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Research Report

Time bisection and reproduction: Evidence for a slowdown of the internal clock in right brain damaged patients

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ABSTRACT

Previous studies show that the right hemisphere is involved in time processing, and that damage to the right hemisphere is associated with a tendency to perceive time intervals as shorter than they are, and to reproduce time intervals as longer than they are. Whether time processing deficits following right hemisphere damage are related and what is their neurocognitive basis is unclear. In this study, right brain damaged (RBD) patients, left brain damaged (LBD) patients, and healthy controls underwent a time bisection task and a time reproduction task involving time intervals varying between each other by milliseconds (short durations) or seconds (long durations). The results show that in the time bisection task RBD patients underestimated time intervals compared to LBD patients and healthy controls, while they reproduced time intervals as longer than they are. Time underestimation and over-reproduction in RBD patients applied to short but not long time intervals, and were correlated. Voxel-based lesion-symptom mapping (VLSM) showed that time underestimation was associated with lesions to a right cortico-subcortical network involving the insula and inferior frontal gyrus. A small portion of this network was also associated with time over-reproduction. Our findings are consistent with a slowdown of an 'internal clock' timing mechanism following right brain damage, which likely underlies both the underestimation and the over-reproduction of time intervals, and their (overlapping) neural bases.

Abbreviations: RBD, right brain damaged; LBD, left brain damaged; VLSM, voxel-based lesion-symptom mapping.

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1. Introduction

Time processing is a multifaceted skill, crucial for managing several aspects of our daily activities. For example, we continuously estimate the length of time intervals while performing actions and making decisions (e.g., *running, waiting at a traffic light*) (Frassinetti, Cappelletti, & Bueti, 2016; Koch, Oliveri, & Caltagirone, 2009; Vallesi, Shallice, & Walsh, 2007). The ability to estimate objective (or physical) time is a robust and stable function. Significant alterations of time processing are described following brain damage, psychiatric disorders, or pharmacological intake (Meck, 1996, 2003; Paule et al., 1999). How do we process millisecond-to-second time ranges?

Timing has long been conceptualized as the output of a dedicated system (Rammsayer & Ulrich, 2001; Treisman, 1963). According to the *Scalar Expectancy Theory* (*SET;* Gibbon, Church, & Meck, 1984), an 'internal clock' emits pulses that are subsequently stored in an accumulator, and the number of pulses counted determines the perceived duration of an interval: the greater the number of pulses, the longer the estimation of the interval duration (e.g., Capizzi, Visalli, Faralli, & Mioni, 2022). The pulses stored into the accumulator are then transferred to working memory (i.e., memory stage), and an additional decision stage would finally compare the pulses accumulated in working memory to those already stored in a reference memory system to identify an appropriate response. Other authors (Hopson, 2003; Zakay & Block, 1994), in addition to a central (pacemaker) mechanism processing temporal information, have proposed the involvement of general attentional processes gating the flux of incoming temporal inputs.

Several approaches have been employed to investigate our ability to process temporal intervals in the millisecond-to-second range, for example using time bisection and time reproduction tasks. Time bisection tasks (e.g., Grondin, 2008, 2010; Mioni et al., 2018; Mioni, Zakay, & Grondin, 2015; Vatakis, Balcı, Di Luca, & Correa, 2018) comprise a learning phase and a test phase. In the learning phase, "short" and "long" standard durations are preliminary encoded. In the test phase, probe time intervals are administered, and subjects are required to classify them as short or long with respect to the standard durations. According to the SET model, participants classify a perceived duration as short or long by comparing the number of pulses accumulated in working memory with the number of pulses stored for the short and long standard durations in reference memory (Capizzi et al., 2022; Gibbon et al., 1984). A systematic tendency to (mis)classify probe time intervals as short (i.e., more similar to the short than to the long standard duration) is indicative of time underestimation, whereas a systematic tendency to (mis)classify probe time intervals as long is indicative of time overestimation. In time reproduction tasks, participants are usually first presented with a sample duration, and then required to reproduce the entire duration of the previously presented interval (e.g., through button presses; Grondin, 2008; 2010; Zakay, 1990), which is then compared with the actual interval duration. Time reproduction tasks, in addition to time estimation, require the preparation and execution of a motor response (see for example Mioni, Stablum, McClintock, & Grondin, 2014).

