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Temporal orienting deficit after prefrontal damage

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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 versus long line) to inform participants about the time of appearance (early versus late) of a target stimulus, and the duration of the cue-target time intervals (400 versus 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 do 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 work 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, making our response to the stimulus faster. This effect relates to temporal orienting; that is, the capacity to voluntarily and strategically direct attention voluntarily and strategically to a point in time, based on the subject's expectations of the time when an event will take place (Coull and Nobre, 1998; Nobre, 2001; Correa *et al*., 2004). 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 versus late) of the target or stimulus that 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

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observed as a shorter reaction time in valid trials as compared to invalid ones (Correa and Nobre, 1998; Correa and Nobre, 2008; Coull *et al*., 2000, 2004; Correa *et al*., 2004, 2006*b*).

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 (Karlin, 1959; Coull and Nobre, 1998; Correa *et al*., 2004), such that no reaction time 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, reaction times 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, 2006*b*).

Neuroanatomical correlates of the temporal orienting have been related to prefrontal structures (Coull and Nobre, 1998; Coull, 2000, 2009; Nobre, 2001; Coull *et al*., 2004; Hackley *et al*., 2009). 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. for review see Meck, 2005) may also play a relevant role in temporal orienting. First, neuropsychological studies in patients with Parkinson's disease (Artieda *et al*., 1992; Harrington *et al*., 1998; Jones *et al*., 2008) and functional MRI research have both shown the involvement of the striatum (caudate nucleus and putamen) and substantia nigra in temporal estimation tasks (Rao *et al*., 2001; Coull *et al*., 2004; Jahanshahi *et al*., 2006). 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 *et al*., 2005) and electrophysiological studies (Praamstra and Pope, 2007) carried out in patients with Parkinson's disease, 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. However, 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 that allow 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 lateralization of the temporal orienting effect to the left hemisphere (Coull and Nobre, 1998; Miniussi *et al*., 1999; Coull, 2004), or whether it is bilaterally distributed instead (Coull *et al*., 2000). We also tested a group of patients with basal ganglia lesions; 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 explore simultaneously other related ways of getting prepared in time, such as those underlying the foreperiod effect and sequential effects (Correa *et al*., 2004, 2006*b*). Exploring the potential interrelations between the three effects related to temporal preparation is an important objective, because they have usually been studied from separate traditions of research (Nobre *et al*., 2007). The foreperiod effect implies that reaction time decreases as the foreperiod becomes 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; Niemi and Näätänen, 1981; also see Los, 1996; Los *et al*., 2001*a*; Los and Heslenfeld, 2005; Los and 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 and functional MRI (Vallesi *et al*., 2007*b*, 2009) and in neurological studies with patients (Stuss *et al*., 2005; Vallesi *et al*., 2007*a*).

Sequential effects depend on the duration of the previous foreperiod. This effect consists of an increase in reaction time when the previous foreperiod was longer than the current foreperiod, or a decrease in reaction time 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 and Van den Heuvel, 2001*b*; Los and Heslenfeld, 2005); see also Steinborn *et al*. (2008). Sequential effects have not been related systematically with any brain area, although several studies suggest that they do not depend on prefrontal structures (Vallesi *et al*., 2007*a*, *b*; Vallesi and Shallice, 2007). Moreover, other studies show dissociations between sequential effects and temporal orienting (Los and Van den Heuvel, 2001*b*; Correa *et al*., 2004, 2006*b*; Los and Heslenfeld, 2005). 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 and Shallice, 2007). Thus, the group of patients with a lesion in their basal ganglia 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 alongside unaffected temporal orienting.

Methods

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. Of the 15 control subjects, seven subjects were chosen as controls for the seven basal ganglia patients because of their similar ages. The groups were matched in age, sex and years of education (Table 1). All the patients had suffered an acute lesion leading to dysfunction. Before the lesion, they were functionally independent, had no neurological or psychiatric disorders and had normal intellectual level.

