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Brain networks of temporal preparation: A multiple regression analysis of neuropsychological data

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ABSTRACT

There are only a few studies on the brain networks involved in the ability to prepare in time, and most of them followed a correlational rather than a neuropsychological approach. The present neuropsychological study performed multiple regression analysis to address the relationship between both grey and white matter (measured by magnetic resonance imaging in patients with brain lesion) and different effects in temporal preparation (Temporal orienting, Foreperiod and Sequential effects). Two versions of a temporal preparation task were administered to a group of 23 patients with acquired brain injury. In one task, the cue presented (a red versus green square) to inform participants about the time of appearance (early versus late) of a target stimulus was blocked, while in the other task the cue was manipulated on a trial-by-trial basis. The duration of the cue-target time intervals (400 versus 1400 ms) was always manipulated within blocks in both tasks. Regression analysis were conducted between either the grey matter lesion size or the white matter tracts disconnection and the three temporal preparation effects separately. The main finding was that each temporal preparation effect was predicted by a different network of structures, depending on cue expectancy. Specifically, the Temporal orienting effect was related to both prefrontal and temporal brain areas. The Foreperiod effect was related to right and left prefrontal structures. Sequential effects were predicted by both parietal cortex and left subcortical structures. These findings show a clear dissociation of brain circuits involved in the different ways to prepare in time, showing for the first time the involvement of temporal areas in the Temporal orienting effect, as well as the parietal cortex in the Sequential effects.

Introduction

Temporal preparation allows us to time our responses to the optimal moment. The literature on temporal preparation indicates that three main temporal preparation effects can be distinguished. First, the *temporal orienting effect* reflects our ability to direct attention voluntarily to a point in time, based on the expectation about the moment that an event will happen (Correa et al., 2004; Coull and Nobre, 1998; Nobre, 2001). Functional neuroimaging studies have linked temporal orienting to a left fronto-parietal network (Coull et al., 2004), whereas neuropsychological studies have associated temporal orienting with the right prefrontal cortex (Triviño et al., 2011; Triviño et al., 2010). Second, the *Foreperiod effect* (i.e., the effect of the preparatory interval between a warning signal and a target) is indexed by faster reaction times when there is a long foreperiod relative to when the foreperiod is short. This effect has been interpreted as reflecting a strategic expectancy for the target as time passes (Karlin, 1959; Niemi and Näätänen, 1981) or as a proactive motor inhibition not yet extinguished in short foreperiods (Boulinguez et al., 2008). And it has been related to the right dorsolateral prefrontal cortex (Stuss et al., 2005; Vallesi et al., 2007a; Vallesi et al., 2007b) (though see Triviño et al., 2011; Triviño et al., 2010, for evidence of bilateral involvement). *Sequential effects* also occur when individuals respond faster when the previous foreperiod is equal to or shorter than the current foreperiod, while individuals are slower when the previous foreperiod is longer. In contrast to the temporal orienting effect, sequential effects are automatically guided by external stimuli rather than by internal expectations (Capizzi et al., 2012) and do not rely on the prefrontal lobes, since they are preserved after both left and right prefrontal

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lesions (Triviño et al., 2011; Triviño et al., 2010), and they are unaffected by loading working memory (contrary to temporal orienting; see Capizzi et al. (2013)).

To date, neuropsychological studies of temporal preparation effects have been constrained to an "a priori" selection of patients based on the assumed neural localization of the underlying factors (Triviño et al., 2010; Triviño et al., 2011). In other cases lesion overlap analyses have been used to characterize the brain areas associated with impaired temporal preparation (Stuss et al., 2005; Vallesi et al., 2007a). However this methodology tends to emphasize independent effects of different voxels that may be affected without considering the effect that other damaged areas may have on the results. In the present paper we examined temporal preparation deficits in neuropsychological patients following a method based on multiple regression analysis, which relates the performance of each patient to his/her own primary and secondary lesions. In doing this, our analysis considers not only the effects of distinct cortical and subcortical lesions but also the disconnection of white matter tracts and it provides models where the predictive value representing each area is influenced by other implicated areas. We used two versions of a temporal task; a version in which the expectancy was blocked as in our previous studies with brain injured patients (Triviño et al., 2010; Triviño et al., 2011), and another version in which the cue was manipulated on a trial-by-trial basis as in other neuropsychological studies in the field (Stuss et al., 2005; Vallesi et al., 2007a). Although in both cases two different foreperiods (one short and one long) were manipulated within each block of trials, the two versions of the task modulate the way in which the subjects use the expectancy provided by the cue. Specifically, the trial-by-trial condition is more demanding, whereas the blocked condition reduces the resources needed (e.g., attention or working memory) so the task can be performed more automatically leading to larger temporal orienting effects (Correa et al., 2006). These differences could be reflected in the involvement of different brain networks. Therefore, using this novel approach in the temporal preparation field, and based on the previous literature, we expected to define differential networks supporting the distinct components of temporal preparation.

Methods

Participants

There were 23 patients with acquired brain injury (21 males and 2 females): 20 patients had suffered a stroke, 2 patients had had anoxia, and 1 patient encephalitis. The mean age of the patients was 63.7 years (SD: 12.4). All the patients underwent an MRI. Twenty-one patients completed the blocked version of the task (see below for details) and all 23 patients completed this and the trial-by-trial version. Behavioural analyses were conducted on the patients who completed both conditions but condition-specific lesion-symptom mapping was conducted on all patients who completed the respective condition.

The MRI analysis of the patients was performed comparing their images with a group of controls without lesions, in order to determine the grey matter (GM) lesion locations. The MRI volumes of the control group were taken from the Open Access Series of Imaging Studies (OASIS). The control group was formed by 38 people matched in gender (32 males and 6 females) and age (mean: 62.6; SD: 12.3) to the patient group.

