Psicológica (2020), 41, 66-83
doi: 10.2478/psicolj-2020-0004

Temporal preparation in patients with Neglect syndrome

Mónica Triviño [*1], Estrella Ródenas[2], Ángel Correa[2,3]

[1]*San Rafael University Hospital, c/ San Juan de Dios, 16, 18006, Granada, SPAIN*

[2]*Mind, Brain and Behaviour Research Center. University of Granada, Campus de Cartuja s/n, Granada, SPAIN*

[3]*Department of Experimental Psychology. University of Granada, Campus de Cartuja s/n, Granada, SPAIN*

The right parietal cortex has been widely associated with a spatial orienting network. Its damage frequently produces the Neglect syndrome consisting in deficits in spatial attention to the left hemifield. Neglect has also been related to temporal deficits (such as the estimation of the duration of a stimulus or the discrimination of two stimuli that occur at the same spatial location but at different time intervals). Such attentional deficits have been much less studied in the temporal as compared to the spatial domain. The current research focused on the study of temporal attention processes in patients with Neglect syndrome, specifically, on temporal preparation. We recruited 10 patients with Neglect syndrome, 10 patients without Neglect syndrome, as well as 11 healthy individuals. Each participant completed an experimental task which measures three main temporal preparation effects described in the literature: Temporal orienting and Foreperiod effects (both related to control mechanisms and prefrontal areas) and Sequential effects (automatic in nature and related to parietal and subcortical structures). The results showed a deficit in the sequential effects only in those patients who suffered from Neglect syndrome. The results suggest a causal relation between Neglect syndrome and the automatic mechanisms of temporal preparation. Since our sample of Neglect patients had suffered lesions mainly in the parietal cortex, the results are discussed taking into account the role of the parietal lobe in the processing of time and the models explaining sequential effects.

[*] **Corresponding author:** Mónica Triviño Mosquera. San Rafael University Hospital, c/ San Juan de Dios, 16, 18006, Granada (SPAIN). E-mail: mtrivino@ugr.es. **Acknowledgements:** This work was supported by the Junta de Andalucía (Research Project Reference: SEJ-3054, http://www.juntadeandalucia.es).

The right parietal cortex has been related to a spatial orienting network (Posner and Petersen, 1990) and its lesion produces the so-called Neglect syndrome. Neglect is associated with lesions in the right hemisphere involving the parietal lobe or the deep white matter that extends into the insula, basal ganglia and prefrontal regions, and fronto-parietal tracts such as the upper longitudinal fascicle and the upper occipito-frontal fascicle (Verdon et al., 2009). The patients suffering Neglect syndrome show difficulties in orienting their attention in space. Specifically, they ignore the stimuli at the contralateral field to the injury. Since this syndrome arises mostly after lesions in the right hemisphere, the unattended hemifield is usually the left one.

In addition to the well-known spatial deficits, Neglect syndrome has further been related to impairments both in time estimation (e. g., Calabria et al., 2011; Danckert et al., 2007; Husain et al., 1997) and in the so-called 'the when parietal pathway' (Battelli et al., 2007; Batelli et al., 2008). This circuit is lateralized to the right parietal lobe and supports temporal processes mediated by attention, for example, the discrimination of two stimuli that occur at the same spatial location but at different time intervals. Battelli and cols. (2007; 2008) suggest that the impairment in the 'when' pathway might underlie important attentional deficits in Neglect patients. However, such attentional deficits have been much less studied in the temporal as compared to the spatial domain. Therefore, the current research aimed to focus on the study of temporal rather than spatial attention processes in patients with Neglect syndrome, specifically, on temporal preparation.

Temporal preparation allows us to time our responses to the optimal moment. Temporal preparation can be studied in the laboratory by presenting a first stimulus (so-called "warning signal" or "temporal cue"), an interval of variable duration ("preparatory interval" or "foreperiod"), and a second stimulus, to which participants have to respond ("target"). By using this procedure, three temporal preparation effects have been described in the literature (reviewed by Capizzi & Correa, 2018).

First, the *Temporal orienting effect* reflects our ability to direct attention voluntarily to a cued point in time, based on the expectation about the moment when a target stimulus will probably happen. For example, an "early" cue (e.g., a short bar) indicates with high probability (p=.8) that the target onset will occur after a 400-ms foreperiod ("late" cue is paired with a 1400-ms preparatory interval; Correa et al., 2004; Coull & Nobre, 1998; Nobre, 2001). Functional neuroimaging studies have linked the *Temporal orienting effect* to a left fronto-parietal network (Coull, Cotti & Franck, 2016; Coull et al., 2004), whereas neuropsychological studies have associated

temporal orienting with both the right prefrontal cortex (Triviño et al., 2010; Triviño et al., 2011) and bilateral temporal lobes (Triviño et al., 2016).

Second, the *Foreperiod effect* (i.e., the effect of the duration of the preparatory interval between a warning signal and a target) is indexed by faster reaction times (RTs) 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 (Niemi & Naatanen, 1981), and has been related to either the right prefrontal cortex or bilateral prefrontal cortex, depending on the study (Stuss et al., 2005; Triviño et al., 2010; Triviño et al., 2011; Triviño et al., 2016; Vallesi, Mussioni et al., 2007; Vallesi, Shallice el al., 2007).

In *Sequential effects,* individuals respond faster when the previous foreperiod is equal to (or shorter than) the current foreperiod, while they respond slower when the previous foreperiod is longer (see Los, 2010 for a review). In contrast to the temporal orienting effect, sequential effects are automatically guided by exogenous stimuli rather than by controlled, endogenous expectations (Capizzi et al., 2012), as they are unaffected by loading working memory in dual-task procedures (contrary to temporal orienting; see Capizzi et al., 2013). The neural basis of sequential effects, however, is largely unknown. So far, we know that *Sequential effects* do not rely on either the prefrontal lobes (they are preserved after both left and right prefrontal lesions; Triviño et al., 2011; Triviño et al., 2010) or the basal ganglia (they have been seen preserved in patients with Parkinson's Disease; Mioni et al., 2018).