What are the neural bases of time processing? Previous evidence points to a right-lateralized network underlying performance in both time bisection and reproduction tasks. Hashiguchi et al. (2022), for example, using a time bisection task, reported that activity in the right anterior insular cortex and right inferior frontal gyrus was positively correlated with time perception accuracy. While the insular component could be related to the accuracy of temporal discrimination, integrating information from visceral and environmental signals (Craig, 2009), the prefrontal component could support the decision stage, in which standard and target durations are compared (Cromer, Roy, & Miller, 2010; Jiang et al., 2007; Vallesi, McIntosh, & Stuss, 2009). Bueti, Walsh, Frith, and Rees (2008) investigated brain activity while encoding time intervals to be bisected versus reproduced. Activity in the right inferior parietal cortex was found for the time reproduction task but not for the time bisection task. It was suggested that this region could play a role in interfacing the sensory and motor processes required in a time reproduction task, playing a role in translation of temporal information into action. The temporo-parietal cortex could also play a role in time discrimination between pairs of visual stimuli (Morillon, Kell, & Giraud, 2009). As the authors noted, the activation of the temporo-parietal cortex (auditory cortical system) in a visual task that does not tap auditory processing underlines its role in temporal processing, possibly by mediating the representation and integration of stimulus duration, a key feature of the auditory sense (Morillon et al., 2009).

Neuropsychological studies have consistently shown temporal deficits in right brain damaged (RBD) patients (Calabria et al., 2011; Danckert et al., 2007; Harrington, Haaland, & Knight, 1998; Koch, Oliveri, Carlesimo, & Caltagirone, 2002; Magnani, Oliveri, Mancuso, Galante, & Frassinetti, 2011; Oliveri et al., 2009; Oliveri, Magnani, Filipelli, Avanzi, & Frassinetti, 2013). Of most relevance to this study are those investigating time perception and estimation. Harrington et al. (1998), using a duration perception task with intervals in the range of milliseconds, found that right brain damaged (RBD) patients underestimated the passage of time compared to left brain damaged (LBD) patients and controls. The same time underestimation in RBD patients was observed by Oliveri et al. (2013) and Magnani et al. (2011) using a time bisection task, and in a single-case study by Koch et al. (2002) using a verbal estimation task probing longer intervals (>5 sec). According to Oliveri et al. (2013), in healthy subjects the flow of time in the perceived interval has the same velocity as in the real interval. By contrast, in RBD patients, the brain lesion would interfere with the alignment between real and perceived time, with the passage of time of the perceived interval beating slower than that in the real interval. Thus, a right brain lesion may induce a slowdown of the encoding rate from the internal clock, resulting in time underestimation.

If a right brain lesion causes a slowdown of the encoding rate from the internal clock, then RBD patients, in addition to underestimate time (e.g., in time bisection tasks), should in principle also be impaired at reproducing the length of time intervals, for example reproducing intervals as shorter than they are. However, there is only one study on time reproduction in RBD patients, who were actually found to reproduce

time intervals as longer than the real ones (Magnani et al., 2011). One possibility is that the over-reproduction of time intervals is due to patients underestimating the length of the time interval while reproducing it, which would lead to reproducing a longer time interval. The evidence of time over-reproduction following a lesion of the right hemisphere, however, awaits confirmation, as does the purported relation between RBD patients' deficits in time bisection and reproduction tasks.

In summary, previous evidence has shown that RBD patients exhibit a tendency to underestimate the duration of time intervals in time bisection tasks and a tendency to reproduce time intervals as longer (Alexander, Cowey, & Walsh, 2005; Harrington et al., 1998; Magnani et al., 2011; Oliveri et al., 2009; Vallesi, Binns, & Shallice, 2008). Although both deficits can be interpreted with a slowdown of the encoding rate from the internal clock, no study thus far has linked them explicitly. If time underestimation and over-reproduction are attributable to a common underlying internal clock impairment, the two deficits should necessarily co-occur in RBD patients. Otherwise, the two deficits could be attributed to different processes and associated with different neural bases. To test this, we had RBD patients, LBD patients, and healthy controls perform a time bisection task and a time reproduction task. To explore the generality of time processing across different timescales, we used stimuli varying in length between each other by milliseconds (300 msec) or seconds (2000 msec). Based on previous evidence, we hypothesized a deficit in timing mechanisms for intervals varying in the range of milliseconds in RBD patients compared to LBD patients and healthy controls, in the form of a concomitant time underestimation (as in Oliveri et al., 2013; Magnani et al., 2011) and over-reproduction. Whether or not the deficit extended to intervals varying in the range of seconds (i.e., 2000 msec) will help specify the neural bases of time processing across different timescales.

