1$. In the same way, the effect of foreperiod was close to significance in the invalid condition, $F(1,27)=3.14$, $p=0.087$, but not in the valid condition, $F(1,27)=1.90$, $p=0.179$. The proposed indices therefore focused on the clearest effects, namely, validity effects at the short foreperiod (temporal orienting effect) and foreperiod effect in the invalid condition.

These two indices were computed for both RTs and false alarms (i.e., the proportion of responses to the no-go condition). In order to compare the two temporal preparation tasks, data from each index were submitted to a 3 (Group: Right frontal, Left frontal, Control) x 2 (Task: Symbolic Cue vs. Rhythm Cue) mixed analysis of variance (ANOVA), with the first variable as a between participants factor and the other as a within participants variable. Subsequent planned comparisons were carried out to analyze the differences between tasks in each group.

Practice trials and the first trial of each block were eliminated from the analyses. No-go trials were also eliminated from the RT analyses, as well as anticipation errors, in which participants responded before the target appeared (0.12% of trials rejected), or missing responses, in which participants did not respond when the target appeared (0.04% rejected). RT responses were filtered removing the trials with RT below 100 ms (0.04%) or above 1000 ms (0.74%). Mean RTs per experimental condition were computed with the remaining observations. False alarms were computed as the percentage of responses executed in the nogo condition.

Temporal Estimation Tasks

In order to measure processes related to fine-grained time processing in the milliseconds range, participants performed a Duration Discrimination task (providing an index of the estimation of the interval used in the temporal orienting tasks: 400 and 1400 ms) and a Temporal Order Judgment task. The tasks were administered on the same 15-inch screen PC laptop computer, using also E-prime software to run the tasks and collect de data. These tasks were performed the first and last, respectively, before and after the two temporal preparation tasks. The duration discrimination task was run first in order to familiarize participants with the interval to be used. Each task lasted 5 to 8 minutes. Finally, each of the four tasks (i.e., the two temporal preparation and the two temporal estimation

tasks) included a temporal estimation task in the minutes range. For a more detailed description of the stimuli, procedure and design of these tasks, see the Appendix.

RESULTS

DEMOGRAPHIC RESULTS

Each patient was matched to a control subject in age, sex and education. A single-factor ANOVA was used to analyze differences in age and education. Each frontal group was compared to the control group. No significant differences were found concerning age and years of education (F<1 in both cases). The premorbid IQ of patients was compared to the current IQ of control subjects and no significant differences were found with either the right (F<1) or the left frontal group (p>.2). However, as one would expect, the current IQ of frontal patients after was significantly lower than that of control, both for the right frontal, $F(1,18)=4.58$, $p=.046$, and the left frontal group, $F(1,8)=22.1$, $p=.002$. See Table 2.

NEUROPSYCHOLOGICAL ASSESSMENT

Each patients group was compared to the control group using a single-factor ANOVA on the score in each neuropsychological test. The typical deficits of frontal lesions were observed, such as dysexecutive syndrome with a significant impairment of divided attention, interference control ability, abstraction, temporal sequencing, fluency and mental flexibility. We also observed memory impairment, mainly presenting perseverations and poor use of encoding and recall strategies. The left frontal group showed a specific impairment on verbal learning, free recall and recognition, with differences marginally significant when compared to right frontal group. There were no differences in personality and other psychological disorders (all ps>.10). No significant differences were found between patients with right and left frontal lesion regarding any other of the neuropsychological variables (ps>.10). Further detailed analyses are provided in Table 2.

Table 2. Summary of cognitive functions and neuropsychological tests used in the clinical assessment, and the results comparing each frontal group to the control group as well as the comparisons between both right and left frontal groups.

FUNCTION ***Test & Subtest***	**RESULTS**					
	GROUPS			**COMPARISONS**		
	Right Frontal μ (sd)	Left Frontal μ (sd)	Control Group μ (sd)	Right F vs. Control	Left F vs. Control	Right F vs. Left F
Intelligence Quotient (IQ)						
Premorbid Intellectual Functioning						
Bilbao & Seisdedos (2004) formula	115 (16.7)	109 (12.2)	116 (9.3)			
Current Intelligence Quotient						
Verbal IQ of WAIS-III	103 (14.3)	95 (4.3)	115 (10.9)	**	***	
Manipulative IQ of WAIS-III	93 (23.9)	89 (16.3)	115 (11.9)	*	**	
Total IQ of WAIS-III	98 (19.4)	93 (10.2)	116 (9.3)	*	***	
Premotor Function						
Premotor Functions (Barcelona Test)						
Rhythm (errors)	0.7 (0.6)	0.0 (0.0)	0 (0.0)	***		
Bimanual coordination	2.0 (0.0)	2.0 (0.6)	2 (0.0)		*	
Motor alternances	1.3 (0.6)	2.0 (0.6)	2 (0.0)	***	*	
Graphic alternances	1.7 (0.6)	2.0 (0.0)	2 (0.0)	*		
Reciprocal inhibition (errors)	0.3 (0.6)	0.0 (0.6)	0 (0.6)			
Verbal Memory						
Test Aprendizaje Verbal España Complutense, TAVEC						
Learning	55 (8.1)	46 (11.3)	55 (8.2)		+	+
Short term free recall	10 (4.3)	7 (2.8)	13 (2.5)	+	***	
Long term free recall	10 (4.2)	8 (2.3)	13 (2.5)	+	***	
Intrusions (in both free and cued recall)	6 (5.9)	4 (2.9)	3 (4.2)			
Semantic strategies in learning (A+B list)	8 (8.4)	4 (5.2)	10 (12.1)		*	
Semantic strategies in recall (short+ long)	4 (2.2)	2 (1.1)	7 (4.1)	*	**	
Serial strategies in learning (A+B list)	4 (5.5)	5 (5.4)	4 (6.3)	*	*	
Serial strategies in recall (short+ long)	1 (2.0)	0.6 (1.1)	1 (3.0)			
Perseverations	11 (7.5)	8 (9.6)	5 (4.7)	*		
Recognition	15 (1.3)	10 (7.2)	15 (1.3)		*	+
Falses positives in recognition	1 (1.6)	2 (2.2)	1 (0.9)		*	
Visual Memory						
Rey Complex Figure Test						
Immediate Recall (PC)	52 (36.6)	53 (34.48)	70 (25.9)			
Working Memory						
Phonological loop						
Digit Span Subtest of WAIS-III	10 (2.4)	10 (2.1)	11 (2.8)			
Visuospatial sketchpad						
Spatial Span Subtest of WMS-III	9 (4.3)	9 (4.0)	12 (3.5)			
Central executive						
Letter-Number Subtest of WAIS-III	10 (3.2)	10 (2.9)	12 (2.1)			
Attention						
Sustained attention						
Trail Making Test, A – errors	0 (0.0)	0 (0.0)	0 (0.3)			
Selective attention						
Picture Completion Subtest of WAIS-III	10 (5.7)	11 (3.2)	14 (2.7)	*	*	
Divided attention						
Trail Making Test, B – errors	2 (2.4)	1 (1.8)	0 (1.2)	*		
Interferente						
Stroop Color and Word Test	56 (5.7)	55 (13.9)	50 (10.1)	+		
Executive Functions						
Verbal abstraction						
Similarities Subtest of WAIS-III	13 (2.9)	10 (2.4)	14 (2.2)	+	**	
Visual abstraction						
Matrix Reasoning Subtest of WAIS-III	10 (2.8)	8 (2.3)	12 (2.2)	*	**	
Temporal sequencing						
Picture Arrangement Subtest of WAIS-III	7 (2.7)	7 (2.4)	12 (3.2)	**	**	
Constructive praxia						
Block Design Subtest of WAIS-III	9 (4.9)	9 (4.2)	12 (2.8)	*	+	
Copy of the Rey Complex Figure Test	62 (32.1)	79 (13.9)	97 (3.9)	**	**	
Fluency						
FAS fluency test	31 (8.2)	28 (10.8)	42 (9.7)	*	*	
Animal fluency test	18 (3.2)	15 (2.4)	23 (5.0)	**	**	
Mental flexibility and categorization (WCST)						
Errors % (PC)	43 (33.4)	63 (52.3)	50 (21.6)			
Perseverative responses % (PC)	39 (39.5)	48 (57.4)	71 (26.8)	*		
Perseverative errors % (PC)	47 (41.2)	47 (56.9)	68 (27.4)			
Non-perseverative errors % (PC)	48 (24.5)	54 (23.1)	38 (22.9)		*	
Number of categories completed (PC)	3 (1.7)	4 (2.5)	5 (1.6)	*		
Planning (Zoo Map Test of BADS)						
Execution Time (in sec) – Parte 1	298 (297.8)	177 (143.2)	199 (95.9)			
Execution Time (in sec) – Parte 2	108 (47.8)	89 (55.3)	56 (27.4)	**		
Total profile	2 (1.1)	2 (2.1)	3 (0.9)			
Personality and Psychological Disorders *Millon Clinical Multiaxial Inventory, MCMI-III*	No significant differences in any scale between either groups					

+p<.10; *p<.05 ; ** p<.01 ; *** p<.001

sd=standard deviation; WAIS-III=Weschler Adult Intelligence Scale 3th edition; WMS-III=Weschler Memory Scale 3th edition; TAVEC= Spanish version of California Verbal Learning Test; WCST= Wisconsin Card Sorting Test; BADS= Behavior Assessment of Disexecutive Syndrome; PC=percentile.

BEHAVIOURAL RESULTS

Temporal preparation tasks

Detailed data are presented in Table 3. Temporal preparation indexes (described above) were computed using both mean RTs and percentage of false alarms. Indexes are presented in Table 4 for both Symbolic and Rhythm Cued Tasks.

Table 3. Mean RTs and percentage of false alarms (in parentheses) per experimental condition from all groups (Right Frontal, Left Frontal and Control) broken down by Cue (Symbolic vs. Rhythm), Foreperiod (Short FP vs. Long FP) and Validity (Valid – val vs. Invalid – inv).

		Symbolic Cue				**Rhythm Cue**			
		Short FP		**Long FP**		**Short FP**		**Long FP**	
		Val	**Inval**	**Val**	**Inval**	**Val**	**Inval**	**Val**	**Inval**
Right Frontal	Mean RT (False alarms)	391 (9.4%)	402 (7.5%)	406 (13.3%)	403 (17.5%)	422 (6.7%)	467 (15.0%)	429 (15.5%)	407 (7.5%)
Left Frontal	Mean RT (False alarms)	451 (5.2%)	490 (5.0%)	463 (11.8%)	490 (10.0%)	469 (18.4%)	472 (0.0%)	450 (15.5%)	443 (18.3%)
Control	Mean RT (False alarms)	379 (16.0%)	402 (16.7%)	380 (18.9%)	362 (11.7%)	380 (13.7%)	407 (22.0%)	385 (21.4%)	355 (8.9%)

Table 4. Mean RT (left) and percentage of falses alarms (right) per temporal preparation index (Temporal orienting and Foreperiod effects) from all groups (Right Frontal, Left Frontal and Control) broken down by Task (Symbolic vs. Rhythm).