To sum up, the main objective of this study was to measure the effect of lesions in the right hemisphere due to strokes (compromising mainly the parietal lobe and/or subcortical white matter) and producing (or not) the Neglect syndrome, on the three abovementioned effects of temporal preparation, with an experimental paradigm previously used in patients with damage in the prefrontal cortex and in the basal ganglia (Triviño et al., 2010; Triviño et al., 2011). If the parietal lobe and adjacent subcortical regions are specifically involved in the automatic temporal preparation, both groups of patients (with and without Neglect) will show impaired *Sequential effects* as compared to a matched group of healthy subjects. However, if Neglect syndrome is specifically related to attentional deficits in the temporal domain, this group will show a selective deficit of controlled temporal preparation (*Temporal orienting* and *Foreperiod* effects) as compared to the other groups.

MATERIALS AND METHOD

Participants. The sample included 31 participants divided into 3 groups. The Neglect syndrome group consisted of 10 patients with lesions mainly in the right parietal lobe. This damage included the inferior-posterior part of it, or a damage of the circuits that connect the cingulate, thalamus or basal ganglia with parietal areas. All the participants in this group confirmed the diagnosis of Neglect Syndrome according to neuropsychological assessment applied by an experienced clinical neuropsychologist. The group without Neglect syndrome was composed of 10 patients with lesions mostly at the right subcortical region without Neglect Syndrome. The 11 participants of the Healthy control group were matched in age with patients with brain damage. The two groups of patients had been suffered ischemic or haemorrhagic strokes in the right middle cerebral artery. The exclusion criteria were the existence of left hemisphere lesion (in both groups of patients), previous neurodegenerative diseases, severe psychiatric disorders, uncorrected visual alterations, visuo-motor coordination deficits (according to medical records) or impaired sustained attention. See Table 1.

Table 1. Demographic and neurological data of the study participants.

GROUP	N	AGE	LOCALIZATION OF THE INJURY & RADIOLOGY REPORT
Patients with Neglect Syndrome	10	mean =68.60 s.d.=9.41	CT: hematoma in upper right frontoparietal region CT: extense stroke in right MCA territory MRI: extense subacute stroke in right MCA territory CT: infarcted area in the right MCA territory MRI: extensive ischemic right fronto-parieto-temporal lesion that also affects the insula and the silvian cortex, as well as the caudate and lenticular nucleus CT: right parieto-occipital hematoma MRI: extense stroke in the territory of the right MCA with midline deviation CT: right MCA ischemia producing the lateral ventricles compression CT: hemorrhagic foci in right MCA territory CT: hemorrhage in right basal ganglia with intense peripheral edema and mild midline deviation with lateral ventricular compression
Patients without Neglect Syndrome	10	mean = 70.40 s.d.=12.59	CT: right thalamus-capsular hematoma MRI: hyperintense lesion in right paraventricular area CT: ischemic stroke in right basal ganglia CT: hematoma in the basal ganglia CT: hematoma in right basal ganglia with perilesional edema CT: hypodense lesions in right basal ganglia CT: acute ischemic infarction in right basal ganglia CT: ischemic stroke in the deep territory of the right MCA MRI: hyperintense lesion in the posterior arm of the internal capsule TAC: ischemic stroke in right basal ganglia
Healthy control	11	mean=65.64 s.d.=10.47	

Note: s.d.: standard deviation of the mean; CT: computerized tomography; MRI: magnetic resonance imaging; MCA: middle cerebral artery.

Ethical Standards. The study was approved by the ethics committee of Virgen de las Nieves Hospital (Granada) and the research met the ethical standards of the Declaration of Helsinki. Written, informed consent was obtained from all of the participants. A surrogate consent procedure was administered when the patients had a compromised capacity to consent. In those cases, next of kin or a legally authorized representative consented on behalf of the participants. This consent procedure was also approved by the same ethics committee.

Neuropsychological Assessment. All participants underwent a neuropsychological evaluation (see Table 2 in the Results section for information about the tests and functions explored) with two objectives: 1) determining the exclusion or inclusion to the study in general and to a particular group, and 2) to study differences in the neuropsychological profile among the three groups. The total duration of the evaluation was approximately 2 hours per participant and was applied by an expert clinical neuropsychologist.

Behavioral Task. The temporal preparation task was a simple RT task extensively used to measure the three effects of temporal preparation (Temporal orienting, Foreperiod and Sequential effects) in different populations (Correa et al., 2010; Correa et al, 2011; Triviño et al., 2011).

Apparatus and stimuli. The experimental task was programmed with the E-prime software (Schneider et al., 2002). A laptop with a 15-inch screen was used for its administration. The stimuli were presented in the centre of the screen on a black background. Each trial included a fixation point consisted of a square of grey colour (0.25º x 0.25º of visual angle), a temporal cue consisting of a horizontal red line which may have two different lengths: short line (0.38º x 0.95º) or long line (0.38º x 2.1º) and, finally, a target determined by the letters "X" or "O" (0.38º x 0.76º). The probability of occurrence of both letters was identical (p = 0.5). Two different letters were used (instead of just one) in order to be able to compare the results with previous studies that use this same task (Correa et al., 2006, Triviño et al., 2010; Triviño et al., 2011).

Procedure. The All participants were first given a complete neuropsychological evaluation. Those fulfilling the inclusion criteria then performed the temporal preparation task.

Participants remained seated approximately at 60 cm from the computer screen. The task started with a fixation point presented for a random interval between 500 and 1500 ms. Subsequently, the temporal cue appeared for 50 ms, which length indicated with high probability (p = .75) the time interval (foreperiod) after which the target would appear: the long cue

indicated the long foreperiod, the short cue indicated the short foreperiod. After the temporal cue, the screen remained black for either 350 ms or 1350 ms, depending on the foreperiod condition of that trial. Each of these conditions represented half of the task trials and were administered pseudo-randomly but equiprobably to achieve approximately the same number of trials per each *Sequential effects* condition. The cues led to two types of trials: valid trials, where the cue actually predicted the time at which the target actually appears (75% of trials), and invalid trials, in which the cue correctly informed on the target onset only in the 25% of trials. *Sequential effects* were computed using the valid trials. Finally, the target appeared for 100 ms and participants had to respond as quickly as possible by pressing the 'B' key on the computer keyboard. The screen remained black until the response was executed or during 2000 ms. Then, the next trial began (Figure 1).