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 the exclusion of four patients. By using these criteria, we aimed to assure that any deficit shown by basal ganglia patients was not due to prefrontal dysfunction as a result of disruption to the frontostriatal circuits.

Table 1 summarizes data on the aetiology of the lesions. Radiological reports of patients with frontal and basal ganglia lesions are reported in the Supplementary table. 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 Centre and Aliter Clinical Psychology Centre, 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 the patient 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 radiological reports, and CT and magnetic resonance images. 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 h 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 magnetic resonance images obtained from the medical history of patients were drawn with MRIcron computer software (Rorden and Brett, 2000), which provides MRI slices with 1 mm resolution of a standard brain where the lesion can be drawn.

Table 1 Demographic and neurological data

Group	Age (years)	Years of education	Sex	Aetiology	Time elapsed from lesion (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			
Basal ganglia	58.87 (8.97)	9.71 (4.57)	4 M 3 F	6 Stroke 1 Astrocytoma	19.86 (18.03)	5 Right 2 Left
Control basal ganglia	47.86 (12.3)	12.71 (3.82)	4 M 3 F			

Data are averaged for group and standard deviation (in parenthesis) is included. M = male; F = female; TBI = traumatic brain injury.

Table 2 Summary of cognitive functions and neuropsychological tests used in the clinical assessment

Function		Test		Results					
				Frontal versus control group			Basal ganglia versus control group		
				Frontal mean (SD)	Control mean (SD)		Basal ganglia mean (SD)	Control mean (SD)	
Premorbid intellectual functioning		Bilbao and 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)	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 Colour 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)	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)		1.4 (1.6)	2.8 (0.8)	*	1.8 (1.0)	2.6 (0.9)	
Personality	Personality and psychological disorders (Millon Clinical Multiaxial InventoryI-I)	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)	

Table 2. Continued

Function	Test		Results				
			Frontal versus control group			Basal ganglia versus control group	
			Frontal mean (SD)	Control mean (SD)		Basal ganglia mean (SD)	Control mean (SD)
classification according to DSM-IV-TR	Behavioural dysinhibition	Dysthymia	62.6 (20.7)	37.7 (25.7)	*	55.4 (17.6)	52.6 (31.6)
		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)

These results compare the frontal group to their 15 matched-control subjects and the basal ganglia group compared to their 7 matched-control subjects. DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision; PC = percentile; SD = standard deviation; WAIS-III = Weschler Adult Intelligence Scale 3rd edition; WMS-III = Weschler Memory Scale 3rd edition.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Behavioural task

Apparatus and stimuli

The experiment was performed on a 15 inch screen laptop computer. E-prime software (Schneider *et al*., 2002) was used to program the experiment, run the experimental task and collect data on reaction time 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, 2006*b*). The temporal cue was a short red line ($0.38^\circ \times 0.95^\circ$ visual angle from a distance of 60 cm from the screen) or a long red line ($0.38^\circ \times 2.1^\circ$). 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' ($0.38^\circ \times 0.76^\circ$). Subjects had to detect any of the two letters—which appeared with identical probability ($P = 0.5$)—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.

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 if 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.

The experiment consisted of one block with 64 practice trials, followed by four blocks with 120 experimental trials each. There was a break of at least 1 min after each block. An optional break was offered halfway through each block for participants to rest if they wished to. This 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, because it produces more robust temporal orienting effects as compared to trial-by-trial manipulations (Correa *et al*., 2006*b*). 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 (i.e. 400 ms after the temporal cue was shown). In the valid