Experimental task

Apparatus and stimuli

E-prime software (Schneider et al., 2002) controlled the presentation of the stimuli and data collection. The experiment was run on a 15-in. screen laptop computer and all the stimuli appeared in the centre of the screen. Each trial was made up of a fixation point ("+" symbol), a temporal cue and a target. The cue was either a red or green rectangle, 14 mm in width × 17 mm in height, subtending visual angles of 1.34° and 1.62° at a viewing distance of 60 cm, respectively. The target was either the letter 'O' or the letter 'X', 4 mm in width × 8 mm in height, subtending visual angles of 0.38° and 0.76° respectively. The two target letters appeared with a probability of 0.50. Participants pressed the 'B' key when either an 'O' or 'X' appeared. Two letters were used instead of one in order to be able to compare the results with future studies in which a discrimination task is used.

Procedure

Participants sat approximately 60 cm from the screen. Instructions concerning the task were displayed on the screen at the beginning of the experimental session. Participants were explicitly informed that the temporal cue would help them to predict when the target would appear. The meaning linked to the colour of the cue was counterbalanced, such that half of participants were told that the green square indicated the target would appear "early", while the red square indicated the target would appear "late", and vice versa for the remaining half of the participants. Auditory feedback (a 400-Hz tone of 100 ms) was provided on error trials. Participants were encouraged to respond as quickly and accurately as possible. A sketch of the sequence of events on a trial is depicted in Fig. 1.

The fixation point was displayed in black on a grey background for a random interval between 500 and 1500 ms. The temporal cue, a red or green square, then appeared for 50 ms. The cue was subsequently removed and the screen remained blank for a variable delay of 350 or 1350 ms, depending on the SOA for that trial. Finally, the target was displayed for 100 ms and this was then replaced by a blank screen until the response. After response, the next trial began. When no response was made, the next trial began following a delay of 2000 ms.

The experimental task lasted about 40 min, including one block of 64 practice trials and eight blocks of 128 experimental trials. There was a 1-minute rest break at the end of each block. The 128 target trials within each block consisted of 96 validly cued trials and 32 invalidly cued trials, thus producing a validity proportion of 0.75. On half of the valid trials, the cue indicated that the target was likely to appear "early" and the target appeared 400 ms after cue onset. On the other half of the valid trials, the cue indicated that the target was likely to appear "late", and the target appeared 1400 ms after cue onset.

With two exceptions, the patients performed two versions of the task with a minimum of 1 day separation between the two sessions. In one task, the cue was counterbalanced between blocks, so the "early" or "late" expectancy remained the same during the entire block. In the other version of the task, the cue was manipulated on a trial-by-trial basis, so the temporal expectancy could vary across trials. The order of execution of the tasks was also counterbalanced across the participants.

Treatment of the data

Mean reaction times were submitted to a 2 (Cue Expectancy: blocked/trial-by-trial) ×2 (Foreperiod: 400/1400 ms) ×2 (Previous Foreperiod: 400/1400 ms) ×2 (Validity: invalid/valid) mixed factor design. All variables were manipulated within-participants.

In order to perform the lesion analysis described below, we computed an index for each temporal effect based on our previous studies (Correa et al., 2006; Triviño et al., 2011; Triviño et al., 2010). Thus, the *Temporal Orienting effect* was indexed by the main effect of Validity in the short foreperiod condition, subtracting valid from invalid trials. The temporal orienting effect depends on the foreperiod, so that it is only observed at the short foreperiod when catch trials are not included (Correa et al., 2004). The **Foreperiod effect** was indexed as the main effect of Foreperiod in the invalid condition, subtracting long foreperiod from short foreperiod trials. In this case, valid trials were excluded since the literature shows 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 and Nobre,

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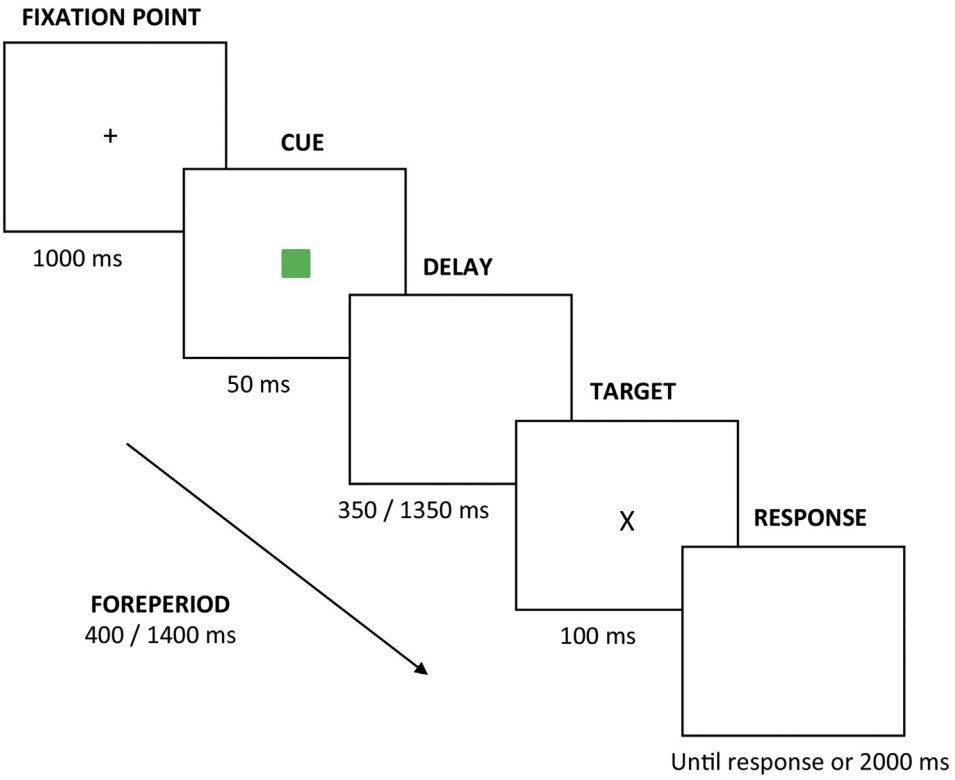

Fig. 1. Main procedure of the experimental task.