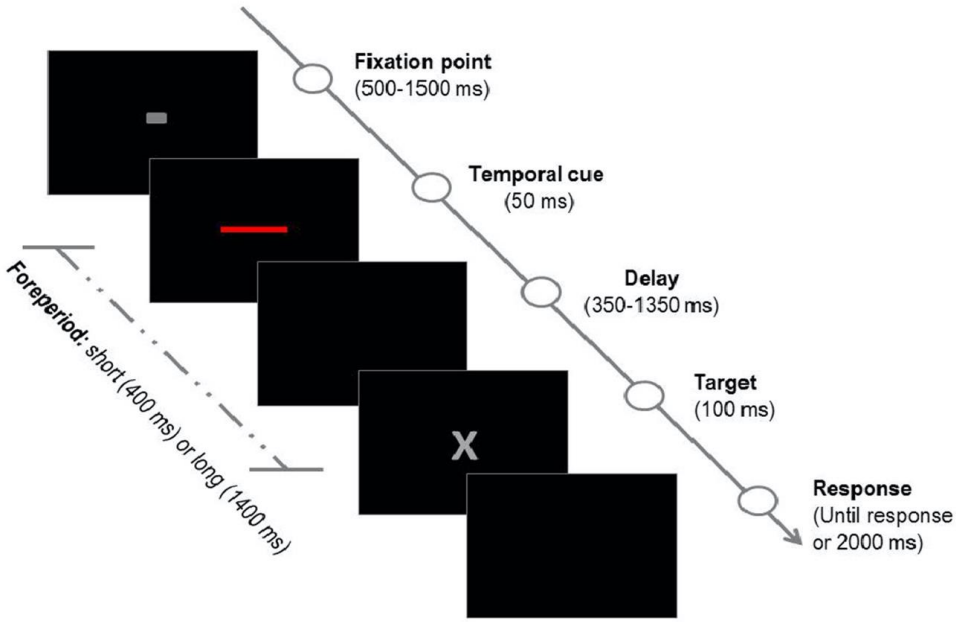

Figure 1. Procedure of the temporal preparation task.

The task included a practice block and four experimental blocks. The practice block consisted of a total of 16 valid trials: eight "early" cue and eight "late" cue trials. In this block the participants received feedback (accuracy, reaction time, anticipation, delay and errors in the response) at the end of each trial.

Each of the four experimental blocks was composed of 32 trials, with two blocks of early cue and two blocks of late cue (presented in counterbalanced order across participants). Temporal expectation was

therefore manipulated between blocks, because it optimizes the finding of temporal cuing effects (Correa et al., 2006). In the experimental blocks, only the feedback regarding the anticipation or delay of the response was presented. The task allowed a break between blocks. Each subject performed the task in two different sessions with, at least, 24 hours apart, thus obtaining a total of 8 blocks per participant.

Statistical analysis. Since some of the demographic and neuropsychological variables did not meet the normality criteria, a nonparametric Mann Whitney U test was performed to compare each group with lesion (with and without Neglect syndrome) with the control group.

In the behavioural task, practice trials and the first trial of each block were not included in the analysis. Anticipation errors, in which participants responded before the target appeared (0.21% of trials rejected), or missing responses, in which participants did not respond when the target appeared (6.03% rejected) were not analysed further due to insufficient observations. Mean reaction times of correct responses between 100 ms and 1000 ms (3.32% rejected) were used to compute the z-scores which are recommended to minimise the type I error in the scenario of general slowing (e.g., Hedge, Powell & Sumner, 2018).

First, a preliminary analysis of the controlled and automatic effects was carried out, as in Triviño et al. (2011), to check the presence of our main temporal effects. That is, z-scores of correct responses were submitted to an Analysis of Variance (ANOVA) with a 2 (Foreperiod: short, long) x 2 (Validity: valid, invalid) design to test for temporal orienting (validity) and foreperiod effects, and an ANOVA with a 2 (Foreperiod: short, long) x 2 (Previous Foreperiod: short, long) design to test for foreperiod and sequential effects.

Next, we analysed the three indices of temporal preparation as in Triviño et al. (2011; 2016) to test for the group effect. The *Temporal orienting* index was obtained in the short foreperiod subtracting the z-scores of the invalid minus valid trials. The *Foreperiod* index was obtained in the condition of invalid trials by subtracting the z-scores in the long foreperiod minus the short foreperiod trials. The *Sequential effects* index was obtained in the current short foreperiod by subtracting the z-scores of the previous long foreperiod minus the previous short foreperiod. Separate ANOVAs with Group (Healthy control, patients with Neglect, patients without Neglect) as a between participants factor were performed for each index.

Finally, a Bayesian ANOVA analysed with Group as factor (JASP Team, 2016, retrieved from https://jasp-stats.org). This analysis contrasts the likelihood of the data fitting under the null hypothesis with the likelihood of

fitting under the alternative hypothesis. It is not biased against the null hypothesis, and the evidence for the absence of an effect can be established only on the observed data. Therefore, we can conclude whether the alternative hypothesis is more probable than the null hypothesis or vice versa. In Bayesian statistics, a Bayesian Factor (B_{10}) = 1 indicates no evidence in favour of either the null or the alternative hypothesis. Bayesian Factors < 1 indicate evidence inclined toward the null hypothesis, while Bayesian Factors > 1 indicate that we can opt for the alternative hypothesis (Jarosz and Wiley, 2014).

RESULTS

Demographic and neuropsychological results. There were no significant differences between groups in age (all *ps* > 0.350). Regarding the neuropsychological assessment (see Table 2), the group with Neglect syndrome, as expected, committed more omissions to the left –in both the extinction and cancellation tests– than the other two groups (without Neglect syndrome and Healthy controls).

Table 2. Mean and standard deviation of the mean (between parentheses) in the different neuropsychological tests administered, as well as the differences found between groups in each of them and their degree of significance. Note that the comparisons were made between the Healthy control group and the two groups with brain injury independently, with the exception of the extinction and cancellation tests in which only the comparison between the two groups with injury was made.