		Mean Reaction Time (RT)				**Percentage of False Alarms (FA)**			
INDEX		**Temporal Orienting Effect**		**Foreperiod Effect**		**Temporal Orienting Effect**		**Foreperiod Effect**	
TASK		**Symbolic**	**Rhythm**	**Symbolic**	**Rhythm**	**Symbolic**	**Rhythm**	**Symbolic**	**Rhythm**
Right Frontal	Mean (s.d.)	3.3 (13.3)	45.3 (16.3)	2.1 (12.7)	60.6 (17.0)	-2.3% (5.7%)	9.2% (6.6%)	-2.8% (7.6%)	8.3% (9.0%)
Left Frontal	Mean (s.d.)	38.9 (17.8)	2.5 (21.9)	0.4 (16.9)	28.7 (22.8)	-0.1% (7.6%)	-18.5% (8.9%)	-5.0% (10.2%)	-18.3% (12.1%)
Control	Mean (s.d.)	26.3 (10.7)	30.6 (13.1)	42.6 (10.1)	55.4 (13.6)	3.6% (4.6%)	8.3% (5.3%)	8.9% (6.1%)	13.1% (7.2%)

Mean RT analyses

A 3 (Group: Right Frontal, Left Frontal, Control) x 2 (Task: Symbolic Cued vs. Rhythm Cued) mixed ANOVA was performed for each temporal preparation index. Regarding the **Temporal Orienting effect**, the interaction between Group and Task was close to significance, $F(2,25)=2.96$, $p=0.070$, $\mu p^2 =0.19$. In subsequent planned comparisons for each group, as we expected, the right frontal group showed significant differences between

tasks, $F(1,25)=4.60$, $p=0.042$, with no Temporal Orienting effect on the Symbolic Cued Task, $F<1$, but showing significant Temporal Orienting effect on the Rhythm Cued Task, $F(1,25)=7.69$, $p=0.010$. The left frontal group did not show significant differences between tasks, $F(1,25)=1.92$, $p=0.179$, although as we also expected, this group showed the effect in the Symbolic Cued Task, $F(1,25)=4.76$, $p=0.039$. However, no temporal orienting was found in the Rhythm Cued Task, $F<1$. Finally, the control group did not show differences between tasks, $F<1$, because the temporal orienting effect was present in both Symbolic and Rhythm Cued Tasks, $F(1,25)=6.06$, $p=0.021$ and $F(1,25)=5.46$, $p=0.027$, respectively. See Figure 2.

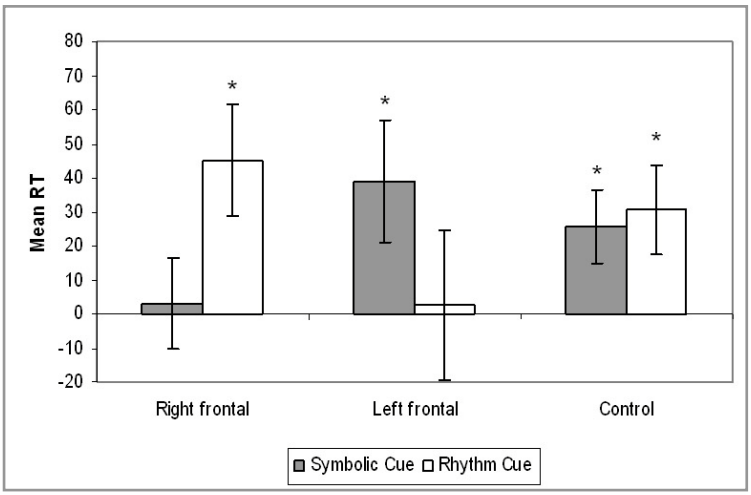


Figure 2. Mean reaction time (RT) results for the Temporal Orienting effect (RT-invalid minus RT-valid) in short foreperiod condition for both Symbolic and Rhythm Cued Tasks. Error bars represent the standard error of the mean. Asterisks mean significant effect.

With regard to the **Foreperiod effect**, the main effect of Task was significant (i.e. larger effect on Rhythm Cued task), $F(1,25)=6.92$, $p=0.014$, $\mu p^2 =0.21$, although the interaction between Group and Task was not significant, $F(2,25)=1.53$, $p=0.236$, $\mu p^2 =0.11$. In planned comparisons, the right frontal group again showed differences between tasks, $F(1,25)=8.21$, $p=0.008$. As we expected, they did not show the Foreperiod effect on the

Symbolic Cued Task, F<1, but did show it on the Rhythm Cued Task, $F(1,25)=12.71$, $p=0.001$. The left frontal group did not show significant differences between tasks, $F(1,25)=1.92$, $p=0.179$, with no Foreperiod effect either in the Symbolic Cued Task, F<1, nor in the Rhythm Cued Task, $F(1,25)=1.58$, $p=0.219$. The control group showed no differences between tasks, F<1, because the Foreperiod effect was clearly present in both Symbolic and Rhythm Cued Tasks, $F(1,25)=17.59$, $p=0.0003$ and $F(1,25)=16.49$, $p=0.0004$, respectively. See Figure 3.

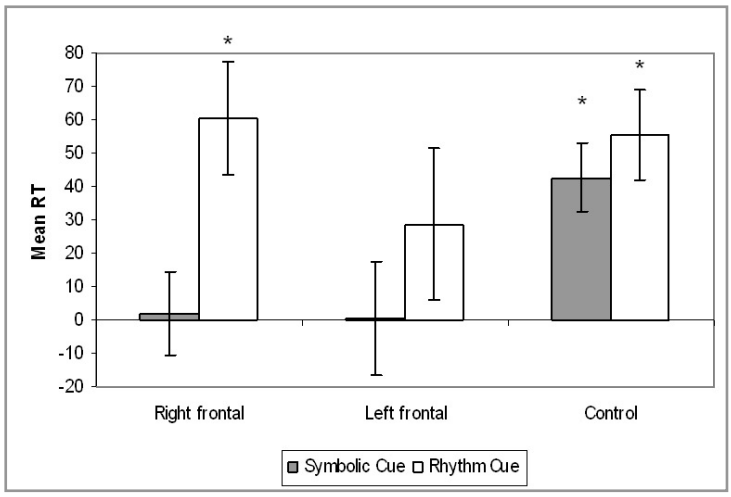


Figure 3. Mean reaction time (RT) results for the Foreperiod effect (RT-short minus RT-long) in invalid conditions for both Symbolic and Rhythm Cued Tasks. Error bars represent the standard error of the mean. Asterisks mean significant effect.

False Alarms Analyses

A 3 (Group: Right Frontal, Left Frontal, Control) x 2 (Task: Symbolic Cued vs. Rhythm Cued) mixed ANOVA was carried out for each temporal preparation index. In the **Temporal Orienting effect** analysis, the main effect of Group was marginally significant, $F(2,25)=2.62$, $p=0.093$, $\mu p^2 =0.17$, and there were no significant main effects of Task, nor interaction between Group and Task, both ps>0.146. In the subsequent planned comparisons for each group, none of the groups showed significant effect of the Task, all

ps>0.137, except for the left frontal group who showed a significant effect in the percentage of false alarms compared to right frontal and control groups. Specifically, the left frontal group made more false alarms in the valid condition than in the invalid showing a negative index (-18.5%), $F(1,25)=4.80$, $p=0.038$. In the **Foreperiod effect** analyses, there were a significant main effect of Group, $F(2,25)=3.38$, $p=0.050$, $\mu p^2 =0.21$, with a significant effect in the left frontal group compared to right frontal and control groups, $F(1,25)=6.21$, $p=0.020$. The left frontal group showed again a negative index (-11.7%) compared to the right frontal (2.8%) and control (11.0%) groups. There were not main effect of Task or interaction between Group and Task (*ps*>0.503). Furthermore, in subsequent planned comparisons there were no significant differences between tasks in any group, all *ps*>0.377.

Temporal estimation tasks

Each patients group was compared to the control group for each score in the temporal estimation tasks. These results are presented in Table 5 (for more detailed analyses, see the Appendix).

The right frontal group showed the overestimation pattern typically described after frontal lesions. This tendency to overestimate was present in all tasks. Specifically, compared to controls, right frontal patients showed a significant larger JND (*Just Noticeable Difference*) in both the Millisecond Duration Discrimination Task and the Temporal Order Judgement Task (all *ps*<0.015). However, PSE (*Point of Subjective Equality*) was only marginally significant in the short interval (400 ms) of the Millisecond Duration Discrimination Task, (*p*<0.054). Regarding the Minutes Estimation task, right frontal patients showed a significant overestimation pattern in all the tasks, all *ps*<0.044, except for the Millisecond Duration Discrimination Task (marginally significant only at the first moment of

estimation, $p<0.055$). There were not significant differences in the left frontal group when compared to controls in any of the tasks, all $ps>0.225$. Only in the Minutes Estimation Task, right and left frontal groups showed significant differences, $F(1,25)=6.85$; $p=0.015$ (i.e., right overestimated whereas left underestimated). To sum up, the right frontal group showed overestimation in all tasks, while the left frontal group were normal in the millisecond range and showed underestimation in the minutes range.

Table 5. Absolute (Abs.) and percentage (%) punctuations of Just Noticeable Difference (JND), Point of Subjective Equality (PSE) and Moment of Estimation for Milliseconds Temporal Discrimination, Temporal Order Judgment and Minutes Estimation Tasks, as well as the results comparing each frontal group to the control group and comparisons between both right and left frontal groups using percentage punctuations. Standard deviations (sd) are in parenthesis.

TASK ***Score & Estimation moment***	**RESULTS**								
	GROUPS						**COMPARISONS USING % PUNTUATIONS**		
	Right Frontal		Left Frontal		Control Group		Right F vs. Control	Left F vs. Control	Right F vs. Left F
	Abs. (sd)	% (sd)	Abs. (sd)	% (sd)	Abs. (sd)	% (sd)			
Milliseconds Temporal Discrimination Task									
JND – Short Interval (350 ms)	90.8 (14.6)	25.9% (4.2)	81.9 (18.5)	23.4% (5.3)	52.4 (10.7)	15.0% (3.0)	*		
JND – Long Interval (1350 ms)	275.3 (40.5)	20.4% (3.0)	193.9 (51.3)	14.4% (3.8)	157.3 (29.6)	11.6% (2.2)	*		
PSE – Short Interval (350 ms)	375.5 (13.2)	107.3% (3.8)	341.4 (16.8)	97.5% (4.8)	342.3 (9.7)	97.8% (2.8)	*		
PSE – Long Interval (1350 ms)	1201.2 (3.0)	89.0% (4.2)	1320.3 (71.3)	97.8% (5.3)	1249.4 (41.1)	92.5% (3.0)			
Temporal Order Judgment Task									
JND	52.6 (6.9)		41.9 (9.8)		28.8 (5.1)		**		
PSE	45.3 (15.1)		-14.9 (21.4)		0.3 (11.1)		*		
Minutes Estimation Task									
Milliseconds Discrimination Task									
First Moment	90.2 (88.1)	16.7% (15.2)	-229.8 (124.6)	-37.5% (21.6)	-122.2 (71.9)	-22.6% (12.4)	*		
Second Moment	-77.3 (142.4)	-5.7% (12.5)	-505.6 (201.4)	-41.4% (17.8)	-292.1 (116.3)	-28.3% (10.3)			
Temporal Order Judgement Task									
First Moment	397.1 (119.5)	144.0% (40.1)	18.6 (169.0)	11.2% (56.6)	-5.1 (97.6)	-2.1% (32.7)	**		
Second Moment	445.8 (140.3)	85.1% (26.5)	-33.0 (198.4)	-3.3% (37.5)	-29.5 (114.5)	-5.9% (21.6)	*		
Symbolic Cued Task									
First Moment	290.6 (79.0)	86.3% (23.2)	-107.8 (111.8)	-28.3% (32.8)	32.1 (64.5)	10.3% (18.9)	*		*
Second Moment	388.3 (114.9)	64.3% (19.4)	-51.0 (162.4)	-6.6% (27.4)	47.2 (93.8)	9.0% (15.8)	*		
Rhythm Cued Task									
First Moment	97.1 (135.2)	28.2% (16.6)	-173.2 (181.4)	-28.7% (22.3)	-122.6 (108.4)	-20.2% (13.3)	*		
Second Moment	157.1 (194.8)	19.9% (14.5)	-469.8 (261.4)	-43.5% (19.5)	-213.0 (156.2)	-19.5% (11.6)	*		+

+p<.10; *p<.055 ; ** p<.01 ; *** p<.001

DISCUSSION

This study has provided novel results with neuropsychological patients about the mechanisms involved in implicit timing. The main contribution of this study was the first demonstration that rhythms can compensate the Temporal Orienting deficit in right frontal patients.