2008). However, when trials are invalid, subjects are usually slower with short relative to long foreperiods, showing a robust foreperiod effect. Finally, the **Sequential effects** were indexed as the main effect of the Previous Foreperiod on a current short foreperiod, subtracting the previous short foreperiod from the previous long foreperiod condition (i.e., previous long minus previous short). This simplified analysis, excluding current long foreperiod trials, was based in our previous results (Correa et al., 2006; Triviño et al., 2010) since sequential effects are typically observed at the current short foreperiod independently of cue validity.

Image analysis

The images were first checked for artifacts and manually aligned to the anterior and posterior commissures (AC-PC line). Data were processed and analyzed using Statistical Parametrical Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html), for which we used the default parameters. Within a unified segmentation model (Ashburner and Friston, 2005), images were corrected for bias-field in homogeneities, registered using linear (12 parameters affine) and non-linear transformations (warped), and tissue was clustered into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Segments were further refined by using adaptive maximum a posteriori estimations, which account for partial volume effects, and by applying a hidden Markov random field model, as implemented in VBM8. Importantly, to preserve local GM/WM values, segments were multiplied by the Jacobian determinant of the deformation fields to create modulated images. Segments were smoothed by an 8 mm full-width at half-maximum (FWHM) using an isotropic Gaussian kernel. Afterwards, we conducted analysis on modulated GM segments.

Grey matter lesion analysis

The general linear model implemented in SPM8 was used to conduct voxel-wise comparisons between patients and controls to determine the GM lesion locations. Scanner model, age, handedness and sex served as linear confounds. The significance threshold was set at $p < 0.05$ after family-wise correction for multiple comparisons (pFWE < 0.05). A criterion of $p < 0.0001$, cluster size = 100, was used for two patients. Next, for each patient we counted the number of GM voxels within each cluster in which the grey matter volume was significantly lower than that of controls (hereafter, size of the lesion). Automatic anatomic labeling (AAL, Tzourio-Mazoyer et al., 2002) was used to determine the labels for these anatomical lesions.

White matter disconnection analysis

We mapped the lesion from each patient onto tractography reconstructions of white matter pathways obtained from a group of healthy controls (Rojkova et al., 2016). We quantified the severity of the disconnection by measuring the probability of the tract to be disconnected (Thiebaut de Schotten et al., 2014) using Tractotron software as part of the BCBtoolkit (http://www.brainconnectivitybehaviour.eu). A tract was considered disconnected when a lesion overlapped with a voxel that belonged to this tract with a probability that was above the chance level (probability > 0.5).

Regional relationships between GM, WM and measures of temporal orienting

We used the SPSS (v 15.0) forward multiple regression analysis procedure, in which we tested the significance of the relationship between either the size of the lesion or the probability of tracts disconnection and each of our three main behavioural indices: Temporal Orienting, Foreperiod and Sequential effects. The size of the GM lesion was expressed as the number of voxels in each lesion cluster in relation to the total number of lesion voxels. The WM lesions were expressed as the probability of disconnection. In order to study the neural basis for these effects according to the manipulation of Cue Expectancy (i.e., Blocked vs. Trial-by-Trial), we analyzed the relationship between the GM lesion size or the WM disconnection probability, and the three

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Table 1
Mean RTs, percentage of false alarms (in parentheses) and omissions (in brackets) per experimental condition from both task conditions (Blocked and Trial by Trial Cue) broken down by Foreperiod (Short FP vs. Long FP), Previous Foreperiod (Short FP_{n-1} vs. Long FP_{n-1}) and Validity (Valid vs. Invalid).

	Short FP				Long FP			
	Short FP_{n-1}		Long FP_{n-1}		Short FP_{n-1}		Long FP_{n-1}	
	Valid	Invalid	Valid	Invalid	Valid	Invalid	Valid	Invalid
Blocked Cue	468.9	496.2	485.4	504.2	462.6	448.9	464.9	485.7
	(1.0%)	(1.0%)	(0.4%)	(0.6%)	(0.4%)	(0.3%)	(0.2%)	(1.0%)
	[1.8%]	[1.8%]	[2.3%]	[2.4%]	[1.4%]	[2.0%]	[2.6%]	[1.0%]
Trial by Trial Cue	445.7	476.2	462.0	487.5	463.7	443.4	464.9	464.3
	(0.9%)	(0.7%)	(0.6%)	(0.4%)	(0.4%)	(0.0%)	(0.1%)	(0.0%)
	[1.9%]	[1.0%]	[1.8%]	[2.0%]	[1.4%]	[2.6%]	[2.8%]	[2.3%]

temporal preparation indices separately for each cue expectancy condition.

Results

Behavioural results

Practice trials and the first trial of each block were eliminated from the analysis, as well as those trials in which participants either responded before the target appeared (anticipation errors: 0.5%) or did not respond when it appeared (misses: 1.9%), and trials with RT below 100 ms (1.5%) or above 1000 ms (4.3%). Mean RTs per experimental condition were computed with the remaining observations, which are presented in Table 1.