FUNCTION ***Test and Subtest***	**Neuropsychological assessment**		
	GROUPS		
	Healthy control	**Control with lesion**	**Experimental**
Attention *Sustained attention*			
A Test (Total errors) (DS)	0.10 (0.32)	0.10 (0.32)	0.10 (0.32)
Selective attention			
Picture completion subtest of WAIS-III (ES)	12.30 (1.95)	7.80 (3.19) **	7.00 (2.45) ***
Hemineglect			
Extinction test (Errors to the left) (DS)	N.A.	0.00 (0.00)	7.60 (2.17) ***
Cancellation test (Omissions to the left) (DS)	N.A.	0.00 (0.00)	20.22 (18.80) ***

Verbal Memory Test Aprendizaje Verbal España Complutense, TAVEC			
Learning	49.38 (7.93)	33.50 (6.80) ***	38.31 (8.27) *
Short term free recall	10.08 (3.21)	6.40 (2.63) **	8.40 (2.78)
Short term cued recall	11.11 (2.77)	8.10 (2.92) **	9.06 (2.74) *
Long term free recall	10.09 (3.41)	6.80 (3.12) *	8.53 (3.84)
Long term cued recall	10.77 (3.46)	7.70 (2.83) *	9.53 (2.69)
Intrusions in free recall (Long term)	2.00 (2.36)	3.50 (5.52)	2.20 (2.17)
Intrusions in cued recall (Long term)	0.57 (0.50)	4.40 (4.90) **	2.37 (2.18) *
Perseverations	2.11 (1.59)	2.50 (2.22)	5.48 (5.28)
Recognition (Hits)	14.56 (0.83)	12.50 (2.55) *	14.03 (1.42)
Falses positives in recognition	1.11 (1.20)	3.00 (2.71)	2.62 (2.45)
Visual Memory Rey Complex Figure Test			
Immediate Recall (PC)	48.50 (30.92)	31.98 (27.23)	15.63 (17.15) *
Constructive praxia			
Copy of the Rey Complex Figure Test (PC)	73.00 (27.20)	16.68 (22.2) ***	2.37 (1.41) ***
Executive functions			
Digit Span Subtest of WAIS- III (ES)	11.10 (1.45)	9.20 (2.35)	9.20 (1.99) *
Spatial Span Subtest of WMS-III (ES)	10.20 (1.69)	8.70 (1.64)	5.66 (1.63) ***
Similarities Subtest of WAIS-III (ES)	13.20 (1.32)	11.60 (2.41) *	12.60 (2.37)
Semantic fluency test (Animals) (DS)	18.40 (5.58)	12.00 (2.62) **	12.10 (3.28) **
Phonetics fluency test (Letter F) (DS)	8.90 (3.81)	5.40 (2.46) *	6.40 (4.17)
Keys search test of BADS (Profile)	1.80 (0.79)	0.50 (0.53) ***	0.56 (0.88) **

Note: WAIS-III: Wechsler Adult Intelligence Scale; TAVEC: Spanish version of the California Verbal Learning Test; WMS-III: Wechsler Memory Scale; BADS: Behavior Assessment of Disexecutive Syndrome. ES: escalar score; PC: percentile; DS: direct score; N.A.: no administered. *p<0.05; **p<0.01;*** p<0.001.

None of the patients showed errors in the task of sustained attention (inclusion criteria), but there was impairment on selective attention and working memory as previously described (Husain & Rorden, 2003). Regarding the mnesic abilities, a greater impairment was observed on verbal memory in the group of patients without Neglect syndrome, while patients with Neglect showed greater deficits in visuospatial tasks, such as those related to visual memory, visuoconstructive praxia or visual working memory. Finally, both groups of patients showed deficits in executive functions such as planning and fluency in comparison with the Healthy control group, which execution was normal.

Behavioural Task results. Mean raw RTs and z-scores per experimental condition are detailed in Table 3.

Table 3. Raw reaction times (RT) and z-scores (standard deviation, s.d., in parentheses) per experimental condition from all groups (Neglect syndrome, without (w/o) Neglect syndrome and Healthy control). The data are broken down considering the two analyses carried out: Foreperiod, FP (Short FP vs. Long FP) and Validity (Invalid vs. Valid), and Foreperiod (Short FP vs. Long FP) and Previous foreperiod (Short FP_{n-1} vs. Long FP_{n-1}).

GRUPO	DATA	Short FP		Long FP		Short FP		Long FP	
		Invalid	Valid	Invalid	Valid	Short FP_{n-1}	Long FP_{n-1}	Short FP_{n-1}	Long FP_{n-1}
Neglect syndrome	Raw RT s.d.	643.59 (88.89)	625.99 (75.46)	595.29 (61.58)	597.29 (66.84)	627.51 (76.73)	632.28 (77.25)	594.45 (64.09)	597.96 (65.90)
	z-scores s.d.	0.62 (0.82)	0.36 (0.66)	-0.48 (0.84)	-0.51 (0.64)	0.53 (0.53)	0.56 (0.73)	-0.55 (0.82)	-0.54 (0.72)
w/o Neglect syndrome	Raw RT s.d.	526.01 (72.78)	508.86 (67.98)	472.42 (52.27)	462.30 (53.43)	500.66 (69.28)	532.73 (66.18)	465.59 (44.63)	464.88 (56.95)
	z-scores s.d.	0.72 (0.57)	0.28 (0.92)	-0.38 (0.60)	-0.61 (0.75)	0.06 (0.84)	0.93 (0.46)	-0.49 (0.70)	-0.50 (0.63)
Healthy control	Raw RT s.d.	426.64 (65.94)	395.06 (63.56)	378.42 (55.26)	380.15 (46.47)	392.56 (63.74)	419.93 (63.89)	379.75 (48.04)	379.62 (49.58)
	z-scores s.d.	0.97 (0.71)	-0.03 (0.69)	-0.38 (0.55)	-0.56 (0.68)	-0.05 (0.58)	1.01 (0.57)	-0.53 (0.44)	-0.44 (0.90)

Preliminary analysis. The Foreperiod x Validity ANOVA replicated the main effects of Validity (temporal orienting), F (1, 28) = 11.373, p = 0.002, ηp^2 = 0.289 and *Foreperiod*, F (1, 28) = 30.051, $p < 0.001$, ηp^2 =

0.518[1]. The Foreperiod x Previous foreperiod ANOVA showed a significant interaction between the current and previous foreperiod (sequential effects), F (1, 28) = 7.313, p = 0.012, ηp^2 = 0.207, with a significant effect of the previous foreperiod at the current short foreperiod, F (1, 28) = 23.637, p < 0.001, but not at the current long foreperiod (F < 1).