Moreover, this study replicated our previous findings in patients (Triviño et al., 2010), showing a deficit in the Temporal Orienting effect (driven by symbolic cues) after right frontal damage. We have also replicated the finding that the Foreperiod effect is deficient after either right or left frontal damage. In contrast, other studies found the Foreperiod effect to be lateralized and only absent after right frontal lesions (Stuss et al., 2005; Vallesi, Mussoni et al., 2007). These conflicting results could be due to the different demands of the tasks, since these studies focused on the Foreperiod effect and the cue had no predictive temporal value. Nevertheless, the involvement of prefrontal structures in the controlled temporal preparation processes has been amply demonstrated in these studies, while the Sequential Effects, more automatic in nature, were preserved (Triviño et al., 2010; Vallesi, Mussoni et al., 2007).

Based on this automatic mechanism preserved after prefrontal damage, a regular rhythm was included in the present study to provide temporal information (fast rhythm-early / slow rhythm-late). A significant improvement was observed on the right frontal group so that patients showed significant Temporal Orienting and Foreperiod effects, which were absent when temporal information was provided by a symbolic cue (short line-early / long line-late). The rhythm seemed to facilitate the use of implicit temporal information to respond at the optimum time. It is important to note that this improvement was selective to the right frontal group. In fact, the control group did not show such improvement and

left frontal patients showed no temporal orienting or foreperiod effects when rhythms were presented. This selectivity thus rules out explanations of the effectiveness of rhythms for temporal preparation in terms of unspecific arousing effects. Rather, the results may suggest a double dissociation related to prefrontal lateralization and automatic vs. controlled temporal preparation.

A possible explanation for these results considers the importance of the left hemisphere in the implicit perception of rhythms necessary for speech processing (Geiser, Zaehle, Jancke, & Meyer, 2008), while right hemisphere is involved in the controlled orientation of attention in space and time (Coull et al., 2000; Hackley et al., 2009). Therefore, a lesion in left prefrontal structures would allow participants to use the temporal information provided by a symbolic cue in order to orient attention in time, but they would be unable to process such information when provided by a rhythm. In contrast, a lesion in right prefrontal structures would prevent participants to use the information from a symbolic cue, but they could use such information when provided by a rhythm. Although these results should be interpreted cautiously due to the smaller sample of the left frontal group, they provide a novel suggestion for a neural model in which automatic temporal preparation is left-lateralized and controlled temporal preparation is right-lateralized. This proposal is in line with the finding of smaller automatic sequential effects in patients with left premotor lesions (Vallesi, Mussoni et al., 2007), and may be tested with TMS methodology in future research.

Focusing on the results obtained in the right frontal group, one possible explanation is that patients have a specific deficit in the controlled temporal preparation processes, so that the introduction of an automatic temporal cue allows them to use temporal information appropriately. In fact, rhythms have been associated with improved time estimation ability

and pitch perception (Barnes & Jones, 2000; Large & Jones, 1999; McAuley & Jones, 2003) and faster response on detection tasks (Sanabria et al., 2011).

Another explanation could be that right frontal patients suffer a more basic deficit in time estimation using distorted temporal information. Our right frontal patients clearly presented an overestimation in the range of milliseconds and minutes, showing that they perceived time as passing quickly. Therefore, in this case, patients might be prepared to wrong moments in time according to the overestimation they showed, leading them to respond prematurely.

Otherwise, left frontal patients showed no significant differences compared to control group in their ability to estimate time; nevertheless they showed a significant impairment of the Temporal Orienting effect in the Rhythm Cued task, and a deficit in the Foreperiod effect in both tasks, which would support the independence between the two timing functions.

More research is needed in this area. If temporal overestimation is the core deficit in right frontal patients, we would expect these patients to prepare in time, but in an anticipatory way. Future studies with electroencephalography (EEG) could clarify as the CNV (Contingent Negative Variation) has been associated with the anticipatory responses. Thus, if the core deficit is the overestimation but patients show the ability to prepare temporarily, the CNV should be advanced in time. While if the core deficit lies in temporal preparation processes and the implicit use of temporal information, maybe the CNV should be attenuated or altered as it has been observed in Parkinson Disease (Praamstra & Pope, 2007).

In conclusion, this study provides evidence on how the introduction of rhythms improves the ability of right frontal patients to orient themselves in time. Future research will reveal whether our proposal of a neural model of dissociated implicit timing, with automatic temporal preparation lateralized at left frontal cortex and controlled temporal preparation lateralized at right frontal cortex, is supported by new data.

Regarding the practical implications of the study, on the one hand, the replication of previous results with a brief task (less than 10 minutes) could have clinical assessment purposes. On the other hand, the improvement on temporal preparation with rhythms could have rehabilitation purposes. If right frontal lesion patients can orient in time after temporal rhythms, they could be trained to use rhythmic patterns to predict the occurrence of temporal events.

APPENDIX A. Temporal estimation tasks

METHOD

MILLISECONDS DURATION DISCRIMINATION TASK

Stimuli and Procedure

Participants were seated about 60 cm from the computer screen. They were to estimate whether a comparison interval was longer or shorter than a standard interval. Therefore, each trial included a fixation point, a standard interval and a comparison interval. The stimuli were presented at the centre of the screen over a black background. The fixation point consisted of a dark gray square (0.03º x 0.03º of visual angle at a viewing distance of 60 cm). The duration of a red '@' symbol (2.20º x 2.20º) was used as the standard interval, while the duration of a white '@' symbol was used as the comparison interval. The up- and down-arrow keys on the keyboard were used to indicate whether the comparison interval was longer or shorter than the standard interval, respectively. All participants were instructed to keep their gaze on the centre of the screen, just where the fixation point appeared, as well as to respond as accurately as possible without time limit. Each trial began with the fixation point presented for a random interval ranging between 500 and 1000 ms. Next, the standard interval (red '@') was presented for a short (350 ms) or a long (1350 ms) duration, followed by the fixation point (again shown between 500 and 1000 ms). After this, the comparison interval appeared for a duration that could be either 5%, 15%, 25% or 50% above or below the duration of the standard interval. Thus, for the short-standard interval (350 ms) condition, the comparison interval on each trial could be either 175, 263, 298, 333, 368, 403, 438 or 525 ms. In the long-standard interval (1350 ms) condition, the comparison interval were 675, 1013, 1148, 1283, 1418, 1553, 1688 and 2025 ms. Finally, the

screen remained blank until the participant made a response without time limit. The next trial only began when the participant responded.

The task included 4 experimental blocks, 2 with the short-standard interval and 2 with the long-standard interval. Blocks of short and long intervals were presented in alternating runs, and the order of presentation was counterbalanced across participants. Each experimental block included 6 trials for each comparison interval, leading to 48 trials in total. The different durations were presented randomly within the block.

Design and Analyses of Behavioural Results

Data from this task were plotted as the proportion of 'long' responses as a function of target durations (see Figure A.1). In order to compute the just noticeable difference (JND) and the point of subjective equality (PSE), data from each participant were transformed to Z scores, and the Z score distributions were fitted to linear regressions (Finney, 1964). The slopes and intercept point of such linear trends were used to compute the JNDs and PSEs for each participant for both short and long standard durations. Large values of JND means poor temporal discrimination. In the case of PSE, positive values meant overstimation of the comparison interval and negative values meant understimation of the comparison interval. Four participants showed negative JNDs. Two of them showed a correct JND but in a reversed pattern (i.e., they used the keys in the opposite way), so the scores were corrected and included in the analyses. The other two participants (from the right frontal group) were excluded from the subsequent analyses because they showed a poor temporal resolution (i.e., their JNDs fell outside the range of foreperiods tested in the study). Therefore, the sample for this task consisted of 8 right frontal patients, 5 left frontal patients and 15 control subjects.

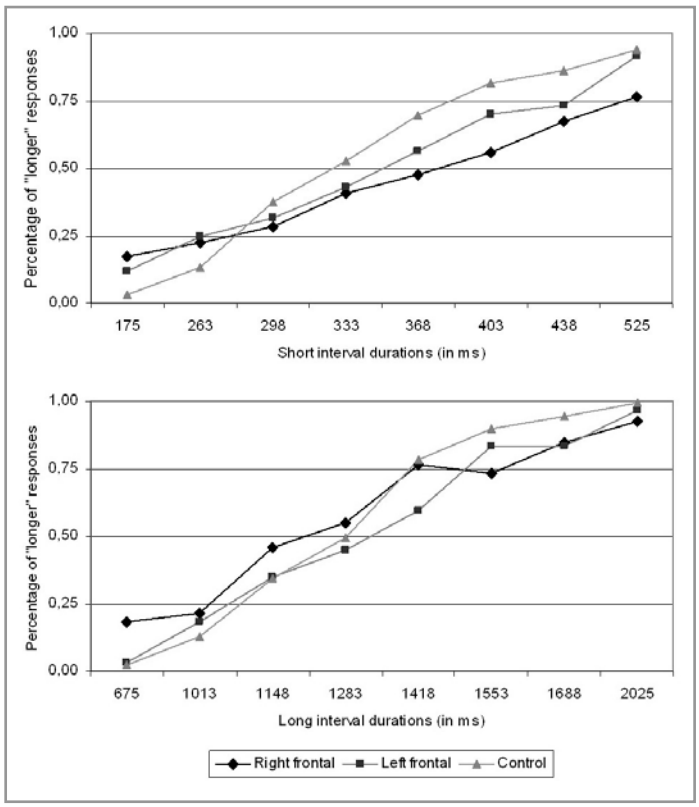


Figure A.1 Mean proportion of 'longer' responses as a function of duration intervals for right frontal (diamonds), left frontal (squares) and control (triangles) groups. **Top.** Short duration interval (350 ms). **Bottom.** Long duration interval (1350 ms). Note that the psychometric function showed a softer slope for the right frontal group, which means poorer temporal discrimination.