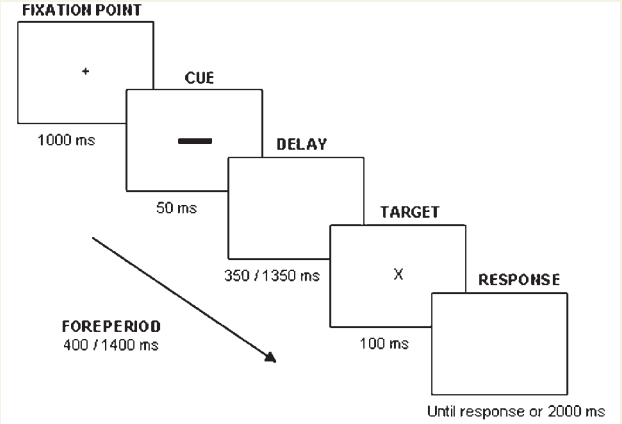

Figure 1 Sequence of events on a trial.

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 did not. The order of sessions was counterbalanced across participants. In order to analyse exactly the same dataset, the 20% of catch trials were eliminated from the analyses with the task without catch trials.

Design and analysis of behavioural results

Mean reaction times were submitted to a 3 (Lesion Group: Frontal, Basal Ganglia, Control) $\times 2$ (Target uncertainty: 0% versus 20% catch trials) $\times 2$ (Foreperiod: short versus long) $\times 2$ (Previous foreperiod: short versus long) $\times 2$ (Validity: valid versus 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 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 analysed 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 patients with frontal lesions and their control subjects in the neuropsychological variables linked to the frontal deficit. We did not expect differences 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 was not expected to 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 analysed 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 groups ($F<1$).

Basal ganglia group

Basal ganglia patients were matched with the seven oldest healthy controls. The analysis carried out with a single-factor ANOVA did not show significant differences between both groups as regards age [$F(1,12)=3.064$; $P=0.105$] years of education [$F(1,12)=1.967$; $P=0.186$] 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 $P>0.05$; Table 2). As regards the other 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 other executive function assessment, 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 (all $P>0.05$).

Basal ganglia group

A single-factor ANOVA was performed for each score, comparing the group with basal ganglia lesions and their corresponding controls. Significant differences were found between both groups regarding memory and premotor functions ($P<0.05$). However, as expected, the group with basal ganglia lesions 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 Fig. 3A–D in Supplementary material for more specific details regarding 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.

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 reaction time 2.5 SD slower or faster than the mean for each participant and session were considered outliers (2.83%) and also therefore eliminated from the analyses. Mean reaction times per experimental condition were computed with the remaining observations, which are presented in Table 3.