Main analysis of the three indices of temporal orienting. The ANOVAs with the factor Group (healthy control, patients with Neglect, patients without Neglect) on the three temporal preparation indices showed no significant differences between groups in *Temporal orienting,* F (2, 28) = 1.319, p = 0.283, ηp^2 = 0.086, B_{10} = 0.487 and *Foreperiod,* F (2, 28) = 0.143, p = 0.867, np^2 = 0.010 , B_{10} = 0.229. However, the groups showed significant differences in *Sequential effects*, F (2, 28) = 5.596, p = 0.009, ηp^2 = 0.286, B_{10} = 5.966 (Figure 2). The Bayesian factor supported the results from the ANOVAs, since the B_{10} was much larger in the case of sequential effects. Planned comparisons showed that sequential effects were significantly reduced in the patients with Neglect syndrome as compared to both the Healthy control group, F (1, 28) = 10.218, p = 0.005, ηp^2 = 0.350, B_{10} = 8.995, and the patients without Neglect syndrome, F (1, 28) = 5.993, p = 0.025, ηp^2 = 0.250, B_{10} = 2.723. Sequential effects did not differ between healthy control and patients without Neglect groups, F *(1, 28)* = 0.344, p = 0.564, ηp^2 = 0.018, B_{10} = 0.442.

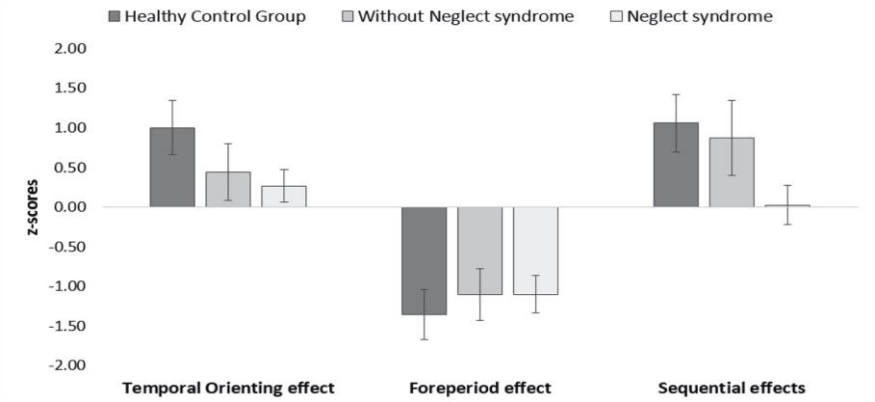

Figure 2. Temporal preparation indices (*Temporal orienting, Foreperiod and Sequential effects*) for Healthy control, Patients without Neglect syndrome and Neglect Patients. Vertical bars represent standard error of the mean.

[1] The Foreperiod x Validity interaction did not reach significance, but the subsequent analysis showed the expected pattern, that is, the validity effect was only significant in the short foreperiod, F (1, 28) = 8.45, p = 0.007, but not in the long one (F < 1), and the foreperiod effect was larger in invalid trials, F (1, 28) = 27.89, p < 0.001, than in valid trials, F (1, 28) = 10.17, p = 0.003.

DISCUSSION

The present investigation showed a selective deficit in *Sequential effects* in the group with Neglect syndrome compared to both patients without Neglect and healthy subjects. In contrast, the groups showed similar effects of *Temporal orienting* and *Foreperiod*. The Bayesian analysis confirmed the specific impairment of the *Sequential effects* in the patients with Neglect syndrome while their execution in *Temporal orienting* and *Foreperiod* effects was preserved. Specifically, these analyses indicate that the differences and similarities between the groups observed in the three indices of temporal preparation do not depend highly on sample size. The Bayesian factor was substantially larger in the Sequential effects (BF10 > 5) —and increased when both Neglect patients and healthy controls were compared (BF10 > 8)—, while it was < 1 in both Temporal orienting and Foreperiod effects.

These results show an altered profile in temporal preparation in those patients with Neglect syndrome, in which the effects considered automatic (i.e., Sequential effects) are deficient, while the controlled effects (i.e., Temporal orienting and Foreperiod effects) are preserved. This profile is inverse to that observed in patients with prefrontal lesions (Triviño et al., 2010; Triviño et al., 2011; Vallesi, Mussoni etal., 2007; Vallesi, Shallice et al., 2007). The difference between patients with prefrontal damage and patients with Neglect syndrome (and therefore mainly with parietal lesions) is the first evidence, using neuropsychological data, of a double dissociation between controlled and automatic temporal preparation processes. A dissociation demonstrated in behavioural and electrophysiological studies (Capizzi et al., 2012; Correa et al., 2004, Correa et al, 2006; Los & Heslenfeld, 2005; Los & Van den Heuvel, 2001) and in neuroimaging and transcranial magnetic stimulations studies (Correa et al., 2012; Coull & Nobre, 2008; Coull et al., 2016; Triviño et al., 2016). Although the mechanisms underlying the three effects are assumed to be different, the prefrontal cortex seems to be crucial for strategies used in temporal preparation based on symbolic cues (temporal orienting) or in the elapsed time (foreperiod), while parietal circuits seem essential for preparation according to the duration of the previous interval (sequential effects).