In order to perform the full analysis combining short and long standard durations, absolute JND and PSE scores were transformed to percentages relative to the duration of each standard. With percentages scores, PSE means overstimation of the comparison interval when the score is higher than 100% and understimation of the comparison interval when it is lower than 100%. JNDs and PSEs scores were submitted to a 3 (Group: Right frontal, Left frontal, Control) x 2 (Standard duration: short vs. long) mixed analyses of variance (ANOVA) with the first variable as a between participants factor and the other as a within participants variable.

TEMPORAL ORDER JUDGMENT TASK

Stimuli and Procedure

In this task, the participants were to indicate at which side, left or right, a stimulus appeared first. The fixation point consisted of a dark gray cross (0.04º x 0.04º of visual angle at a

viewing distance of 60 cm) presented at the centre of the screen, as well as two empty dark gray squares (2.10º x 2.10º) placed on the left and right of the fixation point (6.58º from fixation point to the internal border of each square). Two red rings ('O') appeared on the screen (1.05º x 1.05º), one in the middle of the left square and the other in the middle of the right square. The 'Z' and 'M' keys on the keyboard were used to indicate that the left or right ring appeared first, respectively. All the participants were instructed to keep their gaze on the centre of the screen, as well as to respond accurately and without time limit. Each trial began with the fixation point presented for a random interval ranging between 500 and 1000 ms. Next, one of the rings appeared either at left or right side of the fixation point, and after a variable interval of 17, 34, 50 or 100 ms, the other ring appeared on the other side. The two rings remained on the screen until the participant made a response. The next trial started after the participant's response.

The task included 4 experimental blocks with 48 trials each. Each block was divided into 24 trials (6 for each interstimuli interval) where the ring on the left appeared first and 24 trials where the ring on the right was first, presented in random order.

Design and Analyses of Behavioural Results

Data from this task are also plotted as S-shaped curve, in which the proportion of 'right first' responses is plotted as a function of target durations. A conversion to Z scores were performed in order to obtain a linear regression. The JND and PSE were calculated for each participant. In this task, three participants (two from the right frontal group and one from the left frontal group) were excluded due to a poor temporal resolution (i.e., their JNDs fell outside the range of foreperiods tested in the study). Therefore, the sample consisted of 8 right frontal patients, 4 left frontal patients and 15 control subjects. Positive PSE values meant a right side bias (i.e., a tendency to respond "right first") and negative

PSE values meant a left side bias. The groups were compared using a single-factor ANOVA for JND scores (PSE scores were not analyzed because they were not informative about the participants' timing performance), with the Group (Right frontal, Left frontal, Control) as between participants factor.

MINUTES ESTIMATION TASK

Procedure

At the beginning of each task, participants were informed that at certain times of the experiment they would be asked to estimate the time elapsed since the exact moment they were reading the instructions. They were instructed to keep track of time just with their "internal clock", and therefore they took off watches and mobile phones. Subjects had to estimate the passage of time twice (at the middle and at the end of the task) since the estimation was performed every two blocks of trials. A message appeared on the screen which asked participants to estimate the minutes since the beginning of the task and to type the number using the number keypad. After confirming their answers, participants could make a break before continuing with the task.

Design and Analyses of Behavioural Results

Each response made in the range of minutes was transformed to the range of seconds. That score was subtracted from the actual time elapsed since the beginning to the two estimation moments (at the middle and at the end of the task), thereby obtaining a temporal estimation bias for each moment in each task. A positive temporal bias meant overestimation of time and negative temporal bias meant underestimation of time. Since the duration of each task was different, the absolute scores were converted to percentages. A 3 (Group: Right frontal, Left frontal, Control) x 2 (Estimation moment: first vs. second)

mixed analyses of variance (ANOVA) for each temporal task was performed, with the first variable as a between participants factor and the other as a within participants variable.

RESULTS

MILLISECONDS DURATION DISCRIMINATION TASK

Percentages punctuations were analyzed for both the Just Noticeable Difference (JND) and the Point of Subjective Equality (PSE) scores. These data are shown in Table A.1 (as well as in Table 5 of the main text).

Table A.1 Absolute (Abs.) and percentage (%) punctuations of Just Noticeable Difference (JND) and Point of Subjective Equality (PSE) for both Milliseconds Temporal Discrimination Task (left) and Temporal Order Judgment Task (right). In milliseconds discrimination task, the punctuations are broken down by Interval (short vs. long).

	Milliseconds Temporal Discrimination Task								**Temporal Order Task**	
	Short Interval-350				**Long Interval-1350**					
	JND Abs.	**JND %**	**PSE Abs.**	**PSE %**	**JND Abs.**	**JND %**	**PSE Abs.**	**PSE %**	**JND Abs.**	**PSE Abs.**
Right Frontal	90.8	25.9%	375.5	107.3%	275.3	20.4%	1201.2	89.0%	52.6	45.3
Left Frontal	81.9	23.4%	341.4	97.5%	193.9	14.4%	1320.3	97.8%	41.9	-14.9
Control	52.4	15.0%	342.3	97.8%	157.3	11.6%	1249.4	92.5%	28.8	0.3

In the JND analysis, a main effect of group was observed, $F(2,25)=3.48$, $p=0.046$, $\mu p^2 =0.21$, with a highest JND in the right frontal group (23.2%) followed by the left frontal group (18.9%) and controls (13.3%). Planned comparisons revealed significant differences between right frontal and control groups ($F(1,25)=6.72$, $p=.015$), but not between left frontal and controls ($F(1,25)=1.54$, $p=.225$). There was a main effect of the Standard duration, $F(1,25)=6.70$, $p=0.015$, $\mu p^2 =0.21$, showing a worse temporal judgment in the short duration (21.4%) than in the long duration (15.5%). The interaction between Group and Standard duration was not significant, $F<1$.

In the PSE analysis, there was no main effect of Group, $F<1$. A main effect of Standard duration was observed, $F(1,25)=8.18$, $p=0.008$, $\mu p^2 =0.25$, showing overestimation temporal bias in the short duration (100.9%), while subestimation in the long duration (93.1%). The interaction between Group and Standard duration was significant, $F(2,25)=3.84$, $p=0.035$, $\mu p^2 =0.23$. In planned comparisons, marginally significant differences were observed between right frontal and control groups only in the short standard duration, $F(1,25)=4.08$, $p=0.054$, but not in the long duration, $F<1$. There were no differences between left frontal and controls in none of the durations, both $Fs<1$. See Figure A.2.

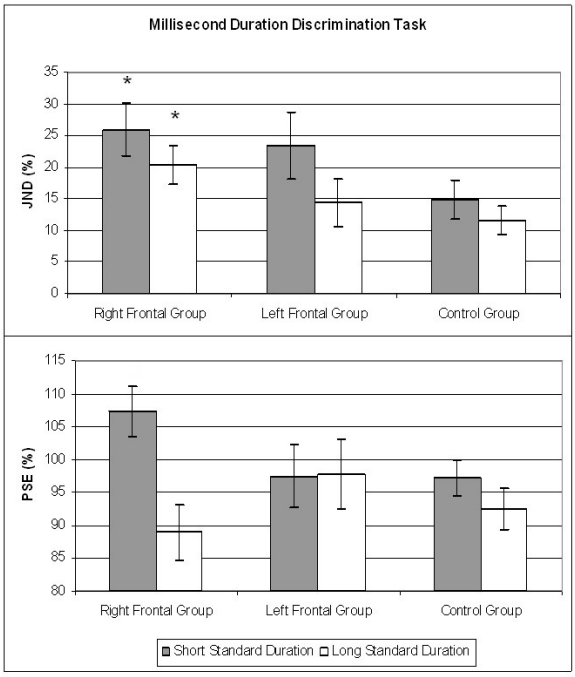


Figure A.2 Millisecond Duration Discrimination task. Percentage of JND (*top*) and PSE (bottom) scores as a function of group (right frontal, left frontal and control groups) for the short standard duration (grey bars) and the long standard duration (white bars). Error bars represent the standard error of the mean. Asterisks mean significant effect.

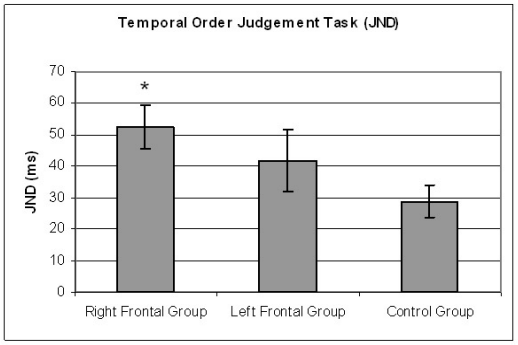


Figure A.3 Temporal Order Judgement task. Absolute JND score as a function of group (right frontal, left frontal and control groups) for the short standard duration (grey bars) and the long standard duration (white bars). Error bars represent the standard error of the mean. Asterisks mean significant effect

TEMPORAL ORDER JUDGMENT TASK

Absolute JND scores were analyzed. These data are presented in Tabla A.1 (and Table 5 of the main text). A main effect of group was observed, $F(2,24)=3.92$, $p=0.033$, $\mu p^2 =0.24$, with the highest JND in right frontal group (52 ms) followed by the left frontal group (42 ms) and controls (29 ms). Planned comparisons showed significant differences only between right frontal and control groups, $F(1,24)=7.64$, $p=0.010$, but not between left frontal group and controls, $F(1,24)=1.41$, $p=0.247$. See Figure A.3.

MINUTES RETROSPECTIVE ESTIMATION TASK

Percentage punctuations of temporal estimation bias are represented in Table A.2 (and Table 5 of main text) and were analyzed for each task.

Table A.2 Absolute and percentage (%) punctuations of Retrospective Estimation in Minutes per each Time Estimation and Temporal Preparation tasks, broken down by Moment of estimation (first vs. second).

		Minutes Retrospective Estimation Task							
		Time Estimation Tasks				**Temporal Preparation Tasks**			
		Millisecond Temporal Discrimination		**Temporal Order Judgement Task**		**Symbolic Cue Task**		**Rhythm Cue Task**	
		First moment	**Second moment**	**First moment**	**Second moment**	**First moment**	**Second moment**	**First moment**	**Second moment**
Right Frontal	Absolute (%)	90.2 (16.7%)	-77.3 (-5.7%)	397.1 (144.0%)	445.8 (85.1%)	290.6 (86.3%)	388.3 (64.3%)	97.1 (28.2%)	157.1 (19.9%)
Left Frontal	Absolute (%)	-229.8 (-37.5%)	-505.6 (-41.4%)	18.6 (11.2%)	-33.0 (-3.3%)	-107.8 (-28.3%)	-51.0 (-6.6%)	-173.2 (-28.7%)	-469.8 (-43.5%)
Control	Absolute (%)	-122.2 (-22.6%)	-292.1 (-28.3%)	-5.1 (-2.1%)	-29.5 (-5.9%)	32.1 (10.3%)	47.2 (9.0%)	-122.6 (-20.2%)	-213.0 (-19.5%)

Regarding the **Milliseconds Discrimination Task**, a main effect of Estimation moment was observed, $F(1,27)=7.97$, $p=0.008$, $\mu p^2 =0.23$, showing a larger temporal bias in the second moment (-25.2%) than in the first moment (-14.5%). The interaction between Group and Estimation moment almost approached significance, $F(2,27)=2.80$, $p=0.078$, $\mu p^2 =0.17$. When the right frontal group was compared to controls, there were marginally significant differences at First moment of estimation, $F(1,27)=3.97$, $p=0.055$ (i.e.,

overestimation). There were not differences between left frontal and control groups in none of the moments, both $F<1$. See Figure A.4.