The 3 (Lesion Group: Frontal, Basal Ganglia, Control) × 2 (Target uncertainty: 0% versus 20% catch trials) × 2 (Foreperiod: short versus long) × 2 (Previous foreperiod: short versus long) × 2 (Validity: valid versus invalid) mixed ANOVA showed a main effect of group [$F(2, 33) = 3.82$; $P = 0.0321$; $\eta^2 = 0.19$] illustrating that the two groups of patients were slower than controls. (In order to account for this main effect of group, all the analyses reported in this paper were repeated, taking the proportional reaction time as the dependent variable, i.e. the mean reaction time for each experimental condition and participant divided by the mean overall reaction time for that participant. Exactly the same pattern of results was observed with this measure. Therefore, for the sake of simplicity mean reaction time is reported.) A significant temporal orienting effect was observed, as shown by the main effect of validity [$F(1,33) = 76.21$; $P < 0.0001$; $\eta^2 = 0.70$]. As indexed by the Foreperiod × Validity × Target uncertainty interaction [$F(1,33) = 4.62$; $P = 0.0389$; $\eta^2 = 0.12$], and usually observed in the literature, this temporal orienting effect depended on the foreperiod when no catch trials were included [$F(1,33) = 10.99$; $P = 0.0022$], so that temporal orienting was only observed at the short foreperiod [$F(1,33) = 36.21$; $P < 0.000$], 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 $P < 0.01$). More importantly, the Validity × Group interaction was significant (Fig. 3A) [$F(2,33) = 5.96$; $P = 0.0062$; $\eta^2 = 0.26$], showing that patients with frontal lesions had a significantly reduced temporal orienting effect as compared to controls [$F(1,27) = 14.45$; $P = 0.0007$; $\eta^2 = 0.35$]; whereas patients with basal ganglia lesions showed a temporal orienting effect similar to that shown by controls ($F < 1$). Although patients with frontal lesions also showed a significant temporal orienting effect [$F(1,13) = 11.47$; $P = 0.0049$; $\eta^2 = 0.47$], the effect they showed (invalid reaction time minus valid reaction time = 9 ms) was 2.5 times smaller than that shown by controls (23 ms), whereas patients with basal ganglia patients showed approximately 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 [$F(1,33) = 72.16$; $P < 0.0001$; $\eta^2 = 0.69$], so that the reaction time only decreased at the long versus short foreperiod when no catch trials were presented [$F(1,33) = 9.91$; $P = 0.0035$; $\eta^2 = 0.23$], whereas reaction time increased at the long versus short foreperiod in the session with catch trials [$F(1,33) = 23.75$; $P < 0.0001$; $\eta^2 = 0.42$]. More importantly, the foreperiod effect was also different for each group (Fig. 4) [$F(2,33) = 5.56$; $P = 0.0083$; $\eta^2 = 0.26$]. In the appropriate condition for observing foreperiod effects (i.e. the no catch session), only controls and patients with basal ganglia lesion showed main effects of foreperiod [$F(1,14) = 7.55$; $P = 0.0157$; $\eta^2 = 0.35$ and $F(1,6) = 5.34$; $P = 0.0602$; $\eta^2 = 0.47$; respectively], whereas patients with frontal lesions showed no effect ($F < 1$). With catch trials, both patients with frontal lesion and control groups showed a significant increase in reaction time at the long, as compared to the short foreperiod [$F(1,13) = 30.05$; $P = 0.0001$; $\eta^2 = 0.70$ and $F(1,14) = 7.39$; $P = 0.0166$; $\eta^2 = 0.35$; respectively], whereas the basal ganglia group showed no effect ($F < 1$). As shown in Fig. 4, the interactions between Group, Foreperiod and Target uncertainty, and between Target uncertainty and Group were not significant (both $P < 0.25$), showing that the general reaction time slowing down due to the presence of catch trials along the foreperiod was similarly present in the three groups.

Regarding sequential effects, the effect of Previous foreperiod was significant [$F(1,33) = 53.64$; $P < 0.0001$; $\eta^2 = 0.62$] as was the interaction between Previous foreperiod and Target uncertainty [$F(1,33) = 12.83$; $P = 0.0010$; $\eta^2 = 0.28$], showing that the effect of Previous foreperiod (faster reaction time for previous short versus long foreperiod) was more pronounced in the session without catch trials. These Previous foreperiod effects were also independent of group (both $F < 1$). The Foreperiod × Previous foreperiod interaction was also significant [$F(1,33) = 20.07$; $P < 0.0001$; $\eta^2 = 0.38$], reflecting the typical asymmetrical sequential effect, as shown in Fig. 5. Importantly, this interaction was independent of group [$F(1,33) = 1.06$; $P = 0.3571$; $\eta^2 = 0.06$]. The three groups were faster when the previous foreperiod was short versus long for the current short foreperiod (all $P < 0.005$). For the current long foreperiod, controls and patients with frontal lesions showed no effect of the previous foreperiod (both $P > 0.23$), whereas the group with basal ganglia lesions were faster on previous long foreperiod trials [$F(1,6) = 5.97$; $P = 0.0502$]. In other words, controls and patients with frontal lesions clearly showed asymmetrical sequential effects, whereas the group with basal ganglia lesions showed a more symmetrical pattern.