The nature of Sequential effects has been explained from two main models. First, the trace-conditioning model (Los, 1996; Los and Van del Heuvel, 2001) proposes that implicit trace-conditioning principles would be the basis of the sequential effects. Thus, if the current foreperiod (short or long) matches the previous one, the response will be reinforced, leading to shorter reaction times; but it will be extinguished if the moment is bypassed, leading to longer RTs. Moreover, Vallesi and colleagues (Vallesi, 2010;

Vallesi & Shallice, 2007) propose a dual-process model by which sequential effects would be the result of both automatic arousal from the previous foreperiod and the monitoring of conditional probability at the current trial. Finally, a novel account considers a repetition priming as the mechanism explaining the RT facilitation by sequential effects when previous and current foreperiods are repeated instead of alternated (Capizzi et al., 2015). In line with the two latter models, previous research has related the Neglect syndrome with a disruption of the ascending arousal system (Boukrina & Barrett, 2017), and impaired spatial priming (Shaqiri and Anderson, 2013), which might interfere with the learning of statistical regularities also in the temporal domain. It is difficult nevertheless to conclude whether our findings supported a specific model of sequential effects, since we did not measure trace conditioning, arousal or repetition priming in Neglect patients.

Regarding the relationship between Neglect syndrome, the parietal lobe dysfunction and temporal processing, several studies have shown that lesions in the right parietal cortex, more specific in the right temporo-parietal junction (TPJ), are related to an impaired execution in time estimation (Calabria et al., 2011; Danckert et al., 2007; Husain et al., 1997) and temporal order judgment –TOJ– tasks (Agosta et al., 2017; Berberovic et al., 2004; Husain et al., 2003; Roberts et al., 2012; Robertson et al., 1998). These neuropsychological studies also demonstrate the relation between the Neglect syndrome and these altered temporal processes (15 from 18 Neglect patients in Agosta et al., 2017; 18 from 25 patients in Roberts et al., 2012). The relation between the right inferior TPJ and temporal processing has also been revealed both by an impairment in TOJ tasks after applying Transcraneal Magnetic Stimulation (TMS) in this area in healthy individuals (Agosta et al., 2017) and by an improvement by applying tRNS (transcraneal random noise stimulation) (Tyler, Contò & Batelli, 2018). Moreover, in a previous study (Triviño et al., 2016), we showed that the lesion size of the parietal lobes correlated with the size of *Sequential effects* when the temporal cue was manipulated in a blocked fashion (it remained the same throughout a block of trials) (Triviño et al., 2016).

It can be argued that time estimation is necessary for time preparation. Indeed, for sequential effects to be observed, individuals should differentiate between the target onset after the previous and the current foreperiod, as well as discriminate the duration of both foreperiods. Thus, reinforcement and extinction mechanisms, arousal from de previous foreperiod and the conditional probability monitoring, would need a correct time estimation, which is an impaired function in Neglect patients involving lesions in the right inferior TPJ. However, in a previous study with prefrontal damaged patients (Triviño et al., 2011), we observed that prefrontal patients showed

an impairment in temporal estimation (overestimation and underproduction in the millisecond range) but an inverse pattern to Neglect patients in temporal preparation: a deficit in the Temporal orienting and Foreperiod, but not in Sequential effects. The results suggested that the deficit in time estimation did not seem to be sufficient to prepare in time automatically (i.e., Sequential effects) because the preparation according to the duration of the previous interval could be done implicitly. In this regard, controlled effects (i.e., Temporal orienting and Foreperiod effects) would require an explicit estimation of time, at least, to reorient to the long interval. As Coull and Nobre (2008) proposed, it seems that temporal estimation (or the so-called *explicit timing*) and temporal preparation (*implicit timing*) can be dissociated. Indeed, the tasks of temporal estimation are associated with the activation of motor circuits (mainly basal ganglia or premotor cortex), while the tasks of temporal preparation are related to prefrontal and parietal regions (Coull & Nobre, 2008).

In relation to the group without Neglect syndrome, having subcortical lesions mainly in basal ganglia, did not produce any deficits in temporal preparation, in line with previous research (Triviño et al., 2010). Specifically, in Triviño et al. (2010) we found that the group with lesions in right basal ganglia did not show any impairment of the three temporal preparation effects compared to a group of healthy participants. Altogether, these results suggest that subcortical structures like the basal ganglia might not be essential for the temporal preparation effects studied here, as in the study performed by Mioni et al. (2018) with Parkinson's disease. This finding contrasts with a recent study showing that temporal preparation based on rhythms (i.e., a process of temporal preparation that is highly automatic, similarly to sequential effects; Correa et al., 2014; Cutanda, Correa & Sanabria, 2015; Triviño et al., 2011) was impaired in Parkinson's disease, which can be considered a model of basal ganglia dysfunction (Breska & Ivry, 2018). Breska and Ivry (2018) further found that patients with cerebellar degeneration showed impaired temporal orienting. Therefore, while the focus of temporal preparation research has been in cortical structures (e.g., left intraparietal sulcus, IPS (Coull & Nobre, 1998; Coull et al., 2004), right dorsolateral prefrontal cortex, DLPFC (Vallesi et al., 2007) or prefrontal and temporal cortexes (Triviño et al., 2016), it will be interesting that future investigation clarified the specific role of subcortical structures (cerebellum, basal ganglia) and their connections with the cortex in different processes of temporal preparation.

In relation to the presence of another typical symptomatology of the neglect syndrome that can influence the execution of the temporal preparation task, it could be argued that the difficulties to process the contralateral hemifield to the lesion could impair the perception of the length of the

presented lines (short vs. long), since they were presented in the middle of the screen and the group with Neglect could be ignoring the left half of the lines. However, this deficit does not seem to influence voluntary temporal orienting guided by expectation, since the temporal orienting effect was not disrupted by lesion in the right parietal group. So it would be interesting for future studies to explore the role of the parietal lobe in the temporal preparation using an experimental paradigm where cue and target were auditory signals since the binaural perception would attenuate the effect of spatial neglect.

Other deficits observed in the group with Neglect syndrome are those of selective attention, working memory or visual memory. All of them could be influencing, but again, a failure in the selective attention to the moment of appearance of the target, in the maintenance of the online information to solve each trial or in immediately remembering the relevant information for the task, would mainly influence the effect of *Temporal orienting,* related to a more controlled, conscious and strategic mechanism (Correa et al., 2004), more dependent on the executive functions and the working memory load (Capizzi et al., 2012; Capizzi et al., 2013).