2. Materials and methods

2.1. Participants

Participants (N = 53) involved in the study were thirty-four patients, including eighteen patients with right focal brain damage (RBD, 13 males, mean age ± st dev 62.1 ± 11.9 years; mean education ± st dev 9.2 ± 3.1) and sixteen patients with left focal brain damage (LBD, 9 males, 63.7 ± 13.4 years; mean education ± st dev 10.1 ± 4.3), and nineteen age-matched neurologically healthy controls (HC, 5 males, 62.3 ± 6.7 years; mean education ± st dev 13.1 ± 3.6 years). Patients were recruited at the Istituti Clinici Scientifici Maugeri IRCCS, Castel Goffredo, Italy (see Table 1 for demographic and clinical data).

We determined the sample size of our study through the G*Power software (v. 3.1.9.7; Faul, Erdfelder, Lang, & Buchner, 2007). Based on the results of a previous study (Magnani, Musetti, & Frassinetti, 2020), we estimated a medium effect size n_p^2 = .19 for the Interval*Group interaction (Critical F = 2.16), and set the significance level at α = .05 and the desired power (1 − β) at .8, leading to a minimum sample size = 51. All subjects gave their informed consent for participation in the study, which was approved by the local Ethics Committee, and all procedures were performed in agreement with the World Medical Association Declaration of Helsinki (2001).

2.2. Neuropsychological assessment

General cognitive functioning, as assessed with the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; HC = mean score ± st dev = 27.4 ± 2.3), was generally preserved, and comparable across RBD patients, LBD patients, and healthy controls [$F(2,50) = 1.04$; $p = .36$; $\eta^2_p = .04$; see Table 1]. Patients also received a more extended neuropsychological assessment (Table 1). The presence of neglect, as assessed with the Behavioural Inattentional Test (BIT – conventional subtests; Wilson, Cockburn, & Halligan, 1987), the Apple's Test (Mancuso et al., 2015), and the Bell's Cancellation Test (Mancuso et al., 2019), was considered an exclusion criterion. The presence of comprehension impairment was assessed with the Token Test (De Renzi & Vignolo, 1962). No significant difference emerged in the scores attained at the neuropsychological battery between RBD and LBD patients ($t < 1.78$; $p > .08$ in all cases; see Table 1).

2.3. Procedure

All participants performed four computerized tasks designed to investigate time processing for short and long intervals. The tasks were programmed using Eprime 2.0 (Psychology Software Tools, Pittsburgh, PA). All tasks were administered in a single experimental session lasting 1.5 h overall, in a counterbalanced order. Participants were instructed not to count aloud or subvocally while doing the tasks (as in Oliveri et al., 2009; Rattat and Droit-Volet, 2012).

2.3.1. Time bisection task

The computerized time bisection task required to verbally classify a series of visual stimuli (red squares) displayed for different durations at the centre of the computer screen as 'short' or 'long' with respect to a previously acquired pair of reference durations (see Fig. 1a). We elected a verbal (as opposed to motor) response (as in Magnani et al., 2011; Candini, D'Angelo, & Frassinetti, 2022) to avoid the possible interference effects between spatial (left/right) positions and temporal (short/long) durations (Bonato, Zorzi, & Umiltà, 2012; Vicario et al., 2008). Firstly, participants encoded the pairs of reference durations relative to the short condition (short: 1400 msec; long: 2600 msec) and to the long condition (short: 3500 msec; long: 11,500 msec). They were then presented with either short time intervals, i.e., varying in length between each other by milliseconds (short condition; 1400, 1700, 2000, 2300, 2600 msec) or long time intervals, i.e., varying between each other by seconds (3500, 5500, 7500, 9500, 11,500 msec) time intervals, and had to verbally classify them as "short" or "long", by stating the word "short"/"long" if they thought the probe interval was more similar to the short/long reference duration. Short time intervals were selected on the basis of those employed by Magnani et al. (2011) in a time reproduction task and, with a different sample, in a time bisection task. Long time intervals were selected to be in the same (i.e.,

Table 1 – Neuropsychological data of left-brain damaged and right brain damaged patients, according to the lesion site.