To summarize, patients with basal ganglia lesions and controls showed similar temporal orienting, the typical foreperiod effect without catch trials and significant sequential effects. The only difference was that the group with basal ganglia lesions did not show any increase in reaction time 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

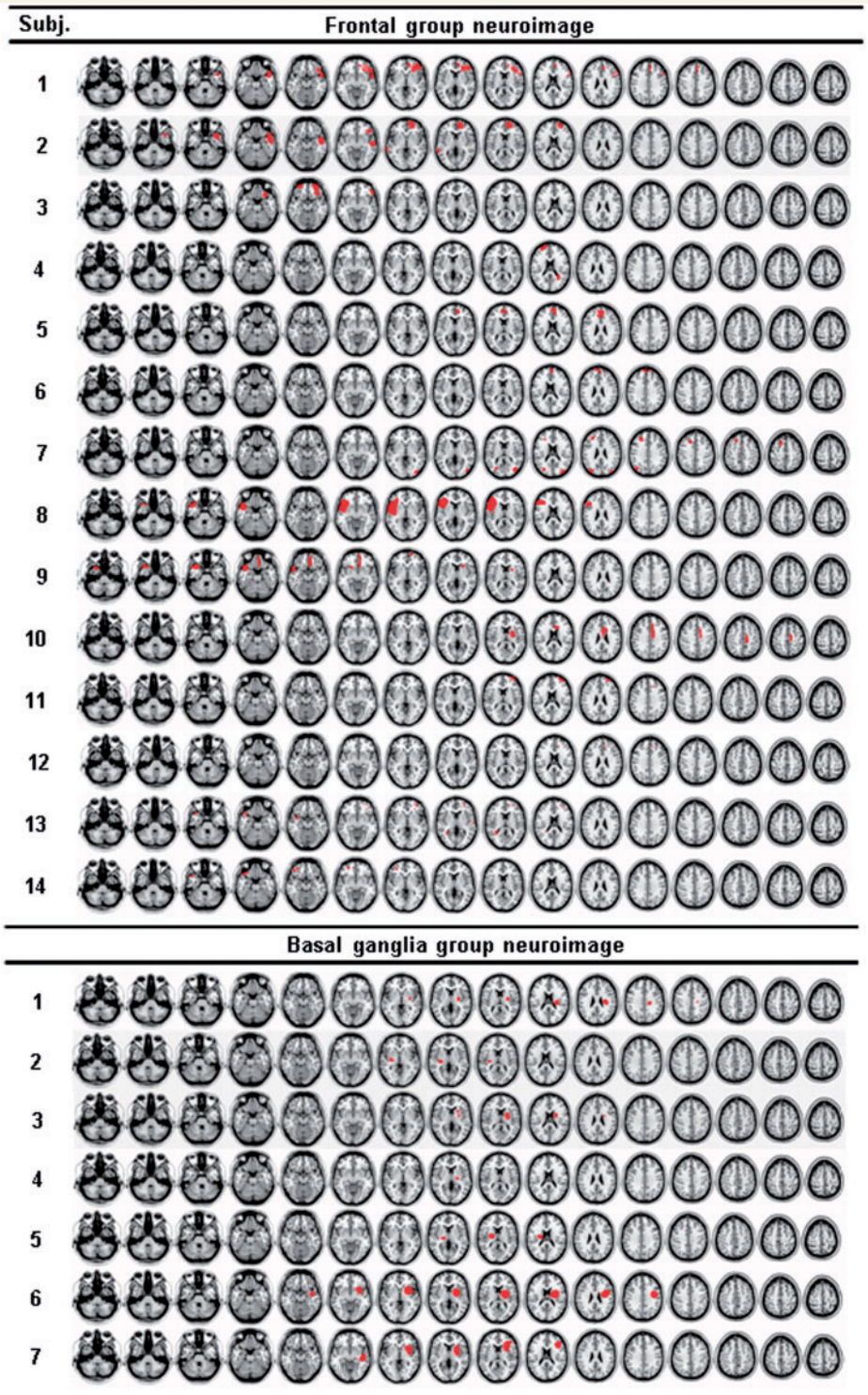

Figure 2 Magnetic resonance images in 7 mm slices for each patient group. All the images were drawn with MRIcroN software. The left hemisphere is represented at the left side of the images and vice versa.