The 2 (Cue Expectancy: Blocked vs. trial-by-trial) × 2 (Foreperiod: short vs. long) × 2 (Previous Foreperiod: short vs. long) × 2 (Validity: valid vs. invalid) mixed ANOVA showed that neither the *Temporal Orienting effect* nor the **Foreperiod effect** were significant, as shown by the main effect of Validity, $F(1,20) = 3.32$, $p = 0.083$, $\eta p^2 = 0.142$, and Foreperiod, $F(1,20) = 2.25$, $p = 0.149$, $\eta p^2 = 0.101$. However, the interaction between Validity and Foreperiod was significant, $F(1,20) = 8.02$, $p = 0.010$, $\eta^2 = 0.286$. There was an effect of Temporal Orienting at the short foreperiod, $F(1,20) = 10.18$, $p = 0.004$, but not at the long foreperiod ($F < 1$); there was also an effect of Foreperiod in the invalid condition, $F(1,20) = 5.43$, $p = 0.030$, but not in the valid condition ($F < 1$). Finally, the **Sequential effects** were significant as shown by the main effect of the Previous Foreperiod, $F(1,20) = 6.73$, $p = 0.017$, $\eta^2 = 0.251$, but the interaction between Foreperiod and Previous Foreperiod was not significant ($F < 1$). Neither the main effect of the Cue Expectancy nor any other interaction with that variable were observed (all $ps > 0.192$).

Subsequently, as mentioned above, we computed the indices for each temporal preparation effect in order to perform the regression analysis where each temporal index was associated with the brain lesion(s). The mean values for each index are displayed in Table 2.

Lesion analysis

Table 3 displays the characteristics of the main (the largest cluster) and secondary lesion areas for each patient: hemisphere, anatomic labels of the peak location (max *t*-test), size in number of voxels (k), and the MNI coordinates for the peak. The lesions were mainly located in frontotemporal structures and extended subcortically to the basal ganglia, the insula and the thalamus.

Regional relationship between GM and WM voxels and measures of temporal preparation

We found a number of regions in which the GM lesion size and the probability of WM tracts disconnection showed selective associations with behavioural performance related to the Temporal Orienting, Foreperiod, and Sequential effects separately for each cue expectancy condition (Blocked vs. Trial-by-Trial). Table 4 displays the anatomical regions involved in the prediction of each behavioural dependent variable, the standardized partial regression coefficients (Beta), the adjusted multiple R^2 that controls for the number of predictors in the regression equation, and the significance of the prediction. Note the high amount of variance explained by the models (Adj R^2) and that the predictions were significant using Bonferroni correction. Partial regression coefficients indicated that the implicated structures form networks with direct and inverse relationships with behavioural performance. Similarly, Table 5 displays the disconnected tracts involved in the prediction of each temporal effect for each cue expectancy condition.

The analysis showed substantial differences in the anatomical regions involved in each effect depending on the manipulation of cue expectancy. Regarding the *Temporal Orienting effect*, the right frontal operculum and bilateral temporal regions (medial and superior temporal gyri) were involved when Cue Expectancy was blocked. However, the left frontal operculum together with a more diffuse network of structures (including left subcortical structures, the right superior temporal gyrus, the right middle cingulum and right cerebellum) were involved when Cue Expectancy changed trial by trial. See Fig. 2. Note that no WM tract predicted the performance in the temporal orienting effect, neither in the blocked nor in the trial-by-trial task.

Concerning the **Foreperiod effect**, as it is shown in Fig. 3, there was a lateralization to the left hemisphere when Cue Expectancy was blocked, with the left frontal inferior operculum and the left temporoparietal junction (postcentral and superior temporal giri) involved. However, it is noteworthy the presence of the right precentral giri and the second branch of the right superior longitudinal fasciculus (SLF-II), showing a trend towards bilateralism. Nevertheless, the lateralization was clearly

Table 2
Mean RT and standard deviation per temporal preparation index (Temporal orienting, Foreperiod and Sequential effects) from both tasks (Blocked and Trial by Trial Cue).

		Temporal Orienting index	Foreperiod index	Sequential effects index
Blocked Cue	Mean	27.81	44.29	19.52
	(s.d)	(37.27)	(60.84)	(53.66)
Trial by Trial Cue	Mean	30.20	29.03	19.83
	(s.d)	(62.32)	(78.73)	(25.05)

Note: *Temporal Orienting index:* Invalid minus Valid in Short FP condition; *Foreperiod index:* Short FP minus Long FP in Invalid condition; *Sequential effects index*: Long FP_{n-1} minus Short FP_{n-1} in the current Short FP condition.

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Table 3
Characteristics of main (the largest cluster) and secondary lesion areas for each patient: hemisphere (H), anatomic labels of the peaks location (max *t*-test), size in number of voxels (k), and the MNI coordinates for the peak (X, Y, Z).