Case	Sex	Age (years)	Education (years)	Aetiology	Delay post-onset (months)	MMSE	Token Test	BIT-C	BCT	AT	
										barrage	asymmetry
LBD 1	M	59	13	H	45	28.49	26.75	145	1	50	0
LBD 2	M	72	13	I	2	27	26.7	NA	NA	NA	NA
LBD 3	M	54	8	I	4	23*	30.8	141	NA	49	1
LBD 4	M	78	5	I	26	30	33.5	145	0	47	−2
LBD 5	F	35	11	H	12	19*	13.25*	139	0	50	0
LBD 6	M	58	8	I	1	26	33.5	144	NA	47	−1
LBD 7	M	67	8	I	2	26	31.5	134	3	45	1
LBD 8	F	76	5	I	30	27.7	33	140	1	50	0
LBD 9	F	56	18	I	8	20.31	27.75	143	1	50	0
LBD 10	M	53	11	H	10	30	34.25	143	0	49	0
LBD 11	F	48	13	TBI	5	26.2	30	NA	0	49	−1
LBD 12	F	59	5	I	1	27	35.25	140	0	48	−1
LBD 13	F	86	18	I	1	29.3	33.25	145	1	45	2
LBD 14	M	77	13	I	1	26.3	32	144	2	50	0
LBD 15	M	77	5	I	68	28.7	32.5	143	1	49	−1
LBD 16	M	64	8	I	4	26	25.75*	143	0	49	1
RBD 1	M	47	13	H	139	26.2	32	144	0	47	−2
RBD 2	M	56	9	H	37	27	33.25	143	1	50	0
RBD 3	M	54	5	I	17	25.9	30	143	1	49	1
RBD 4	F	78	8	I	82	28	35.75	144	0	48	−1
RBD 5	F	85	5	I	84	28.4	31.5	138	0	47	1
RBD 6	M	74	7	I	5	25.3	35	138	1	46	−2
RBD 7	M	60	8	H	2	26	32.5	125*	2	45	−1
RBD 8	M	62	8	I	1	30	NA	NA	0	48	1
RBD 9	M	65	13	I	145	25.2	32.5	138	0	50	0
RBD 10	M	80	15	I	1	21.1*	30.5	137	0	49	1
RBD 11	M	71	5	H	16	25.3	27.25	139	4	48	0
RBD 12	M	53	10	H	117	27	34.25	138	1	49	1
RBD 13	M	62	7	I	2	26.9	34.25	141	1	48	2
RBD 14	F	55	8	I	90	26	33	137	0	50	0
RBD 15	M	68	13	I	18	25.2	31.75	144	0	50	0
RBD 16	M	57	8	I	61	27	34.25	137	4	48	2
RBD 17	F	46	10	T	76	30	31	102*	3	32*	5*
RBD 18	F	44	13	T	1	26.2	31.5	142	5	47	0

LBD = left brain damaged patients; RBD = right brain damaged patients; Education and Age are indicated in years.
Aetiology: I = ischemic; H = hemorrhagic; TBI = traumatic brain injury; T = brain tumor.
MMSE = Mini Mental State Examination (scores are corrected for years of education and age; cut-off > 24); Token Test = cut-off > 26.5; BIT-C = Behavioral Inattention Test – Conventional subtest (cut-off > 129); BCT= Bells Cancellation Test, number of left omissions (cut-off < 5); AT = Apples Test: full apples barrage (cut-off = 45) full apples asymmetry (cut-off = 2); * = pathological score; NA = score not available.

second) range of those employed in the few extant studies on the reproduction of 'long' time intervals (e.g., Gooch, Stern, & Rakitin, 2009), and to have a time distance between successive intervals proportional to that characterizing short time intervals (i.e., ¼ of the difference between the longer and the shorter interval).

Each condition (short, long) comprised 30 trials (6 for each time interval), presented in random order. Before administering the experimental task, a practice session (with accuracy feedback) served to familiarize participants with the reference durations relative to the short and long conditions (n = 10 trials).