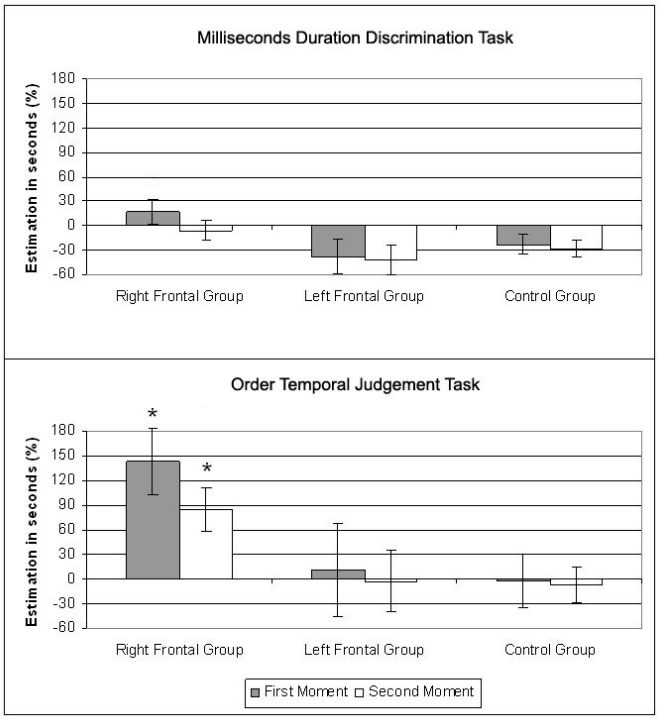


Figure A.4 Minutes Retrospective Estimation Task for explicit timing tasks, i.e. Milliseconds Duration Discrimination Task (*top*) and Order Temporal Judgement Task (*bottom*). Percentage of estimation bias as a function of group (right frontal, left frontal and control groups) for the first moment (grey bars) and the second moment of estimation (white bars). Error bars represent the standard error of the mean. Asterisks mean significant effect.

In the **Temporal Order Task** a main effect of Group was observed, $F(2,27)=4.14$, $p=0.027$, $\mu p^2 =0.23$, with a larger temporal bias in the Right frontal group (114.6%) compared to both left frontal (3.9%) and control (-3.9%) groups. There was a main effect of Estimation moment, $F(1,27)=7.12$, $p=0.012$, $\mu p^2 =0.21$, with larger overestimation at the First moment (51.1%) compared to the Second (25.3%). Finally, in this task there was a significant interaction between Group and Estimation moment, $F(2,27)=4.11$, $p=0.027$, $\mu p^2 =0.23$. Planned comparisons showed the right frontal group showed significant differences with controls in both the first and second estimation moment, $F(1,27)=7.98$, $p=0.008$ and $F(1,27)=7.06$, $p=0.013$, respectively. Specifically, right frontal patients overestimated at both the first (144%) and the second (85.1%) moment, while the control group showed a

negligible underestimation at both the first (-2.1%) and second (-5.9%) moments. Left frontal group did not show any difference with controls, both $F<1$. See Figure A.4.

Regarding the **Symbolic Cued Task**, there was a main effect of Group, $F(2,27)=4.37$, $p=0.022$, $\mu p^2 =0.24$, with an overestimation bias in the Right frontal group (75.3%) followed by control (9.7%) and left frontal (-17.5%) groups. The main effect of Estimation moment was not significant, $F<1$, although tended to depend of Group, $F(2,27)=3.25$, $p=0.054$, $\mu p^2 =0.19$. Planned comparisons showed that differences between the right frontal group and controls were significant in both the first and second estimation moment, $F(1,27)=6.45$, $p=0.017$ and $F(1,27)=4.88$, $p=0.035$, respectively; however left frontal group did not differ with respect to controls, both $ps>0.300$. See Figure A.5.

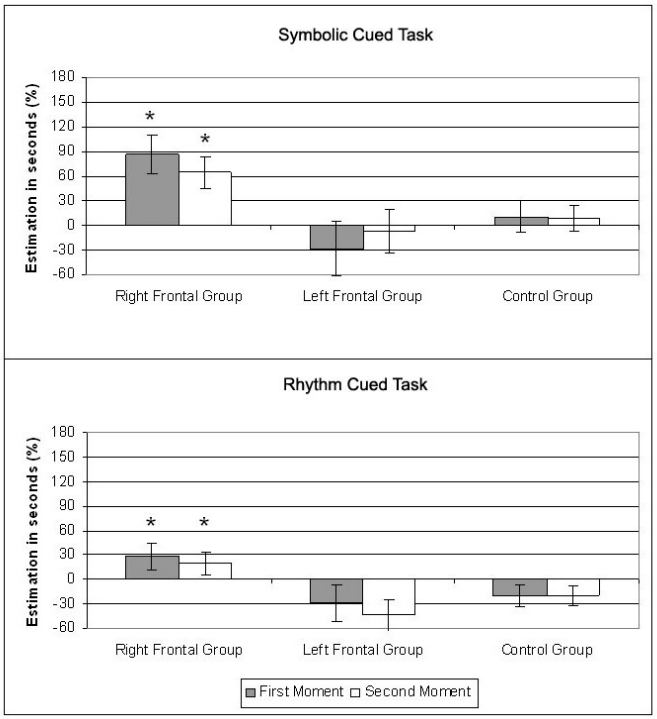
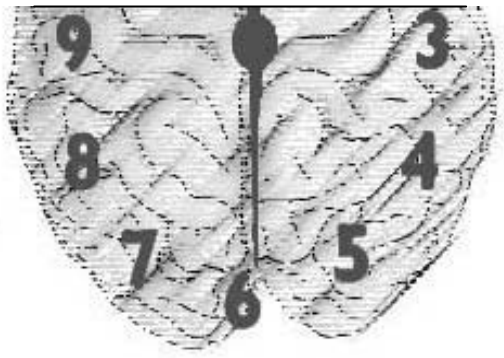


Figure A.5. Minutes Retrospective Estimation Task for implicit timing tasks, i.e. Symbolic (*top*) and Rhythm Cued Tasks (*bottom*). Percentage of estimation bias as a function of group (right frontal, left frontal and control groups) for the first moment (grey bars) and the second moment of estimation (white bars). Error bars represent the standard error of the mean. Asterisks mean significant effect.

Finally, in the **Rhythm Cued Task**, there was a main effect of Group, $F(2,25)=3.63$, $p=0.041$, $\mu p^2 =0.22$. Again the right frontal group showed an overestimation bias (24.0%) compared to the underestimation bias in both left frontal (-36.1%) and control (-19.9%) groups. Neither the main effect of Estimation moment nor the interaction between Group and Estimation moment were significant, $F(1,25)=3.00$, $p=0.095$, $\mu p^2 =0.10$ and $F(2,25)=1.16$, $p=0.327$, $\mu p^2 =0.085$. Planned comparisons showed significant differences between right frontal and control groups in both estimation moments, $F(1,25)=5.15$, $p=0.032$ and $F(1,25)=4.49$, $p=0.044$, respectively; left frontal group did not show any difference compared to controls in any estimation moments, $ps>0.300$. See Figure A.5.

DISCUSIÓN GENERAL



CAPÍTULO 7

DISCUSIÓN GENERAL

El objetivo fundamental de esta investigación ha sido estudiar las bases neurales de los procesos de preparación temporal y, más concretamente, profundizar en la distinción entre los procesos de preparación controlados frente a los automáticos, mediante estudios neuropsicológicos con pacientes con daño cerebral.

La preparación temporal conlleva y está intimamente relacionada con los procesos de estimación temporal. Una revisión de la literatura sobre la percepción del tiempo constata la complejidad de este concepto, que ha llevado a múltiples modelos y clasificaciones sobre el *procesamiento temporal*, conocido en este ámbito como *timing*. En concreto, dentro de la literatura sobre procesamiento temporal destacan, por un lado, los estudios sobre *percepción del tiempo*, donde se utilizan tareas en las que los sujetos deben estimar la duración de un intervalo o discriminar entre la duración de dos estímulos (*timing perceptivo*) o producir o reproducir intervalos (*timing motor*). Y por otro lado, los estudios sobre *preparación temporal* donde los sujetos deben utilizar la información temporal proporcionada para la consecución de la tarea. En las tareas de preparación temporal la información temporal disponible puede ser utilizada de forma *automática* o *controlada*. Dentro de la preparación temporal automática se enmarcan los *efectos secuenciales*, mientras que dentro de la preparación temporal controlada se enmarcan el *efecto de orientación temporal* y el *efecto de foreperiod*.

Estos efectos, descritos a lo largo de la tesis, parecen formar parte de un mecanismo dual de preparación temporal, flexible y estratégico, que permite a los sujetos preparar sus respuestas de forma más controlada o más automática en función de la información

temporal proporcionada por el ambiente (Correa, Lupiáñez, & Tudela, 2006). Según Los y colaboradores (2001), los individuos utilizan estrategias controladas cuando el ambiente es predecible, pero se dejan guiar por procesos más automáticos cuando el ambiente es poco predecible o impredecible. Un estudio con pacientes con daño cerebral nos puede ayudar a descubrir los mecanismos neurales de la preparación temporal y, a su vez, comprender los procesos cognitivos y/o emocionales que hay a la base de los déficit que presentan los pacientes con daño cerebral, lo cual va a repercutir en una mejora del diagnóstico y la rehabilitación. Tal y como se ha planteado en los capítulos 3 y 4, los pocos estudios neuropsicológicos realizados en este ámbito se han centrado en el efecto de foreperiod y los efectos secuenciales, mientras que las bases neurales del efecto de orientación temporal se han explorado principalmente con estudios de neuroimagen funcional. Sin embargo, no hay ningún estudio con pacientes que explore las bases neurales del efecto de orientación temporal ni sus relaciones con los otros dos efectos. En los capítulos 5 y 6 se presentan las investigaciones realizados en la presente tesis con el objeto de contrastar las hipótesis planteadas.

En la primera investigación, presentada en el capítulo 5, estudiamos las bases neurales de los procesos de preparación temporal, centrándonos en el efecto de orientación temporal puesto que, como ya hemos mencionado, no había sido estudiado en pacientes hasta el momento. Las investigaciones que se habían realizado con neuroimagen funcional apuntaban a la posible implicación de circuitos frontobasales en el procesamiento de esta variable. Por ello, seleccionamos un grupo de pacientes con lesión prefrontal, así como un grupo de pacientes con lesión focal y unilateral en los ganglios de la base, a los que sometimos a tareas de orientación temporal y comparamos con un grupo control. Los resultados de este primer estudio mostraron, por primera vez en pacientes, una afectación del efecto de orientación temporal sólo en el grupo con lesión prefrontal derecha. Sin

embargo, el efecto de foreperiod se encontraba alterado en todos los pacientes frontales, independientemente del hemisferio dañado, mientras que en ambos grupos los efectos secuenciales quedaron preservados. A diferencia de los pacientes prefrontales, el grupo con lesión en ganglios basales no mostró afectación en ninguno de los procesos estudiados.