Patient	Main lesion							Secondary lesion						
	H	Peak location	T	k	X	Y	Z	H	Peak location	T	k	X	Y	Z
UB10	Left	Putamen	7.28	212	−26	−6	4							
UB11	Left	Putamen Caudate Head	10.11	4863	−24	−4	−3	Left	Superior Temporal Gyrus	6.98	1197	−60	−39	7
UB12	Left	Putamen Extra-Nuclear Frontal Inferior Oper	11.36	21,675	−21	−36	−11	Left	Superior Temporal Gyrus Middle Temporal Gyrus	6.76	1056	−59	−60	18
UB13	Left	Precuneus	6.80	211	−11	−73	52	Left	Putamen	6.09	102	−26	−4	9
UB14	Left	Caudate	7.19	86	−17	−30	16	Left	Postcentral Gyrus	6.48	133	−35	−31	49
UB15	Right	Superior Temporal Gyrus	7.42	1286	53	−15	−11	Right	Inferior Temporal Gyrus	6.41	234	41	−5	−48
UB20	Right	Insula Rolandic Oper Superior Temporal Gyrus	9.83	9652	36	14	−9	Right	ParaHippocampal Gyrus Fusiform Gyrus	8.73	2122	30	−22	−20
UB21	Right	ParaHippocampal Gyrus Insula Superior Temporal Gyrus Inferior Frontal Gyrus	12.20	19,883	−21	−36	−12	Right	ParaHippocampal Gyrus Fusiform Gyrus	10.27	4477	29	−22	−20
UB23	Right	Insula Superior Temporal Gyrus Inferior Frontal Gyrus	10.52	12,172	53	−13	−3	Right	Caudate Extra-Nuclear Putamen	7.65	1005	9	−1	13
UB24	Right	Inferior Frontal Gyrus Superior Temporal Gyrus Insula	10.07	5425	41	6	−8	Right	Frontal Inferior Oper	6.20	96	60	14	18
UB25	Left	Inferior Frontal Gyrus Middle Frontal Gyrus Insula	10.52	15,545	−41	5	12	Left	Middle Frontal Gyrus	6.44	228	−45	33	28
UB26	Right	ParaHippocampal Gyrus Cerebellum Fusiform Gyrus	11.15	5404	27	−33	−15	Right	Inferior Frontal Gyrus Insula Superior Temporal Gyrus	9.50	7636	32	26	−21
UB3	Left	ParaHippocampal Gyrus Subcallosal Gyrus Superior Temporal Gyrus	11.36	21,675	−21	−36	−11	Right	Anterior Cingulate Insula Frontal Inferior Orbital	8.43	6564	5	15	−6
UB30	Right	Inferior Frontal Gyrus Caudate Anterior Cingulate	9.30	4581	9	5	−2	Left	Cingulate Gyrus Supp Motor Area	8.27	3934	−9	−1	46
UB34*	Right	Inferior Frontal Gyrus	4.77	318	60	14	15	Right	Cingulate Gyrus	4.51	163	2	14	31
UB36	Right	Superior Temporal Gyrus Middle Temporal Gyrus	7.77	2277	57	−52	13	Right	Insula Extra-Nuclear	7.06	2040	39	−15	−8
UB37	Left	Insula Putamen	7.04	880	−35	3	0	Left	Superior Temporal Gyrus	6.70	529	−48	−15	−3
UB42	Right	Superior Temporal Gyrus Middle Temporal Gyrus ParaHippocampal Gyrus Fusiform Gyrus	11.95	21,113	42	−19	−11	Left	Postcentral Gyrus	6.46	155	59	−21	19
UB49*	Left	Inferior Frontal Gyrus	4.88	187	−60	21	18	Right	Superior Frontal Gyrus	4.78	170	8	63	−24
UB51	Right	Superior Temporal Gyrus Middle Temporal Gyrus	9.46	1212	53	−13	−3							
UB68	Right	Insula	7.84	417	38	15	−14	Left	Putamen	8.11	356	−26	−6	−4
UB7	Right	Insula Superior Temporal Gyrus Extra-Nuclear	10.09	20,182	39	6	−9	Left	BA19	7.11	366	−21	−82	−18
UB75	Right	Inferior Frontal Gyrus Superior Temporal Gyrus Insula Middle Temporal Gyrus	11.01	26,554	35	9	−14	Right	ParaHippocampal Gyrus	6.92	225	30	−24	−18

Note: all FWE corrected $p < 0.05$, k > 40, excepting UB34 and UB49 (uncorrected $p < 0.0001$, k > 100).
H = Hemisphere. X, Y, Z are in MNI space.

to the right hemisphere when the Cue Expectancy changed trial by trial, involving prefrontal structures, such as the inferior orbital cortex, the middle frontal gyrus and the anterior cingulum. In this condition, there were no tracts involved.

Finally, the **Sequential effects** showed in general a larger involvement of subcortical structures when Cue Expectancy was blocked, highlighting the role of the left insula, the left putamen nuclei and the right thalamus. Bilateral parietal structures such as the inferior parietal were also implicated. Likewise, the left anterior cingulum and the first branch of the left superior longitudinal fasciculus (SLF-I) were included in the model. With regard to the trial-by-trial manipulation, the Sequential effects were related to the right thalamus and the right superior temporal gyri as well as the left parietal cortex (angular and postcentral gyri), without any white matter tract being involved. See Fig. 4.

Discussion

The present study performed a novel analysis in the temporal preparation field based on multiple regression, which aimed to explore the relationship between specific temporal preparation effects and multiple brain structures. This methodology allowed us to measure the relations of both grey and white matter for each temporal preparation effect.

The results showed significant regression models that explained much of the variance in the behavioural data. The main finding was that each temporal preparation effect was predicted by a different network of structures. In particular, the *Temporal Orienting effect* was related to temporal brain areas, and the prefrontal structures showed a differential lateralization according to the manipulation of the cue expectancy. Specifically, right prefrontal structures were involved when the cue expectancy was blocked, while left fronto-subcortical structures were involved when temporal expectancy was manipulated trial by trial. The involvement of right prefrontal structures in temporal orienting in the blocked cue condition was consistent with previous neuropsychological studies in which a similar manipulation of temporal expectancy was performed (Triviño et al., 2011; Triviño et al., 2010). Previously we found that the temporal orienting effect was impaired in a group of right prefrontal patients as compared to left prefrontal and basal ganglia patients. The presence of left prefrontal structures in the trial-by-trial manipulation here is also consistent with previous functional imaging studies (Coull et al., 2000; Coull and Nobre, 1998; Hackley et al., 2009). These results may reflect right lateralization of function for monitoring and updating temporal information, as well as left lateralization of function for generating task rules: an old proposal that has been recently rescued (Stuss, 2011; Vallesi, 2012).

Regarding the role of the temporal cortex in the temporal orienting effect, previous studies using functional imaging have reported a similar finding, with temporal orienting associated with activation of the middle and superior temporal gyri bilaterally (Coull et al., 2000; Hackley et al., 2009). However, this result has not been emphasized in the temporal preparation literature which has highlighted other areas such as the left inferior parietal cortex (Coull et al., 2013; Coull and Nobre, 2008; Davranche et al., 2011) and supplementary motor cortex (Hackley et al., 2009). Nevertheless, we found a clear relationship between temporal orienting and temporal cortex, which suggests an

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Table 4
Regression analysis. Prediction of behavioral effects from size of lesion according to the Cue Expectancy (Blocked vs. Trial by Trial).