($n = 15$) was taken into account, and when considering only the corresponding seven age-matched controls. In contrast, the group with frontal lesions 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. Due to our sample size, we could only perform this

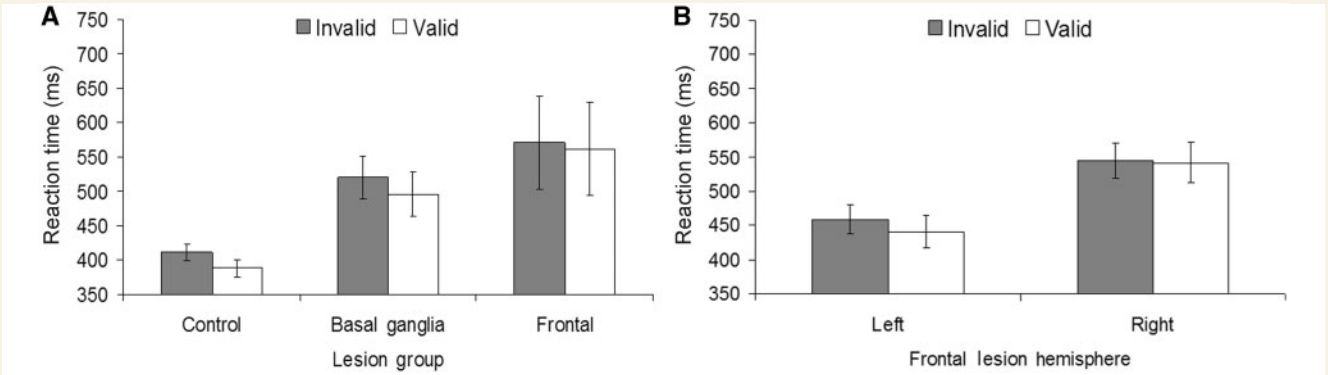

Figure 3 (**A**) Temporal orienting effect in control, basal ganglia and frontal groups. The temporal orienting effect (faster reaction times in valid versus invalid trials) was significantly smaller for the frontal group as compared to both control and basal ganglia groups. (**B**) The temporal orienting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

analysis on the group with frontal lesions, which had five patients with left frontal and six patients with right frontal lesions (the three patients with bilateral lesion were excluded from this analysis). Using the same set of reaction time data as analysed earlier, mean reaction times from the group with frontal lesions were submitted to a 2 (Hemisphere lesion: left versus right) $\times 2$ (Target uncertainty: 0% versus 20% catch trials) $\times 2$ (Foreperiod: short versus long) $\times 2$ (Previous foreperiod: short versus long) $\times 2$ (Validity: valid versus 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 [$F(1,9) = 8.85$; $P = 0.0156$; $\eta^2 = 0.50$], such that validity effects were only significant for patients with left frontal lesions [$F(1,4) = 33.592$; $P = 0.004$, $\eta^2 = 0.89$], but not for patients with right frontal lesions ($F < 1$) (Fig. 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 ($P = 0.0061$) independently of foreperiod ($F < 1$), whereas without catch trials they only showed a significant temporal orienting at the short foreperiod ($P = 0.003$) 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 $F < 1$).

Discussion

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

Our study is the first 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 and Shulman, 2002; Nobre, 2004), both in spatial and temporal dimensions (Coull *et al*., 2000; Hackley *et al*., 2009).