In conclusion, the current study suggests that the right parietal lobe and its associated Neglect syndrome are selectively related to the process of temporal preparation leading to *Sequential effects*. The results suggest that lesions in the parietal cortex, producing in addition the Neglect syndrome, may alter the proper functioning of attentional mechanisms over time, such as temporal estimation. Follow up studies should reveal whether the Neglect deficit is really specific to sequential effects or it can be generalised to other processes of temporal preparation that are automatic, such as preparation guided by isochronous rhythms.

RESUMEN

La corteza parietal derecha ha sido asociada con una red de orientación espacial. Su daño produce frecuentemente el síndrome de Heminegligencia que consiste en déficits en la atención espacial al hemicampo izquierdo. Dicho síndrome también se ha relacionado con déficits temporales (como la estimación de la duración de un estímulo o la discriminación de dos estímulos que ocurren en la misma ubicación espacial pero en diferentes intervalos de tiempo). Sin embargo, tales déficits atencionales han sido menos estudiados en el ámbito temporal que en el espacial. La presente investigación pretende el estudio de los procesos de atención temporal en pacientes con síndrome de Heminegligencia. Se reclutaron 10 pacientes con síndrome de Heminegligencia, 10 pacientes sin Heminegligencia y 11 individuos sanos.

Cada participante realizó una tarea experimental que estudia tres efectos principales de preparación temporal descritos en la literatura: Orientación temporal y Foreperiod (ambos relacionados con mecanismos de control y áreas prefrontales) y Efectos secuenciales (de naturaleza más automática y relacionados con estructuras parietales y subcorticales). Los resultados mostraron un déficit en los efectos secuenciales únicamente en los pacientes con Hemineglígencia. Esto sugiere una relación causal entre el síndrome de Hemineglígencia y los mecanismos automáticos de preparación temporal. Dado que nuestra muestra de pacientes hemineglígentes había sufrido lesiones principalmente en la corteza parietal, los resultados se discuten teniendo en cuenta el papel del lóbulo parietal en el procesamiento del tiempo, y en el marco de los modelos que explican los efectos secuenciales.

REFERENCES

Agosta, S., Magnano, D., Tyler, S., Grossman, E., Galante, E., Ferraro, F., Mazzini, N., Miceli, G., Battelli, L. (2017). The pivotal role of the right parietal lobe in temporal attention. *Journal of Cognitive Neuroscience, 29(5)*, 805-815.

Battelli, L., Pascual-Leone, A., Cavanagh, P. (2007). The 'when' pathway of the right parietal lobe. *Trends in Cognitive Sciences*, *11(5)*, 204-210.

Battelli, L., Walsh, V., Pascual-Leone, A., Cavanagh, P. (2008). The 'when' parietal pathway explored by lesion studies. *Current Opinion in Neurobiology*, *18(2)*, 120-126.

Berberovic, N., Pisella, L., Morris, A.P., Mattingley, J.B. (2004). Prismatic adaptation reduces biased temporal order judgements in spatial neglect. *Neuroreport, 15*, 1199-1204.

Boukrina, O., Barrett, A.M. (2017). Disruption of the ascending arousal system and cortical attention networks in post-stroke delirium and spatial neglect. *Neuroscience & Behavioral Reviews, 83*, 1-10.

Breska, A., Ivry, R. B. (2018). Double dissociation of single-interval and rhythmic temporal prediction in cerebellar degeneration and Parkinson's disease. *Proceedings of the National Academy of Sciences, 115(48)*, 12283–12288. https://doi.org/10.1073/pnas.1810596115

Calabria, M., Jacquin-Courtois, S., Miozzo, A., Rossetti, Y., Padovani, A., Cotelli, M., Miniussi, C. (2011). Time perception in spatial neglect: a distorted representation? *Neuropsychology, 25(2)*, 193-200.

Capizzi, M., Correa, A. Measuring Temporal Preparation. In Vatakis, A., Balci, F., Di Luca, M., Correa, A. (Eds.). (2018). *Timing and Time Perception: Procedures, Measures, and Applications*. BRILL: https://brill.com/view/title/26665. (pp. 216-232).

Capizzi, M., Correa, A., Sanabria, D. (2013). Temporal orienting of attention is interfered by concurrent working memory updating. *Neuropsychologia*, *51*, 326-339.

Capizzi, M., Correa, A., Wojtowicz, A., Rafal, R.D. (2015). Foreperiod priming in temporal preparation: testing current models of sequential effects. *Cognition, 134*, 39-49.

Capizzi, M., Sanabria, D., Correa, A. (2012). Dissociating controlled from automatic processing in temporal preparation. *Cognition, 123(2)*, 293-302.

Correa, A., Cona, G., Arbula, S., Vallesi, A., Bisiacchi, P. (2014). Neural dissociation of automatic and controlled temporal preparation by transcranial magnetic stimulation.

Neuropsychologia, 65, 131–136. https://doi.org/10.1016/j.neuropsychologia.2014.10.023

Correa, A., Lupiáñez, J., Milliken, B., Tudela, P. (2004). Endogenous temporal orienting of attention in detection and discrimination tasks. *Perception & Psychophysics*, *66*, 264-278.

Correa, A., Lupiáñez, J., Tudela, P. (2006). The attentional mechanism of temporal orienting: determinants and attributes. *Experimental Brain Research*, *169(1)*, 58-68.

Correa, A., Miró, E., Martínez, M. P., Sánchez, A. I., Lupiáñez, J. (2011). Temporal preparation and inhibitory deficit in fibromyalgia syndrome. *Brain and Cognition*, *75*(3), 211–216. https://doi.org/10.1016/j.bandc.2010.11.005

Correa, A., Triviño, M., Pérez-Dueñas, C., Acosta, A., Lupiáñez, J. (2010). Temporal preparation, response inhibition and impulsivity. *Brain and Cognition*, *73*(3), 222–228. https://doi.org/10.1016/j.bandc.2010.05.006

Coull, J., Cotti, J., Franck, V. (2016). Differential roles for parietal and frontal cortices in fixed versus evolving temporal expectations: Dissociating prior from posterior temporal probabilities with fMRI. *NeuroImage*, *141*. 10.1016/j.neuroimage.2016.07.036.