Dependent	Predictors	Beta	Adj R^2	F	p
TO Block	Postcentral L	0.57	0.78	14.84	0.0001
	Temporal Mid L	−0.47			
	Frontal Inf Oper R	0.32			
	Temporal Mid R	0.44			
	Temporal Sup R	−0.31			
TO TxT	Insula L	−0.19	0.76	12.39	0.0001
	Pallidum L	−0.11			
	Cerebellum 3 R	0.52			
	Temporal Sup R	0.55			
	Frontal Mid Orb L	0.41			
	Cingulum Mid R	0.30			
FP Block	Temporal Sup L	0.47	0.55	7.11	0.002
	Postcentral L	0.46			
	Precentral R	0.47			
	Frontal Inf Oper L	0.37			
FP TxT	Frontal Inf Orb R	0.87	0.68	16.60	0.0001
	Cingulum Ant R	0.38			
	Frontal Mid R	−0.37			
SQ Block	Insula L	−0.77	0.92	34.76	0.0001
	Parietal Inf R	−0.18			
	Thalamus R	0.51			
	Rolandic Oper L	0.32			
	Parietal Inf L	−0.38			
	Rolandic Oper R	−0.61			
	Putamen L	−0.22			
SQ TxT	Temporal Sup R	0.54	0.59	8.85	0.0001
	Angular L	−0.37			
	Postcentral L	0.35			
	Thalamus R	0.29			

Note: Beta is the standardized partial regression weight; anatomic labels are AAL tags.
TO: Temporal orienting; FP: Foreperiod; SQ: Sequential effects; TxT: Trial-by-Trial.

active role of this structure in temporal preparation, possibly related to a representation of temporal intervals using auditory codes (Guttman et al., 2005; Nobre and O'Reilly, 2004; see also Grahn et al., 2011). Given that the stimuli in this study were visual, it seems that the superior temporal lobe (STL) may be involved in coding temporal intervals using auditory codes. This coding could be of special importance in the temporal orienting effect, where subjects needed to generate a temporal structure that allowed them to anticipate the appearance of the target, perhaps through a subvocal strategy. In fact, the STL was clearly present in the blocked condition where patients often reported that they had used such a strategy. Anyway, the STL involvement should be studied in future studies, since the model generated by this methodology could be mislocating the STL if other critical areas (e.g., frontal and parietal) were related in a combined form (Mah et al., 2014). However, the lack of any white matter tract involved suggests that the cortical areas pointed in the model could be crucial for this temporal effect.

Regarding the *Foreperiod effect*, our results showed its relation with bilateral prefrontal structures. This is consistent with previous results both in neuropsychological studies with patients (Triviño et al., 2011; Triviño et al., 2010; Vallesi et al., 2007a) and in studies using TMS with normal participants (Vallesi et al., 2007b). Specifically, right lateralization of function has been reported when the expectancy of the cue was manipulated trial by trial (Vallesi et al., 2007a; Vallesi et al., 2007b), while bilateral involvement of prefrontal structures —with a tendency towards left lateralization— has been reported in blocked-cue studies (Triviño et al., 2011; Triviño et al., 2010). Our findings therefore confirm that the manipulation of the temporal cue recruits different processes for temporal preparation. In this vein, we have previously shown demands on control and working memory processes only when the cue changes on a trial-by-trial basis (Capizzi et al., 2012), which is consistent with the involvement of the anterior cingulate cortex in the current study (Carter and van Veen, 2007; Kerns, 2006). However, when the cue was blocked the presence of left structures was more prominent, highlighting again the superior temporal gyrus. Activity in this area has been related to the readiness-period between a warning signal and the target, that is, the foreperiod (Cui et al., 2009). The activation of the superior temporal gyrus during this preparation period seems to be modulated by the level of expectation and its activation decreases in the absence of uncertainty.

Finally and regarding *Sequential effects*, when the cue was blocked, bilateral parietal regions, the right thalamus and the disconnection of the left anterior cingulum and the SLF-I were implicated, while the trial-by-trial manipulation was linked to damage to the left parietal, right temporal and right thalamus. These structures, together with the premotor area, the supplementary motor area (SMA) and the cerebellum, have been associated with time estimation (Macar et al., 2006; Meck, 2005). More specifically, the cerebellum-basal ganglia circuit has been linked to the processing of temporal structure, acting as a "pacemaker" which sequences successive actions. However, the basal ganglia-thalamus-cortical circuit appears to engage an "attention-dependent" state whereby the attention is directed towards temporal intervals when the response is modulated by the duration of the previous stimulus or interval but the subject has no specific temporal goal in mind (Buhusi and Meck, 2005; Schwartze et al., 2012). This may reflect an automatic component underlying sequential effects in temporal preparation (Capizzi et al., 2012; Los and Van den Heuvel, 2001). Therefore, our results are consistent with previous research suggesting that the basal ganglia are involved in time perception (Coull et al., 2004; Harrington et al., 1998), which could be related to the ability to prepare automatically in time depending on the length of the previous interval (i.e., sequential effects). Likewise, sequential effects have been related to lesions in the left premotor area (Vallesi et al., 2007a), which could reflect the dysfunction of the basal ganglia-thalamus-premotor network. All these structures are related to a subcortical, medial network, where the anterior cingulate has an important role projecting fibers from thalamic nuclei and ventral striatum, among other limbic structures (Jones et al., 2013).