2.3.2. *Time reproduction task*

In the time reproduction task, the stimuli were 1 cm × 1 cm squares presented at the centre of the computer screen (see Fig. 1b). A blue square was presented for short (short condition; 1400, 1700, 2000, 2300, 2600 msec) or long (long condition; 3500, 5500, 7500, 9500, 115,000 msec) time intervals. Next, a red square appeared on the screen and participants had to press a button when they felt the red square had lasted as much as the reference blue square. The red square remained on the screen until participants pressed a button to indicate that they felt they had reproduced the entire duration of the preceding

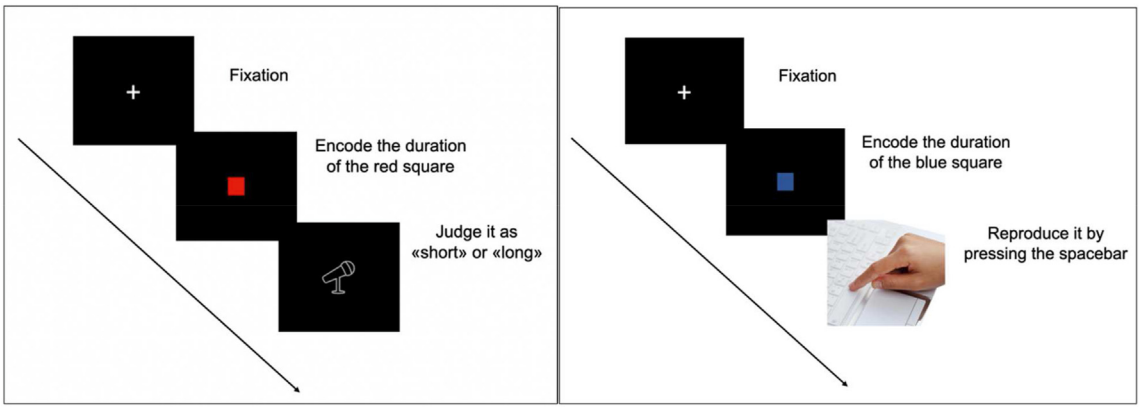

Fig. 1 – A graphic illustration of the computerized Time bisection task (on the left panel) and Time reproduction task (on the right panel). (*a*) A red square was presented, and subjects verbally judged whether the duration of the red square could be classified as "*short*" or "*long*" with respect to two reference durations encoded previously. (b) A blue square was presented at the centre of the screen, and participants were required to reproduce its duration by pressing a button

blue square. Before starting the experimental session, subjects practiced (10 trials) for the short and long conditions. As soon as participants were confident with the task, 30 trials (6 for each time interval) were randomly presented for each condition (short, long). Before administering the task, a practice session (with accuracy feedback) served to familiarize participants with the reproduction of durations ($n = 10$ trials).

2.4. *Statistical analyses*

2.4.1. *Time bisection task*

For each participant, we first examined the proportion of "long" responses on the total number of trials, and then traced an overall 5-point psychometric function plotting the five comparison intervals on the x-axis and the frequency of "long" responses (p-long) on the y-axis. Pseudo-R^2 values were high across groups for both short (HC: mean = .956, SD = .084; LBD: mean = .971, SD = .036; RBD: .924, SD = .076) and long intervals (HC: mean = .978, SD = .031; LBD = .981; SD = .025; RBD: mean = .962; SD = .069), indicating adequate goodness of fit.

For each participant, a Point of Subjective Estimation (PSE) was calculated as the stimulus duration to which the participants responded "short" or "long" with equal frequency. The PSE is associated with the target duration corresponding to a predicted 50% rate of long responses: the smaller the PSE value, the longer the perceived duration. As a measure of time sensitivity, we also calculated, for each subject, the Weber Ratio (WR) as the standard deviation of the fitted cumulative curve (representing the proportion of "long" responses), divided by the PSE. Higher WR values are associated with poorer time sensitivity.

An Analysis of Variance (ANOVA) was conducted on the PSE, taking **Group** (HC, LBD patients, RBD patients) as a between-subject factor. The same ANOVA was computed on WR, to compare time sensitivities across groups. A repeated measures ANOVA was also performed on the mean proportion of "long" responses, including **Group** (HC, LBD patients and RBD patients) as a between-subject factor and **Interval** (1400, 1700, 2000, 2300, 2600 msec for short, and 3500, 5500, 7500, 9500, 11,500 msec for long time intervals) as a within-subject factor. Post-hoc analyses were conducted with the Newman–Keuls test. Effect size was indicated as partial eta square (η^2_p).