En la segunda investigación, presentada en el capítulo 6, pretendíamos profundizar en el estudio de la relación entre los procesos de preparación temporal automática y controlada, así como entre los procesos de percepción del tiempo y de preparación temporal. En concreto y basándonos en los procesos de preparación automáticos que quedan preservados tras daño prefrontal (i.e. efectos secuenciales), pretendíamos comprobar si la inclusión de ritmos podría facilitar la preparación temporal en los pacientes frontales.
Por un lado, los resultados mostraron una réplica del estudio previo cuando se utilizó una señal simbólica, encontrando un déficit en el efecto de orientación temporal sólo en pacientes con lesión frontal derecha, mientras que el efecto de foreperiod quedó alterado de nuevo tras daño frontal derecho o izquierdo. Por otro lado, la introducción de ritmos facilitó la preparación temporal en el grupo frontal derecho que mostró ambos efectos (i.e. orientación temporal y foreperiod) a pesar de tener un déficit en las tareas de estimación temporal (i.e. sobrestimación). Sin embargo, el grupo de pacientes con lesión frontal izquierda, mostró un empeoramiento en el efecto de orientación temporal, en ausencia de déficit en las tareas de estimación temporal.

En resumen, los resultados de estas dos investigaciones implican a la región prefrontal en el procesamiento del tiempo, y muestran un patrón de lateralización hemisférica diferenciado de acuerdo a los procesos explorados. Así, el lóbulo prefrontal no parece participar en procesos más automáticos, como los mediados por efectos secuenciales, y sí en procesos de naturaleza controlada, como los de foreperiod o los de orientación temporal. En este

último caso parece haber una mayor implicación de la región prefrontal derecha. La presentación de señales rítmicas mejora la ejecución de los pacientes prefrontales derechos en tareas de preparación temporal, pero los prefrontales izquierdo no sólo no consiguen mejoría, sino que empeoran el rendimiento en este tipo de tareas, a pesar de que estos últimos pacientes muestran mejores resultados en juicios de estimación temporal.

Para discutir estos resultados dentro de la literatura que existe sobre el tema de procesamiento temporal, vamos a incluir varios apartados que parten del resultado más concreto –la base neural del efecto de orientación temporal – para ir adquiriendo un mayor nivel de abstracción. Por tanto, la estructura básica de estas conclusiones finales es la siguiente: (1) bases neurales de la orientación temporal, (2) preparación temporal controlada: orientación temporal y foreperiod, (3) preparación temporal controlada vs. automática y, por último, (4) percepción del tiempo y preparación temporal, para finalizar con una reflexión sobre el procesamiento temporal, sus bases neurales y sus funciones.

Bases neurales de la orientación temporal

Los estudios previos con neuroimagen funcional apuntaban a una implicación de estructuras frontales y parietales con una mayor lateralización izquierda (Coull et al., 2000; Coull & Nobre, 1998; Coull et al., 2004). Estas autoras sugieren la existencia de una red fronto-parietal izquierda encargada de la orientación de la atención en el tiempo, análoga a la red fronto-parietal derecha implicada en la orientación de la atención en el espacio. Sin embargo, nuestros estudios muestran una clara afectación del efecto de orientación temporal tras daño prefrontal derecho, quedando preservado el efecto tras lesión prefrontal izquierda. Una posible explicación a esta diferencia entre los resultados con neuroimagen funcional y pacientes puede ser debida a las características de las tareas utilizadas, ya que en nuestros estudios la expectativa temporal se manipulaba entre bloques mientras que en los

estudios de Coull y colaboradores (2000; 1998; 2004) se manipulaba intra-bloques. El hecho de que la expectativa vaya variando de un ensayo a otro, puede estar incrementando la demanda cognitiva necesaria para actualizar la información temporal (*updating*) proporcionada por la señal en cada ensayo (Konishi et al., 2008). La capacidad de actualizar información ha sido enmarcada dentro de las funciones del ejecutivo central de la memoria de trabajo (Baddeley, 1986). Esa capacidad de actualización ha sido relacionada con una mayor activación de estructuras prefrontales y parietales izquierdas en estudios de neuroimagen funcional (Collette & Van der Linden, 2002). Cuando la señal presentada varía ensayo a ensayo, se observa una activación del surco intraparietal izquierdo y de los giros frontales medio e inferior izquierdos, que no aparece cuando la información se mantiene igual dentro del mismo bloque (Pessoa, Rossi, Japee, Desimone, & Ungerleider, 2009).

Una segunda explicación puede deberse a otra de las características de las tareas, ya que en los estudios de Coull y cols. (2000; 1998; 2004) no hay *catch trials* (ensayos sin estímulo) mientras que en nuestros estudios había una condición de no respuesta, bien por la presencia de *catch trials*, bien por la presencia de ensayos *nogo*. El hecho de que en todos los ensayos se deba producir una respuesta, lleva a los sujetos a prepararse en el intervalo largo en todas las ocasiones: se preparan cuando la señal es válida y también se preparan cuando la señal es inválida, puesto que si no ha aparecido en el intervalo corto, saben que el estímulo aparecerá en el largo. Esta condición experimental puede hacer que la tarea, en el intervalo largo, conlleve la preparación motora de la respuesta ante un estímulo externo, lo cual activaría regiones fronto-parietales izquierdas relacionadas, con mayor probabilidad, con dicha preparación motora (Bueti & Walsh, 2009; Miniussi et al., 1999; Schluter, Krams, Rushworth, & Passingham, 2001).

Como consecuencia, el hecho de que la manipulación entrebloques reduzca la exigencia cognitiva de actualizar la información temporal ensayo a ensayo, y que la presencia de una condición de no respuesta (i.e. ensayos *catch trials* y ensayos *nogo*) impida una preparación motora en el intervalo largo, sugiere que el déficit observado en el grupo frontal derecho se debe a una alteración específica en la habilidad para usar de forma controlada la expectativa temporal proporcionada. Esto nos llevaría a considerar la existencia de una red fronto-parietal derecha implicada en la orientación de la atención (Corbetta & Shulman, 2002) tanto en la dimensión espacial como temporal (Coull et al., 2000; Hackley et al., 2009).

Preparación temporal controlada: Orientación Temporal y Foreperiod

Con el objetivo de profundizar en la comprensión de los procesos de preparación temporal controlada hemos estudiado la relación entre el efecto de orientación temporal y el efecto de foreperiod ya que, hasta el momento, sólo había estudios comportamentales (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006) y un estudio electrofisiológico que mostraba la relación entre ambos (Correa & Nobre, 2008). Por tanto, mediante la presente investigación se ha realizado el primer estudio neuropsicológico con pacientes acerca de la relación entre los dos efectos.

Desde el punto de vista teórico, han sido definidos como el resultado de dos estrategias distintas: el efecto de orientación temporal consistiría en una preparación de la respuesta como resultado de una expectativa temporal que es proporcionada explícitamente por una señal (Coull & Nobre, 1998); mientras que el efecto de foreperiod sería el resultado de preparar la respuesta conforme pasa el tiempo en función de un cálculo de probabilidades (Karlin, 1959). Sin embargo, cuando se utiliza un paradigma de costes y beneficios para el estudio de ambos efectos simultáneamente, encontramos que se encuentran relacionados y

se modulan mutuamente (Correa & Nobre, 2008). De hecho, cuando la señal es válida no se observa efecto de foreperiod, ya que los sujetos se preparan en función de la expectativa temporal y son igualmente rápidos en el intervalo corto que en el largo. Y cuando los ensayos son inválidos se observa claramente el efecto. Por otro lado, cuando se introducen *catch trials* (ensayos sin estímulo), el efecto de foreperiod no se observa tampoco en los ensayos inválidos, ya que se produce una despreparación general de los sujetos en el intervalo largo. Incluso en un paradigma donde no se introduzca una señal predictiva (véase Karlin, 1959; Niemi & Näätänen, 1981; Stuss et al., 2005; Vallesi, Mussoni et al., 2007; Vallesi, Shallice et al., 2007), el efecto de foreperiod podría ser considerado como una mejor respuesta conforme el tiempo pasa gracias a un cálculo de probabilidades que, justamente, es debido a un incremento de la expectativa de ocurrencia del estímulo análogo al efecto de orientación temporal. Por tanto, ¿son estos efectos el resultado de mecanismos de preparación temporal diferentes o son el mismo mecanismo modulado por las características de las tareas?

De nuevo nuestros estudios aportan resultados con pacientes acerca de la existencia de una base neural compartida pero con ciertas diferencias. En concreto, en los dos estudios hemos observado un déficit del efecto de foreperiod tras daño prefrontal derecho o izquierdo, mientras que el efecto de orientación temporal queda afectado sólo tras daño prefrontal derecho. El carácter controlado y endógeno de ambos efectos concuerda con una participación de estructuras prefrontales relacionadas con procesos de control ejecutivo y procesamiento top-down (Funahashi, 2001; Gazzaley & D'Esposito, 2007). Sin embargo, el hecho de que el daño prefrontal izquierdo no altere el efecto de orientación temporal indica una base neural diferenciada. Además, el que esta disociación haya sido replicada en los dos estudios, con diferentes tareas y con diferentes pacientes, nos lleva a pensar que no se trata de un efecto espurio, sino de una disociación potencialmente

relevante que merece cierta atención. ¿En qué consisten, por tanto, las diferencias entre ambos efectos? No podemos olvidar que el efecto de orientación temporal se analiza principalmente en el intervalo corto (comparando ensayos válidos e inválidos), sin tener en cuenta el paso del tiempo y como respuesta estratégica en un momento temporal concreto. El efecto de foreperiod, por su parte, se analiza comparando las respuestas dadas en el intervalo corto vs. largo con una total certidumbre de aparición del estímulo (nótese que el índice está calculado en los ensayos sin *catch trials* y en los ensayos *go* donde se previene la preparación motora, pero no la preparación temporal), por lo que se introducen irremediablemente variables cognitivas que permiten monitorizar ese paso del tiempo. Sin embargo, debemos tener en cuenta también que en un paradigma de costes y beneficios, como el utilizado en nuestros estudios, el efecto de foreperiod tiene un componente de repreparación en el intervalo largo debido a que el efecto se calcula en la condición de ensayos inválidos. Es decir, no es sólo el paso del tiempo el que lleva a los sujetos a prepararse al intervalo largo, sino que tras un intervalo corto inválido (donde la expectativa temporal no se ha cumplido), los sujetos deben reorientarse de forma controlada al intervalo largo. De hecho, cuando se introducen *catch trials*, los sujetos no muestran el efecto de foreperiod debido a que se despreparan. Este doble componente, donde la reorientación estratégica se añade al cómputo del paso del tiempo, parece reclutar estructuras prefrontales, probablemente relacionadas con la habilidad de monitorizar y resolver un conflicto como el que surge cuando una persona se prepara al intervalo corto y su expectativa no se cumple. Por tanto, esta distinción daría cuenta de la localización tanto derecha como izquierda del daño debido a que los procesos de detección y monitorización de conflictos se han asociado a la actividad del cortex cingulado anterior, pero también al cortex prefrontal dorsolateral izquierdo (Egner & Hirsch, 2005; Mansouri, Tanaka, & Buckley, 2009; Wittfotha, Schardtb, Fahlea, & Herrmanna, 2009).