Finally, the identification of parietal lesions and the disconnection of the SLF-I (which connects the superior parietal lobe to prefrontal structures; see Kamali et al. (2014) to a description of the connectivity of the SLF branches) in the regression model was unexpected, but it could be due to the involvement of parietal cortex in processing magnitude in general, not only spatial but also temporal and numeric (Alexander et al., 2005). Consequently, it seems reasonable to think that the parietal cortex is recruited for all temporal preparation effects, since computing magnitudes would be expected to be important in all cases. However, in the effects related to controlled temporal preparation (i.e., temporal orienting and foreperiod effects), subjects seem to use more complex strategies, transforming and updating temporal information so that the involvement of prefrontal and temporal areas would be emphasized in the models. Sequential effects, on the other hand, may be more automatic in nature, operating without awareness by the individual of the existence of a predictive temporal structure (Schwartze et al., 2012). Under these conditions, the parietal lobe could be crucial to integrating the temporal information provided by the subcortical structures – acting as a 'pacemaker'. However, the parietal implication should be tested

Table 5
Regression analysis. Prediction of behavioral effects from tracts disconnection according to the Cue Expectancy (Blocked vs. Trial by Trial).

Dependent	Predictors	Beta	Adj R^2	F	p
TO Block	None				
TO TxT	None				
FP Block	Superior Longitudinal Fasciculus II R	0.49	0.20	6.02	0.024
FP TxT	None				
SQ Block	Cingulum Anterior L	−1.01	0.46	9.43	0.002
	Superior Longitudinal Fasciculus I L	0.66			
SQ TxT	None				

TO: Temporal orienting; FP: Foreperiod; SQ: Sequential effects; TxT: Trial-by-Trial.

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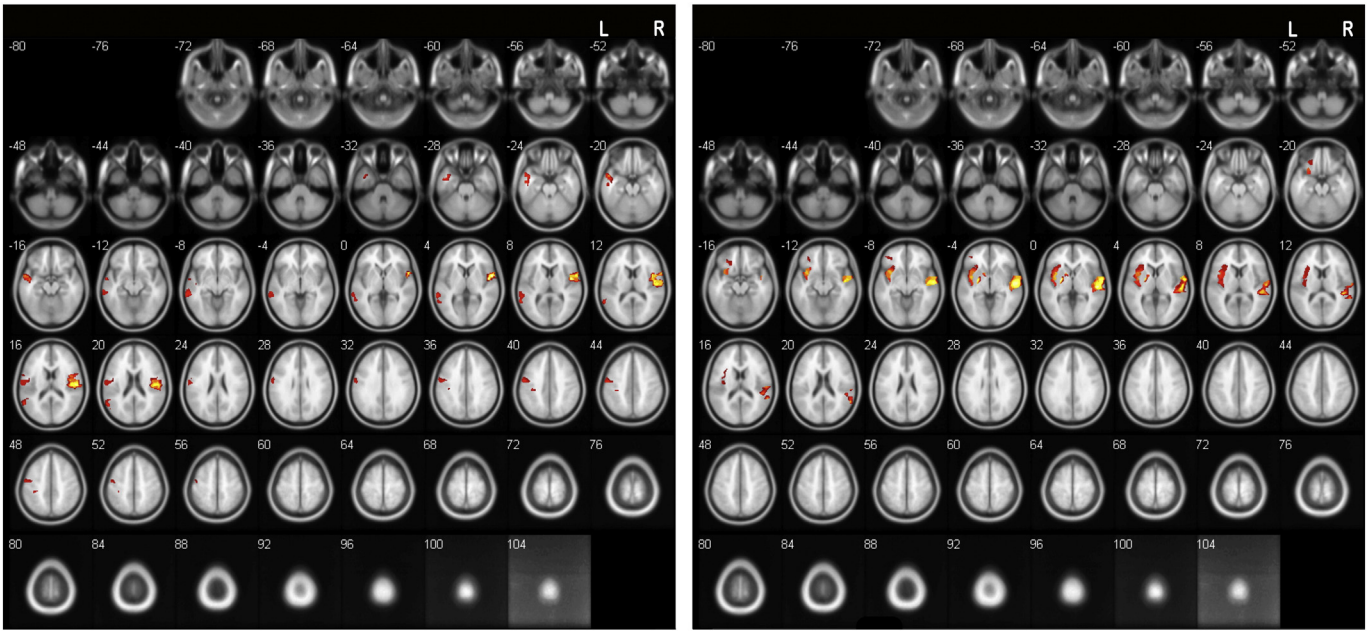

Fig. 2. Differences in the anatomical regions involved in Temporal Orienting effect depending on the cue expectancy condition: Blocked cue (left) vs. Trial-by-Trial (right).

in future studies since the disconnection of the SLF-I could be accounting for it.

The interpretation of the present results should be cautious since, firstly, the regression analysis only provides correlations between variables. Nevertheless the dissociations we report indicate causal relationships between the damaged structures and behavioural performance. Furthermore, the methodological approach we offer allows us to directly relate groups of lesions with temporal tasks. Clearly it would be interesting to pursue these questions with a larger patient sample in order to enhance the prediction of the models, although the variance explained (Adj R^2) in the current study was substantial. Secondly, although very clarifying, this methodology mainly allows us to predict *unicity* and *equivalence* models in which the occurrence of a deficit depends on one or two structures, but prevents us from predicting *association* or *summation* models where a combined lesion produces the deficit (Godefroy et al., 1998). As a consequence, the interpretation of interactions between lesions relies on the prior knowledge on the subject. Therefore, the next step in the study of neural basis of temporal preparation could be to perform different analyses that generate nonlinear models.

Conclusions

In conclusion, the models we generated predicted the presence of different circuits for each temporal preparation effect, as well as the novel presence of the superior temporal lobe (STL) in the *temporal orienting effect* and the inferior parietal cortex in the *sequential effects*.