2.4.2. *Time reproduction task*

Reproduction abilities were analysed in terms of the estimated-to-target duration ratio (RATIO), the absolute error (AE), and the coefficient of variation (CV). The RATIO was obtained by dividing each participant's reproduced duration (R_d) by the target duration (T_d) for that trial [$RATIO = R_d/T_d$]. Coefficients above and below 1.0 were indicative of over-reproduction and under-reproduction, respectively (see also Supplementary Materials for the statistical analyses on reproduced durations). The AE was calculated as the difference between the reproduced duration and the target duration (in absolute value) divided by the target duration [$AE = |R_d - T_d|/T_d$] (Brown, 1985; see also Glicksohn & Hadad, 2012). Large AE levels indicate low performance. The CV was obtained by dividing the standard deviation in time reproduction performance by the mean reproduction value, separately for each interval (Brown, 1997). This measure indicates the variability of time reproduction performance.

Our dependent variables were subjected to repeated measures ANOVAs with Group (*HC, LBD patients and RBD patients*) as a between-group factor and Interval (1400, 1700, 2000, 2300, 2600 msec for short, and 3500, 5500, 7500, 9500, 11,500 msec for long time intervals) as within-subject factor. Post-hoc analyses were conducted with the Newman–Keuls test. Effect size was indicated as partial eta squared (η^2_p).

2.4.3. *Correlation analyses*

To explore the relation between time underestimation and over-reproduction in RBD patients, Pearson correlation analyses were conducted between the proportion of "long" responses in the Time bisection task and the mean reproduction values in the Time reproduction task, separately for intervals with differences, in the order of milliseconds and seconds.

2.4.4. *Lesion mapping*

Brain lesions were identified by means of Computed Tomography and Magnetic Resonance digitalized images (CT/MRI) of

18 RBD patients and 15 LBD patients (1 out of 34 CT/MRI is missing). For each patient, the location and extent of brain damage was delineated and manually mapped in the MNI stereotactic space by using MRIcro software (Rorden & Brett, 2000). First, to approximate the slice plane of the patient's scan, the MNI template was rotated. Second, brain lesions were manually drawn (GVi) onto each correspondent template slice by using anatomically landmarks. Then, drawn lesions were inspected by trained raters (FF and MC) and, in case of disagreement, an intersection lesion map was used. Finally, each lesions map was rotated back into the standard space applying the inverse of the transformation parameters used in the stage of adaptation to the brain scan. The lesion overlay maps were superimposed on a ch2 template using MRICro, separately for RBD and LBD patients.

A lesion-symptom correlation employing a standard voxel-based approach based on lesion overlay [i.e., the voxel-based lesion-symptom mapping (VLSM, Rorden, Karnath, & Bonilha, 2007)] was computed to examine the lesions more frequently associated with time underestimation (proportion of "long" responses in the Time bisection task) and over-reproduction (mean reproduction values in the Time reproduction task; see Supplementary Materials). Separate analyses were conducted for each interval timescale. VLSM was implemented using the non-parametric mapping (NPM; Rorden et al., 2007), which allows comparing the presence or absence of a lesion in a given cortical area on a voxel-by-voxel basis between the two groups by computing independent group t-tests. Only voxels lesioned in at least 16% of the patients were included in the analysis (see also Kimberg, Coslett, & Schwartz, 2007; Medina, Kimberg, Chatterjee, & Coslett, 2010; Sellitto, Ciaramelli, Mattioli, & di Pellegrino, 2016).

In both analyses permutation thresholding with 1000 iterations was used to apply corrections for multiple comparisons. Quantitative estimates of grey and white matter regions involvement were obtained by superimposing the ch2 anatomical template (Tzourio-Mazoyer et al., 2002) and the JHU-white matter template (Hua et al., 2008).

3. Results

3.1. *Time bisection task – short intervals*

A repeated-measures ANOVA on the mean proportion of "long" responses yielded a significant effect of **Group** [$F(2,50) = 10.24$, $p = .0002$, $\eta^2_p = .29$], highlighting a lower frequency of "long" responses in RBD patients (mean = .41) compared to both LBD patients (mean = .52; $p = .006$) and HC (mean = .58; $p = .0003$), and indicating time underestimation in RBD patients. No difference emerged between LBD patients and HC ($p = .15$). The effect of **Interval** was also significant [$F(4,200) = 343.87$, $p = .00001$, $\eta^2_p = .87$], with the mean proportion of "long" responses increasing with interval (1400 = .06, 1700 = .20, 2000 = .52, 2300 = .83 and 2600 = .92; all ps < .002). These effects were qualified by a significant **Group** × **Interval** interaction [$F(8,200) = 6.710$, $p = .00001$, $\eta^2_p = .21$] (Fig. 2a): RBD patients exhibited time underestimation compared to LBD patients and healthy controls for the 2000 msec (ps < .01) and 2300 msec intervals (.67 *vs* .90; $p = .0005$). No difference across groups was observed in the remaining time intervals ($p > .08$ in all cases).