However, some functional MRI studies have reported an involvement of left prefrontal structures and a systematic activation of the left intraparietal sulcus (Coull and Nobre, 1998; Coull *et al*, 2001; Coull, 2004); 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 (1998) 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 earlier. 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 (Lewis and Miall, 2003; Koch *et al*., 2008). However, studies relating basal ganglia lesions

Table 3 Mean reaction times and percentage of errors per experimental condition from all lesion groups (Frontal, Basal Ganglia and Control)

		0% Catch trials								20% Catch trials							
		Short foreperiod$_{n-1}$				Long foreperiod$_{n-1}$				Short foreperiod$_{n-1}$				Long foreperiod$_{n-1}$			
		Short foreperiod		Long foreperiod		Short foreperiod		Long foreperiod		Short foreperiod		Long foreperiod		Short foreperiod		Long foreperiod	
		Val	Inv	Val	Inv	Val	Inv	Val	Inv	Val	Inv	Val	Inv	Val	Inv	Val	Inv
Frontal		503	523	524	517	533	542	535	532	576	569	615	645	586	593	617	644
		(0.3%)	(0%)	(0.2%)	(0%)	(5.9%)	(10.9%)	(2.5%)	(2.1%)	(0.2%)	(0%)	(0%)	(0%)	(3.0%)	(5.6%)	(2.2%)	(3.4%)
		[1.3%]	[3.1%]	[3.1%]	[3.1%]	[1.8%]	[0.9%]	[1.5%]	[1.1%]	[2.3%]	[1.0%]	[3.3%]	[3.7%]	[1.6%]	[1.6%]	[2.3%]	[2.9%]
Basal ganglia		474	513	457	455	497	551	474	491	505	523	527	534	511	551	518	544
		(0.8%)	(0%)	(0.9%)	(0%)	(5.1%)	(17.5%)	(3.2%)	(4.2%)	(0.1%)	(1.5%)	(0.5%)	(0%)	(2.9%)	(3.0%)	(2.1%)	(1.3%)
		[2.2%]	[0%]	[2.3%]	[2.8%]	[2.9%]	[2.2%]	[1.8%]	[1.4%]	[2.9%]	[9.3%]	[2.0%]	[3.3%]	[2.9%]	[4.0%]	[2.7%]	[5.1%]
Control		362	386	364	373	385	416	366	379	387	412	419	444	402	435	414	442
		(0.7%)	(1.1%)	(0.4%)	(0%)	(5.9%)	(10.4%)	(2.4%)	(1.8%)	(0.7%)	(0.6%)	(0.2%)	(0.4%)	(1.8%)	(3.6%)	(1.0%)	(2.9%)
		[0.3%]	[0.6%]	[0.5%]	[0.5%]	[0.6%]	[0.2%]	[0.6%]	[0.6%]	[0.5%]	[0%]	[0.2%]	[0%]	[0.2%]	[0.6%]	[0.5%]	[0%]
Total		438	464	444	445	465	491	453	460	484	494	517	540	495	519	513	541
		(0.5%)	(0.5%)	(0.4%)	(0%)	(5.8%)	(11.8%)	(2.6%)	(2.3%)	(0.4%)	(0.5%)	(0.2%)	(0.2%)	(2.5%)	(4.4%)	(1.7%)	(2.8%)
		[1.0%]	[1.5%]	[1.9%]	[1.9%]	[1.5%]	[0.8%]	[1.1%]	[0.9%]	[1.7%]	[2.1%]	[1.9%]	[2.2%]	[1.3%]	[1.6%]	[1.6%]	[2.1%]

Data are broken down by Target Uncertainty (0% versus 20% Catch Trials), Previous foreperiod (short versus long Foreperiod$_{n-1}$), Current foreperiod (short versus long Foreperiod) and Validity (valid (val) versus invalid (inv)). Anticipation errors are in parentheses and missing responses between square brackets.

Figure 4 Foreperiod effect in control, basal ganglia and frontal groups. The effect is usually observed as a significant reaction time 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 reaction time increase in the long foreperiod is observed compared with the short one. In this case, all the groups show this reaction time slowing. Error bars represent the standard error of the mean.