Este doble componente, sin embargo, no está presente en estudios previos donde el efecto de foreperiod se ha asociado exclusivamente al daño prefrontal derecho (Stuss et al., 2005; Vallesi, Mussoni et al., 2007). En estos estudios la señal no es predictiva, por lo que el efecto de foreperiod se basa sólo en el cómputo del paso del tiempo. Esto explicaría por qué el efecto de foreperiod en estos estudios se encuentra afectados sólo tras daño prefrontal derecho, ya que al eliminar el proceso de reorientación los sujetos requieren sólo estimar el paso del tiempo, lo cual (como se discutirá más adelante) puede estar relacionado con los déficit en estimación temporal que muestran los pacientes con daño prefrontal derecho.

En conclusión, el efecto de preparación temporal y el efecto de foreperiod muestran diferencias funcionales y estructurales, permitiendo una preparación en el tiempo de forma controlada, estratégica y flexible en función de las demandas de la tarea y del ambiente (Correa, Lupiáñez, & Tudela, 2006). Una forma de ahondar en estos procesos sería diseñando tareas-duales de preparación temporal con carga de memoria de trabajo o con conflicto no temporal (tareas tipo *Simon* o *Stroop*), donde se pueda manipular la carga en memoria de trabajo o el conflicto, mientras los sujetos ejecutan una tarea de preparación temporal. Si el efecto de foreperiod requiere de la capacidad de monitorizar el paso del tiempo mediante el reclutamiento de la memoria de trabajo o requiere de la resolución de un conflicto para llevar a cabo la reorientación, debería observarse un menor efecto conforme se incrementa la carga de la *working memory* y/o al incrementar el conflicto no temporal.

Preparación temporal controlada vs. automática

En un tercer nivel de profundización, los resultados de esta investigación nos permiten también avanzar y profundizar en las bases neurales de la preparación temporal estudiando la relación entre los mecanismos de preparación temporal controlada discutidos previamente (i.e. efectos de orientación temporal y foreperiod) y los mecanismos de preparación temporal automática o *efectos secuenciales*. Estudios previos han demostrado una clara disociación entre los efectos secuenciales y el efecto de orientación temporal (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Los, 1996; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001), así como entre los efectos secuenciales y el efecto de foreperiod (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Vallesi, Mussoni et al., 2007; Vallesi, Shallice et al., 2007). De hecho, estos efectos se han atribuido a un mecanismo de condicionamiento de huella (Los, 1996; Los & Van den Heuvel, 2001) que se ha relacionado con estructuras más antiguas filogenéticamente como el hipocampo (Clark & Squire, 1998) o el cerebelo (Kalmbach et al., 2009). Otra explicación alternativa propone que los efectos secuenciales se deben a un descenso de la alerta general producido por la fatiga que implica la preparación hacia un intervalo largo, de manera que la preparación para un intervalo corto subsiguiente se encuentra en estado refractario (Vallesi & Shallice, 2007; Vallesi, Shallice et al., 2007). Por tanto, esperábamos encontrar los efectos secuenciales preservados en los pacientes frontales, con una clara disociación entre mecanismos controlados y automáticos, en la misma línea de Vallesi y colaboradores (2007) pero, en nuestro caso, realizando un estudio simultáneo de los tres efectos. Partiendo de que la preparación temporal mediante ritmos parece basarse en procesos más automáticos, en nuestro primer estudio consideramos la inclusión de un grupo de pacientes con daño en ganglios de la base para explorar las bases neurales de los procesos automáticos de preparación temporal. Asimismo, en nuestro segundo estudio, consideramos que la

introducción de ritmos permitiría una preparación temporal automática en los pacientes frontales, lo cual será discutido más adelante.

En primer lugar, cabe destacar que la presente investigación es el primer estudio con pacientes que muestra la disociación entre el efecto de orientación temporal y los efectos secuenciales. De este modo, los efectos secuenciales se encuentran preservados tras daño prefrontal, así como tras daño focal y unilateral en los ganglios de la base. El hecho de que no estén dañados tras lesión en los ganglios de la base podría hacernos pensar que esta estructura no es fundamental para la preparación temporal automática. Sin embargo, hemos de ser cautelosos debido a que la muestra de pacientes con lesión en ganglios de la base era pequeña (7 pacientes) pero, sobre todo, debido a que las lesiones eran focales y unilaterales por lo que cabría suponer que el lado contralesional pudiera estar compensando el déficit que el daño en esta estructura podría generar en tareas de preparación temporal. Sería interesante replicar estas investigaciones en pacientes con lesiones bilaterales de los ganglios de la base.

Sin embargo, el resultado más relevante en relación a la disociación entre procesos de preparación temporal controlada vs. automática, fue la mejora en la capacidad de prepararse en el grupo con lesión frontal derecha tras la introducción de ritmos predictivos, en comparación con el déficit mostrado con la señal simbólica. Diversos estudios muestran que los ritmos mejoran la capacidad de estimación y preparación temporal aunque no sean predictivos (Barnes & Jones, 2000; Large & Jones, 1999; McAuley & Jones, 2003). Es decir, el simple hecho de introducir un ritmo, hace que los individuos ajusten su respuesta siguiendo el patrón que el ritmo impone. Además, la disociación entre la preparación automática con ritmos y la preparación controlada con una señal simbólica se ha observado

recientemente en un estudio comportamental (Rohenkohl et al., 2011), por lo que nuestros resultados vienen a reforzar esta hipótesis del mecanismo dual.

Por otro lado, el hecho de que la introducción de un ritmo mejore la preparación temporal en los pacientes con daño frontal derecho, pero lo altere en el grupo frontal izquierdo, aporta nuevos resultados acerca de la lateralización de los procesos automáticos de preparación temporal. De hecho, estos resultados sugieren una doble disociación relacionada con la lateralización prefrontal y la preparación temporal automática vs. controlada. Una posible explicación puede ser la importancia del hemisferio izquierdo en el procesamiento de ritmos tanto visuales como auditivos en el rango de milisegundos (Grahan & McAuley, 2009), mientras que el hemisferio derecho está relacionado con la orientación controlada de la atención en el espacio y el tiempo (Coull et al., 2000; Hackley et al., 2009). Por tanto, una lesión en estructuras prefontales izquierdas permitiría a los sujetos usar la información temporal proporcionada por una señal simbólica para orientar su atención en el tiempo, pero serían incapaces de procesar la misma información si fuera proporcionada por un ritmo, al menos con el uso de ritmos visuales y en el rango de milisegundos. Al contrario, una lesión en estructuras prefrontales derechas impediría a los sujetos el uso de la información proveniente de una señal simbólica, pero podrían utilizar la información proveniente de un ritmo. Aunque estos resultados deben ser interpretados con cautela debido al tamaño del grupo de pacientes con lesión frontal izquierda (5 pacientes), sugieren un modelo neural en el que la preparación temporal automática está lateralizada en el hemisferio izquierdo y la preparación temporal controlada está lateralizada en el hemisferio derecho.

Finalmente, nos preguntamos cómo se produce el ajuste temporal que es capaz de producir un ritmo, el cual ocurre de manera automática y sin necesidad de la corteza frontal derecha.

Es decir, nos planteamos el mecanismo que puede explicar los efectos de los ritmos en la preparación temporal. Jones y colaboradores (Barnes & Jones, 2000; Large & Jones, 1999; McAuley & Jones, 2003) proponen que el elemento clave es el acoplamiento (*entrainment*) entre el ritmo externo y los ritmos internos de la atención. Es decir, un ritmo regular del ambiente es capaz de sincronizar los ritmos atencionales haciéndolos coincidir en periodo y fase. Por tanto, si a continuación aparece un estímulo relevante en el momento de acuerdo al ritmo, éste cae bajo el foco de la atención y su procesamiento resulta facilitado. En esta línea Schroeder y Lakatos (2009) proponen las oscilaciones cerebrales de baja frecuencia (e.g., ritmos delta o alfa) como el mecanismo neural que produce este tipo de acoplamientos del ritmo atencional con un ritmo estimular.

Percepción del tiempo y preparación temporal

Nuestra investigación proporciona resultados con tareas de estimación temporal en el rango de milisegundos que permiten profundizar en la relación entre los procesos de percepción del tiempo y de preparación temporal. Estudios con pacientes muestran que el daño en el cortex prefrontal dorsolateral derecho produce un déficit en estimación temporal en rango de milisegundos, consistente principalmente en una sobrestimación y subproducción temporal (Harrington et al., 1998; Picton et al., 2006; Wittman et al., 2004). Si partimos de la existencia de este tipo de déficit, podemos esperar que pueda influir sobre la preparación temporal. Esto es, si un paciente tiende a sobrestimar el paso del tiempo y cree que un determinado intervalo (e.g. 1000 ms) termina antes (e.g. 800 ms), deberíamos esperar que ese paciente utilice esa información distorsionada en una tarea de preparación temporal. Es decir, la sobrestimación temporal produciría una preparación y una respuesta prematuras. De forma alternativa, podemos pensar que este tipo de distorsión en la percepción del tiempo, no afecte la preparación temporal. De hecho, diversos autores proponen una disociación entre estos componentes del procesamiento temporal. En

concreto, en revisiones con neuroimagen funcional (ver Coull & Nobre, 2008; Lewis & Miall, 2003) se sugiere que las tareas de estimación del tiempo (o como las autoras denominan *timing explícito*) se encuentran asociadas a la activación de circuitos motores (principalmente ganglios de la base y cortex premotor), mientras que las tareas de preparación temporal o el denominado *timing implícito* se asocian a la activación de regiones prefrontales y parietales. Sin embargo, no hay ningún estudio que investigue directamente la relación entre la estimación y la preparación temporal.

Nuestro segundo estudio muestra una sobrestimación en el rango de milisegundos y minutos en el grupo de pacientes con daño frontal derecho. Este resultado concuerda con los datos presentes en la literatura, así como con la posibilidad de que el déficit en orientación temporal y foreperiod que presentan estos pacientes se deba a un déficit más básico en su capacidad de estimación del tiempo. El hecho de que la introducción de los ritmos produzca una mejora en su preparación temporal parece sugerir que estos pacientes se pueden preparar en el tiempo mediante los mecanismos que tienen preservados, a pesar de su déficit en la estimación temporal. De hecho, no debemos olvidar que una tarea de preparación temporal con una señal predictiva simbólica (i.e., línea corta significa *pronto* y línea larga significa *tarde*) está pidiendo a los sujetos, de algún modo, que hagan un uso explícito del tiempo, mientras que los ritmos generan una preparación automática donde los sujetos no necesitan usar explícitamente el tiempo para prepararse *pronto* o *tarde*. En este sentido, podríamos considerar que la distinción realizada por Coull y Nobre (2008) entre procesamiento temporal explícito e implícito en función de las instrucciones dadas a los sujetos, no es la única posible. Cabe la posibilidad de que aunque los sujetos no tengan que hacer una estimación explícita del tiempo en una tarea de preparación, la señal proporcione información explícita acerca de la duración de los intervalos y que los sujetos puedan utilizar esa información para prepararse. En este caso, a pesar de la diferencia en las instrucciones de las tareas, procesos más básicos de estimación temporal explícita podrían

ser necesarios para ambos tipos de tareas. Por tanto, si el déficit que muestran los pacientes con lesión frontal derecha se debe a una imposibilidad para prepararse en el tiempo, la introducción de ritmos les llevaría a computar el tiempo de forma implícita y prepararse de forma automática al intervalo corto mostrando el efecto de orientación temporal. Sin embargo, no mostrarían el efecto de foreperiod, puesto que este efecto sigue requiriendo, no sólo un cómputo del tiempo, sino también de la capacidad de detectar el conflicto (es decir, el incumplimiento de la expectativa temprana) y reorientarse al intervalo largo. Si el déficit en estimación temporal explícita es el que está a la base, se podría esperar que los ritmos faciliten ambos efectos. Es decir, los ritmos producirán un cómputo implícito del tiempo y una preparación automática en el intervalo corto, pero además los sujetos podrán prepararse de forma adecuada y estratégica al intervalo largo. Nuestros resultados aportan evidencia sobre esta segunda propuesta.