The one-way ANOVA on PSE values confirmed a significant effect of **Group** [$F(2,50) = 3.64$, $p = .03$, $\eta^2_p = .13$] (Fig. 2b). Post-hoc analyses revealed that RBD patients had higher PSEs (mean = 2661 msec, SD = 1674 msec) compared to both LBD patients (1976 msec, SD = 154 msec, $p = .044$) and HC (1838 msec, SD = 118 msec, $p = .043$), with no difference between LBD patients and HC ($p = .68$).

On the other hand, the one-way ANOVA on WR failed to reveal significant group differences [Group: $F(2,50) = .33$, $p = .72$, $\eta^2_p = .01$], indicating that all groups equally modulated their responses depending on the difference between the standard and the comparison durations (HC = .14; LBD patients = .15; RBD patients = .17; Fig. 2c), which is indicative of preserved time sensitivity across groups.

3.2. *Time bisection task – long intervals*

A repeated measures ANOVA on the mean proportions of "long" responses showed a significant effect of the **Interval** [$F(4,200) = .540$, $p = .0001$, $\eta^2_p = .84$], with the mean proportion of long responses increasing with interval (3500 = .03, 5500 = .17, 7500 = .63, 9500 = .90 and 11,500 = .97; all ps < .03). The effect of **Group** [$F(2,50) = .008$, $p = .99$, $\eta^2_p = .0003$] and the **Group** × **Interval** interaction [$F(8,200) = .540$, $p = .83$, $\eta^2_p = .02$] were not significant (Fig. 2d).

The one-way ANOVA on PSE did not reveal an effect of Group [$F(2,49) = .265$, $p = .77$, $\eta^2_p = .01$], suggesting again no group differences in time bisection for long intervals (Fig. 2e).

The one-way ANOVA on WR values did not reveal significant differences among groups [$F(2,50) = .540$, $p = .585$, $\eta^2_p = .02$] indicating that all groups equally modulated their responses depending on the differences between the standard and the comparison durations (HC = .09; LBD patients = .13; RBD patients = .14; Fig. 2f).

3.2.1. *Interim discussion*

This first set of analyses revealed that perceived time intervals were reflective of the effective duration of target intervals, as the proportion of "long" responses increased with the length of (both short and long) intervals across groups. This result is corroborated by the lack of significant group differences in WR, indicating comparable time discrimination abilities. RBD patients, however, systematically classified temporal intervals with differences in the order of milliseconds as shorter compared to LBD and controls, thus showing a bias towards time underestimation, also apparent in high PSE values.

3.3. *Time reproduction task – short intervals*

The repeated measures ANOVA on RATIO values revealed a significant effect of **Group** [$F(2,50) = 4.986$, $p = .0106$, $\eta^2_p = .17$]. Post-hoc analyses showed higher RATIOs (mean = 1.20; SD = .297) for RBD patients compared to both LBD patients (1.03, SD = .193, $p = .009$) and HC (1.03, SD = .157, $p = .024$), with no difference between LBD patients and HC ($p = .99$), which is indicative of over-reproduction of time intervals in RBD patients. The factor Interval [$F(4,200) = 6.227$, $p = .00009$, $\eta^2_p = .11$] was also significant, with RATIOs decreasing as the