Figure 5 Sequential effects in control, basal ganglia and frontal groups. This effect may be observed as a reaction time 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.

with a deficit in temporal preparation tasks use similar time intervals to those used in our study. The greatest difference between those studies and ours is that most of them focus on patients with Parkinson's disease (Jurkowski *et al*., 2005; Jahanshahi *et al*., 2006; Praamstra and Pope, 2007; Jones *et al*., 2008; 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 patients with Parkinson's disease do not have to provide motor responses in time-estimation tasks, they do not show significant differences from a group of healthy controls. Our seven patients with basal ganglia lesions 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 patients with basal ganglia lesions 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 patients with frontal lesions show a deficit in temporal orienting due to the damage of the frontobasal circuits and the damage of the basal ganglia, which is frequent after a traumatic brain injury due to diffuse axonal injury. Nevertheless, is it possible that lesions of the 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 *et al*., 2007*a*). Similar 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 complete maturation of prefrontal cortex, did not show the foreperiod effect. Earlier studies with patients and transcranial magnetic stimulation 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 in both 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 earlier. [This absence of lateralization may also be explained by the presence of catch trials in one of the sessions of our task, which prevented 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].

Again, the fact that the foreperiod effect was present in the basal ganglia group suggests that the unilateral lesion of the striatum and associated frontobasal circuits does not interfere in the use of the strategic processes involved in this effect. Therefore, this result again suggests that the deficit observed in patients with frontal lesions is not due to the diffuse axonal injury caused by a traumatic event.

As we expected, sequential effects were preserved in patients with prefrontal lesions, which replicates the results of Vallesi *et al*. (2007*a*). The fact that foreperiod and temporal orienting effects were impaired in patients with frontal leisons—but sequential effects were preserved—supports the hypothesis that they are produced by two different temporal preparation mechanisms (Vallesi *et al*., 2007*b*), in contrast to the single process model defended by Los and colleagues (e.g. Los and Van den Heuvel, 2001*b*). 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 and Van den Heuvel, 2001*b*; Los and Heslenfeld, 2005). If the trace conditioning mechanism was damaged in patients with frontal lesions, as might be induced from the finding of no foreperiod effects, we should not have 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 (Los and Van den Heuvel, 2001*b*; Correa *et al*. 2004, 2006*b*; Los and Heslenfeld, 2005).

The finding of preserved sequential effects in patients with frontal lesions 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 point of view (Vallesi and Shallice, 2007). 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 anything they showed a greater effect of the previous foreperiod). If sequential effects were based on trace conditioning (Los and Van den Heuvel, 2001*b*; Los and Heslenfeld, 2005), their neural bases might involve other subcortical structures instead such as the hippocampus (Clark and Squire, 1998) or the cerebellum (Kalmbach *et al*., 2009). The left motor and premotor cortices are 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 and Nobre, 1998) or the monitoring of the conditional probability of stimulus occurrence (Vallesi *et al*., 2007*a*). 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 expectation of such stimuli's appearance. Studies have shown that temporal orienting modifies the time course and latency of the contingent negative variation, an electrophysiological index of temporal preparation that is associated with the activation of central and frontal structures (Miniussi *et al*., 1999; Correa *et al*., 2006*a*). This suggests an interesting area of research; that is, studying the contingent negative variation of frontal patients while they perform temporal orienting tasks, to investigate the temporal orienting mechanism directly rather than its consequences on performance. We expect frontal patients to show reduced contingent negative variation amplitude and/or a reduced synchrony between the contingent negative variation 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 (Harrington and Haaland, 1999; Rao *et al*., 2001; Coull *et al*., 2004), computing and monitoring probabilities in time (Vallesi *et al*., 2007*b*), and possibly inhibitory control of responses to avoid giving them at inappropriate times (Narayanan *et al*., 2006; Davranche *et al*., 2007; Correa and Nobre, 2008).

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 which 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.

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Supplementary material

Supplementary material is available at *Brain* online.

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