Por otro lado, encontramos también que los pacientes con lesión frontal izquierda muestran un déficit en el efecto de foreperiod así como un empeoramiento al introducir los ritmos, en ausencia de un déficit en estimación temporal, lo cual parece sugerir que efectivamente son procesos temporales distintos y disociables. El déficit en el efecto de foreperiod, tal y como se ha discutido previamente, parece estar relacionado con una incapacidad para reorientarse al intervalo largo tras el incumplimiento de la expectativa en el intervalo corto. En este caso, la alteración de procesos de monitorización de conflictos, así como de la memoria de trabajo, podrían estar a la base, en lugar de un déficit en la capacidad de estimación temporal. Si éste fuera el caso, la introducción de ritmos no debería alterar el patrón de respuesta de los pacientes frontales izquierdos. Es decir, ya sea de forma explícita o implícita, estos pacientes computan bien el tiempo y pueden utilizar la información temporal en el intervalo corto, estando el problema en la reorientación estratégica necesaria para el intervalo largo. Sin embargo, estos pacientes no muestran

preparación temporal con la introducción de los ritmos. Este dato parece explicarse por el papel que juega el hemisferio izquierdo a la hora de procesar estímulos rítmicos.

Una manera de estudiar la relación entre estos procesos sería mediante estudios electrofisiológicos. En concreto, si la sobrestimación temporal es el deficit central de los pacientes con daño frontal derecho, deberíamos esperar que estos pacientes se preparen en el tiempo pero que lo hagan de forma anticipada. Por tanto, el componente CNV (Contingent Negative Variation) que ha sido asociado a la anticipación de las respuestas, debería estar presente aunque adelantado en el tiempo. Sin embargo, si estos pacientes tienen un déficit específico en los procesos implícitos de preparación temporal, el componente CNV podrá estar atenuado o alterado tal y como se ha observado en pacientes con enfermedad de Parkinson (Praamstra & Pope, 2007).

Un modelo sobre procesamiento temporal

Los resultados proporcionados por la presente investigación aportan nuevos hallazgos acerca del procesamiento temporal. En concreto, dentro de los procesos de preparación temporal, los ritmos podrían ser enmarcados como facilitadores de la preparación temporal automática junto a los efectos secuenciales. Estas dos formas de preparación, contrastarían con el efecto de orientación temporal y el efecto de foreperiod como procesos controlados o estratégicos de preparación temporal, los cuales parecen tener una relación con la capacidad de estimar el paso del tiempo en el rango de milisegundos.

Aunque se requiere más investigación en el futuro, nosotros proponemos una relación más directa entre preparación controlada y estimación temporal, en el sentido de que el efecto de orientación temporal y el efecto de foreperiod, en realidad, no se basan en un uso implícito de la información (ver Coull y Nobre, 2008) sino explícito. A los sujetos se les

proporciona información temporal explícita cuando se les dice que la línea corta indica "pronto" y la línea larga indica "tarde", instruyéndoles a que utilicen esa información para prepararse en el momento adecuado. Por tanto, un déficit en estimación temporal afectará a la capacidad de prepararse en el tiempo.

Esta propuesta sugiere, por tanto, que los procesos de preparación controlados se encuentran relacionados con los procesos de estimación temporal, principalmente el efecto de orientación temporal. Esta clasificación es más acorde con la base neural compartida entre ambos procesos, es decir, el cortex prefrontal derecho. Mientras que el efecto de foreperiod aporta un componente controlado de reorientación, lo cual podría explicar su afectación tras daño prefrontal derecho o izquierdo. Asimismo, los procesos de preparación automáticos quedan disociados de los procesos de estimación temporal y de preparación controlada, lo cual concuerda con una base neural diferente y, probablemente, asociada a otras estructuras corticales o a estructuras subcorticales como los ganglios de la base o el cerebelo. En la figura 7.1 se presenta gráficamente dicha propuesta.

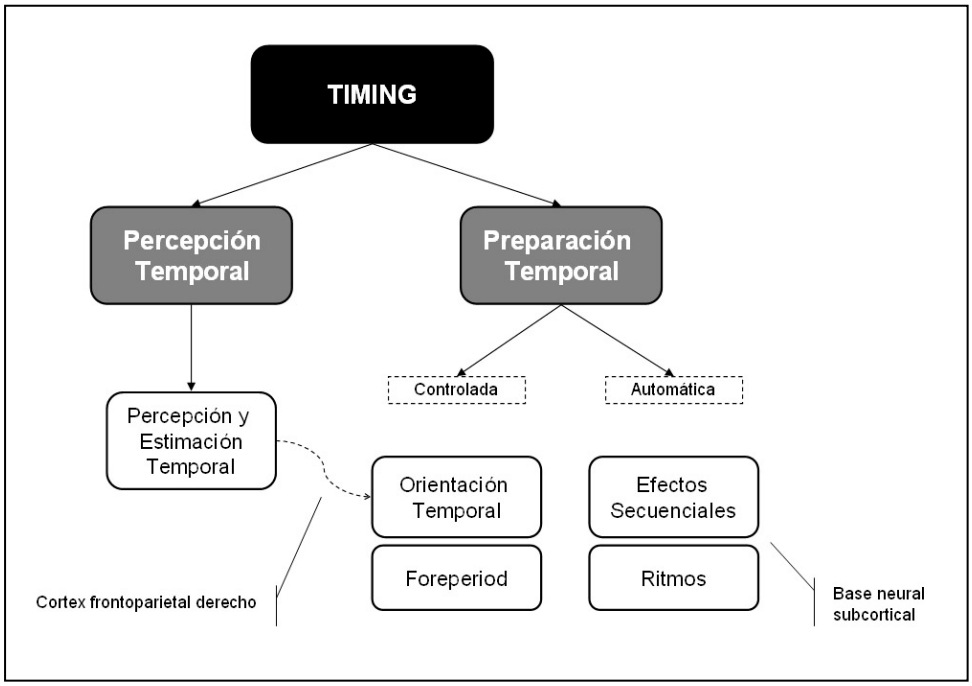


Figura 7.1. Nuestra propuesta donde los procesos de preparación temporal controlados requieren de un uso explícito del tiempo, por lo que se encuentran relacionados funcional y estructuralmente con los procesos de estimación temporal.

CAPÍTULO 8

CONCLUSIONES FINALES

1. Los resultados de la presente tesis doctoral confirman la participación de la región prefrontal en el circuito anatómico implicado en el procesamiento del tiempo.

2. Estos resultados implican al lóbulo prefrontal derecho en el proceso de orientación temporal, una asociación que nunca antes se había estudiado en pacientes neuropsicológicos.

3. Mediante el paradigma de costes y beneficios, la presente investigación muestra por primera vez una disociación funcional y estructural entre el efecto de orientación temporal y el efecto de foreperiod.

4. Asimismo, también muestra por vez primera una disociación clara entre los efectos secuenciales y el efecto de orientación temporal, contribuyendo a diferenciar las bases neurales de los procesos de preparación controlada y automática.

5. Los procesos de estimación temporal también parece verse diferencialmente afectados en pacientes prefrontales dependiendo del hemisferio dañado. Mientras que los pacientes con lesión prefrontal derecha presentan déficit en estas tareas, la ejecución del grupo con lesión prefrontal izquierda está dentro del rango de normalidad.

6. La introducción de señales visuales rítmicas predictivas facilita la preparación temporal en pacientes frontales derechos, a pesar de su déficit en estimación temporal. Esta misma señal empeora el rendimiento en los pacientes prefrontales izquierdos debido, quizás, a la mayor dominancia del hemisferio izquierdo para el procesamiento de ritmos en el rango de milisegundos.

7. Hasta donde nuestro conocimiento alcanza, es la primera vez que se estudian conjuntamente los procesos de percepción del tiempo y de preparación temporal en pacientes frontales, mostrando una relación en el uso explícito del tiempo entre la estimación temporal y los procesos de preparación controlada. Estos resultados nos permiten replantear clasificaciones previas (e.g. Coull y Nobre, 2008) en las que se propone que todos los procesos de preparación temporal son implícitos.

8. Finalmente, el conocimiento de estos procesos implicados en el procesamiento temporal y su base neural nos permitirá una mayor comprensión de lo que sucede en los pacientes con daño cerebral y proponer estrategias de intervención válidas y eficaces. La introducción en los programas de rehabilitación de ejercicios de estimación temporal en el rango de milisegundos, segundos y minutos, junto con el entrenamiento mediante la sincronización con patrones rítmicos, podría mejorar las conductas impulsivas y precipitadas de los pacientes con daño prefrontal, así como reducir la intolerancia a la demora que muchos pacientes muestran.

FINAL CONCLUSIONS

1. The current results confirm the key involvement of the prefrontal cortex in the brain network for time processing.

2. These findings show, for the first time, that the right prefrontal lobe is necessary for temporal orienting of attention.

3. By using the costs and benefits paradigm, the present research has shown, for the first time, functional and anatomical dissociations between temporal orienting and foreperiod effects.

4. Likewise, it is the first in showing a clear dissociation between temporal orienting and sequential effects, which indicates different neural bases for controlled vs. automatic temporal preparation.

5. Time estimation processes were impaired differentially, as a function of hemispheric damage. While right prefrontal patients showed time estimation deficit, left prefrontal patients performed within the normal range.

6. The use of visual rhythms as temporal cues facilitated temporal preparation in right prefrontal patients, despite their deficit in time estimation. In contrast, these rhythms impaired temporal preparation in left prefontal patients, which may be explained by the prominent role of left hemisphere in processing rhythms in the milliseconds range.

7. As far as we know, this is the first comprehensive study of the interactions between time perception and temporal preparation in frontal patients, which shows associations between the explicit use of time during both time estimation and controlled temporal

preparation. These results challenge previous taxonomies (e.g. Coull y Nobre, 2008) considering all temporal preparation processes as implicit.

8. Finally, a higher knowledge of the processes and neural basis of temporal processing will allow us to better understand what happens in patients with brain damage and suggest valid and effective strategies for the neuropsychological rehabilitation. The training in temporal estimation in the range of milliseconds, seconds and minutes, as well as the training with rhythmic patterns could improve the impulsive and hasty responses of patients with prefrontal damage and reduce the delay intolerance that many patients show.

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