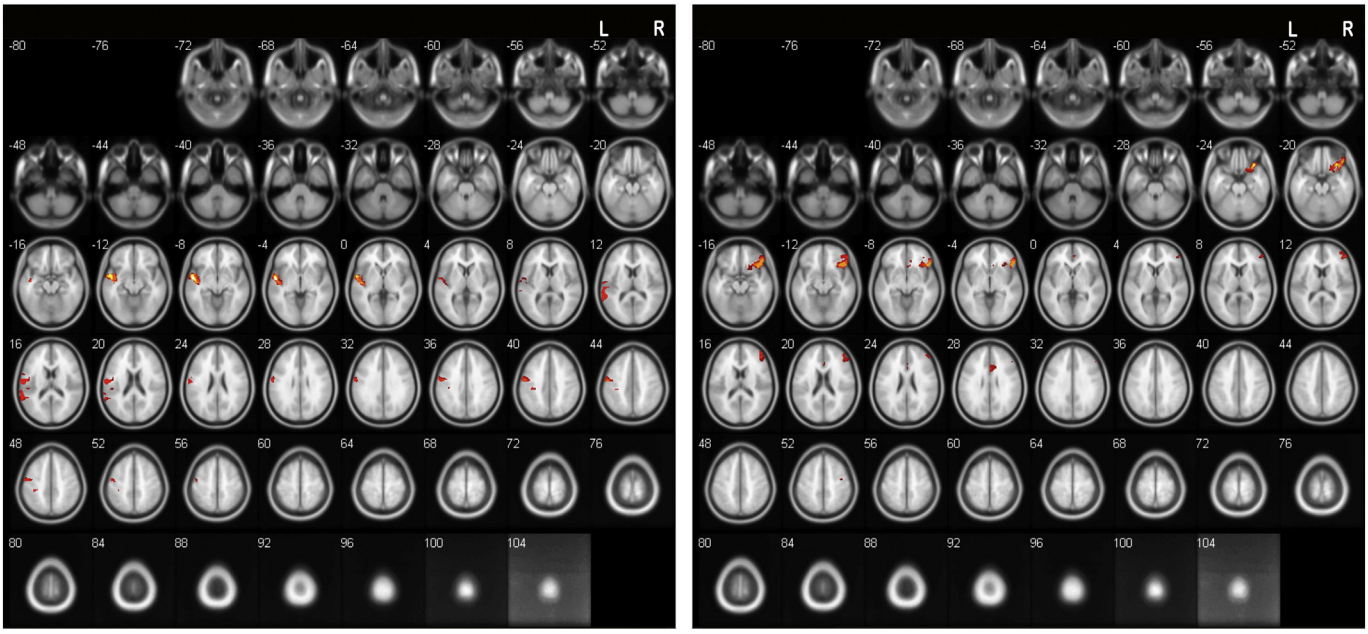

Fig. 3. Differences in the anatomical regions involved in Foreperiod effect depending on the cue expectancy condition: Blocked cue (left) vs. Trial-by-Trial (right).

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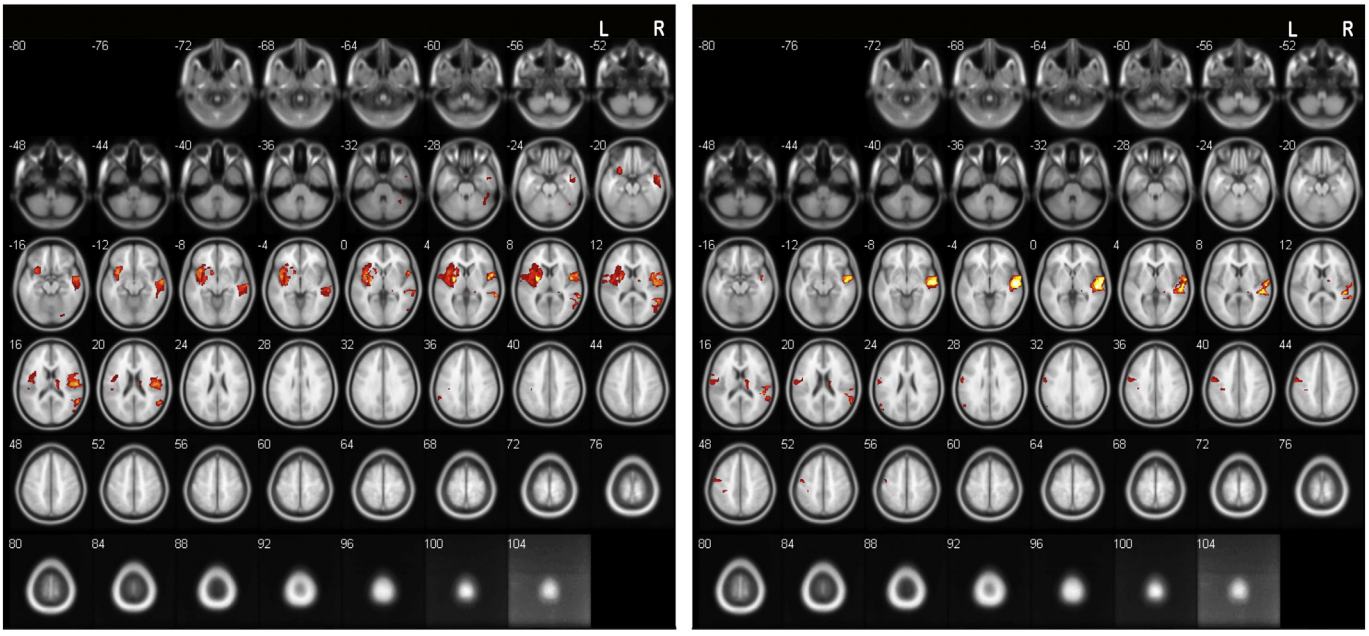

Fig. 4. Differences in the anatomical regions involved in Sequential effects depending on the cue expectancy condition: Blocked cue (left) vs. Trial-by-Trial (right).

Future research should explore the role of these structures in temporal preparation processes with both neuropsychological and TMS studies.

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