Coull, J.T., Nobre, A.C. (2008). Dissociating explicit timing from temporal expectation with fMRI. *Current Opinion in Neurobiology, 18*: 1-8.

Coull, J.T., Nobre, A.C. (1998). Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and f MRI. *Journal of Neuroscience*, *18(18)*, 7426-7435.

Coull, J.T., Vidal, F., Nazarian, B., Macar, F. (2004). Functional anatomy of the attentional modulation of time estimation. *Science*, *303*: 1506-1508.

Cutanda, D., Correa, A., Sanabria, D. (2015). Auditory temporal preparation induced by rhythmic cues during concurrent auditory working memory tasks. *Journal of Experimental Psychology. Human Perception and Performance, 41(3)*, 790–797. https://doi.org/10.1037/a0039167

Danckert, J., Ferber, S., Pun, C., Broderick, C., Striemer, C., Rock, S., Stewart, D. (2007). Neglected Time: Impaired Temporal Perception of Multisecond Intervals in Unilateral Neglect. *Journal of Cognitive Neuroscience*, *19(10),* 1706-1720.

Hedge, C., Powell, G., Sumner, P. (2018). The Mapping Between Transformed Reaction Time Costs and Models of Processing in Aging and Cognition. *Psychology and Aging, 33*(7): 1093–1104.

Husain, M., Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience*, *4*, 26-36.

Husain, M., Shapiro, K., Martin, J., Kennard, C. (1997). Abnormal temporal dynamics of visual attention in spatial neglect patients. *Nature*, *9;385(6612),* 154-156.

Jarosz, A. F., Wiley, J. (2014). What are the odds? A practical guide to computing and reporting Bayes factors. *Journal of Problem Solving, 7*, 2–9. doi: 10.7771/1932-6246.1167

JASP Team (2016). *JASP* (Version 0.8.0.1) [Computer software].

Los, S.A. (1996). On the origin of the mixing costs: exploring information processing in pure and mixed blocks of trials. *Acta Psychologica, 94,* 145-188.

Los, S.A. Foreperiod and Sequential effects: theory and data. In Nobre, A.C. & Coull, J.T. (2010). *Attention and time*. Oxford: Oxford University Press, (pp. 289-302).

Los, S.A., Van de Heuvel, C.E. (2001). Intentional and unintentional contributions to nonspecific preparation during reaction time foreperiods. *Journal of Experimental Psychology: Human perception and Performance, 27,* 370-386.

Mioni, G., Capizzi, M., Vallesi, A., Correa, A., Di Giacopo, R., Stablum, F (2018). Dissociating explicit and implicit timing in Parkinson's Disease patients: evidence from bisection and foreperiod tasks. *Frontiers in Human Neuroscience*, *12,* doi:10.3389/fnhum.2018.00017

Niemi, P., Näätänen, R. (1981). Foreperiod and simple reaction time. *Psychological Bulletin*, *89(1),* 133-162.

Nobre, A.C. (2001). Orienting attention to instants in time. *Neuropsychologia, 39*, 1317-1328.

Posner, M.I., Petersen, S.E. (1990). The attention system of the humanbrain. *Annual Review of Neuroscience*, 13, 25-42.

Roberts, K.L., Lau, J.K.L., Chechlack, M., Humphreys, G.W. (2012). Spatial and temporal attention deficits following brain injury: a neuroanatomical decomposition of the temporal order judgment task. *Congnitive Neuropsychology, 29*, 300-324.

Robertson, I.H., Mattingley, J.B., Rorden, C., Driver, J. (1998). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature, 395*, 169-172.

Shaqiri, A., Anderson, B. (2013). Priming and statistical learning in right brain damaged patients. *Neuropsychologia, 51(13)*, 2526-2533.

Schneider, W., Eschman, A., Zuccolotto, A. (2002). *E-Prime user´s guide*. Pittsburgh: Psychology Software Tools Inc.

Stuss, D.T, Alexander, M.P., Shallice, T., Picton, T.W., Binns, M.A., Macdonald, R., Boroviec, A., Katz, D.I. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia*, *43*, 396-417.

Triviño, M., Arnedo, M., Lupiáñez, J., Chirivella, J., Correa; A. (2011). Rhythms can overcome temporal orienting deficit after right frontal damage. *Neuropsychologia*, *49(14)*, 3917-3930.

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

Triviño, M., Correa, A., Lupiáñez, J., Funes, M.J., Catena, A., He, X., Humphreys, G. (2016). Brain Networks of Temporal Preparation as revealed by multiple regression analysis of neuropsychological data. *NeuroImage*, *142*, 489-497.

Tyler, S.C., Contò, F., Battelli, L. (2018). Rapid improvement on a temporal attention task within a single session of high-frequency transcranial random noise stimulation. *Journal of Cognitive Neuroscience, 30(5)*, 656-666.

Vallesi, A. (2010). Neuroanatomical substrates of foreperiod effects. In A. Nobre and J.T. Coull (Eds.) *Attention and time* (pp. 303-316). Oxford: Oxford University Press.

Vallesi, A., Mussioni, A., Mondani, M., Budai, R., Skrap, M., Shallice, T. (2007). The neural basis of temporal preparation: insights from brain tumor patients. *Neuropsychologia*, *45(12)*, 2755-2763.

Vallesi A., Shallice, T. (2007). Developmental dissociations of preparation over time: deconstructing the variable foreperiod phenomena. *Journal of Experimental Psychology: Human Perception and Performance, 33(6)*, 1377-1388.

Vallesi, A., Shallice, T., Walsh, V. (2007). Role of the prefrontal cortex in the foreperiod effect: TMS evidence for dual mechanisms in temporal preparation. *Cerebral Cortex*, *17(2),* 466-474.

Verdon, V., Schwartz, S., Lövblad, K., Hauert, C., Vuilleumier, P. (2009). Neuroanatomy of hemispatial neglect and its functional components: A study using voxel-based lesion-symptom mapping. *Brain, 133*, 880-894

(Manuscript received: 27 June 2019; accepted: 12 December 2019)