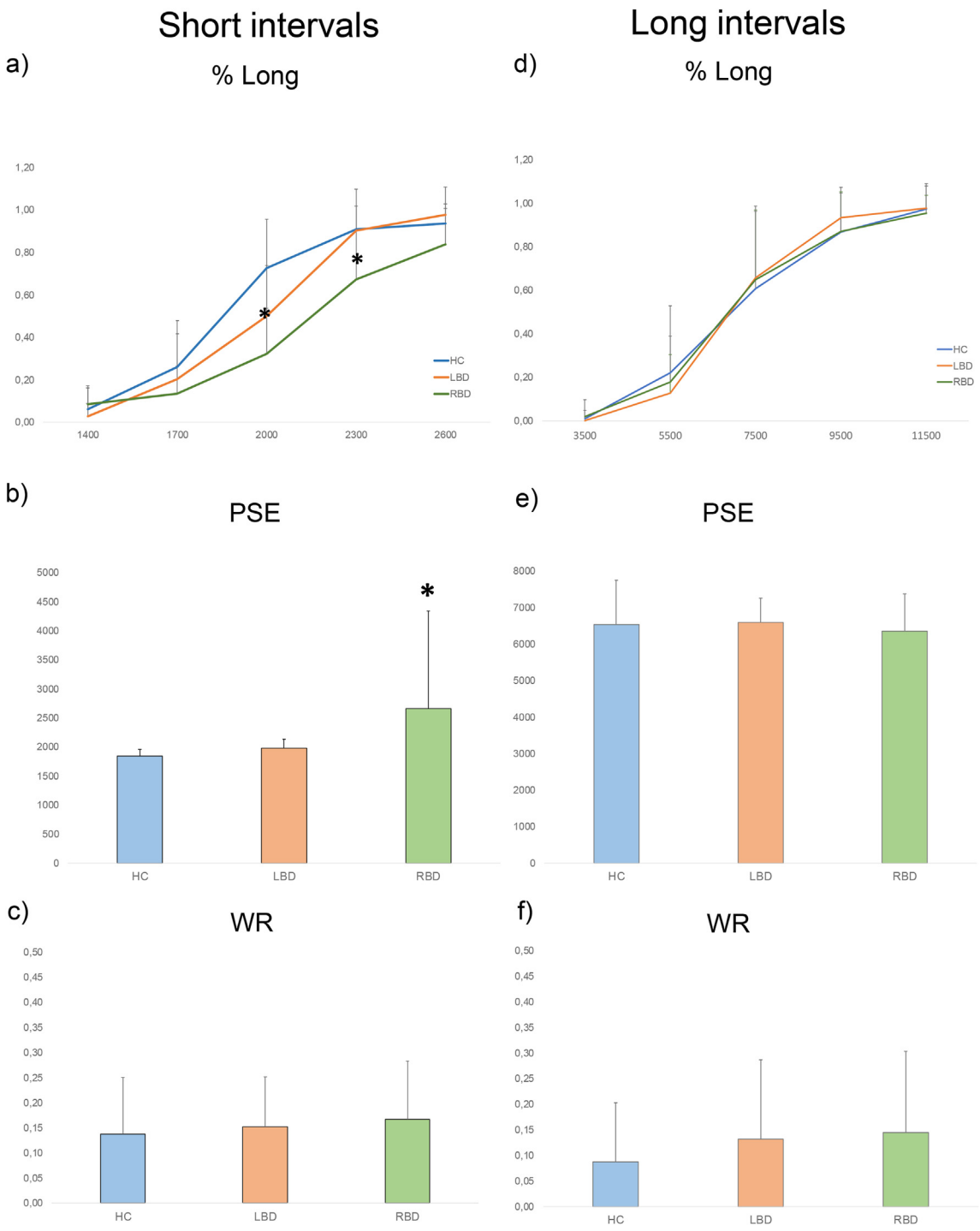

Fig. 2 – Time bisection task. Panel a–d: frequency of 'long' responses by stimulus length (in msec), participant group, and condition. Panel b–e: PSE (i.e., a measure of perceived duration) by participant group and condition. Panel c–f: WR (i.e., a measure of time sensitivity) by participant group and condition. HC = healthy controls, LBD = patients with left brain damage; RBD = patients with right brain damage. Error bars indicate standard deviations from the mean.

interval to-be-reproduced increased (1400 = 1.14, 1700 = 1.13, 2000 = 1.08, 2300 = 1.04 and 2600 = 1.03). These effects were qualified by a significant **Group × Interval** interaction [$F(8,200) = 3.11$, $p = .0024$, $\eta^2_p = .11$], indicating that the RATIOs for stimuli lasting 1400 msec were higher in RBD (1.33) than LBD patients (1.01; $p = .008$) and HC (1.04; $p = .016$). Similarly, the RATIOs for stimuli lasting 1700 msec were higher in RBD patients (1.32) compared to HC (1.03; $p = .012$) and LBD patients (1.05; $p = .015$). In both cases, no difference was found comparing HC and LBD patients (all ps > .99). No significant difference emerged for other interval durations across groups (all ps > .48) (Fig. 3a).

The repeated measures ANOVA conducted on the AEs showed a significant effect of **Group** [$F(2,50) = 4.69$, $p = .0137$,

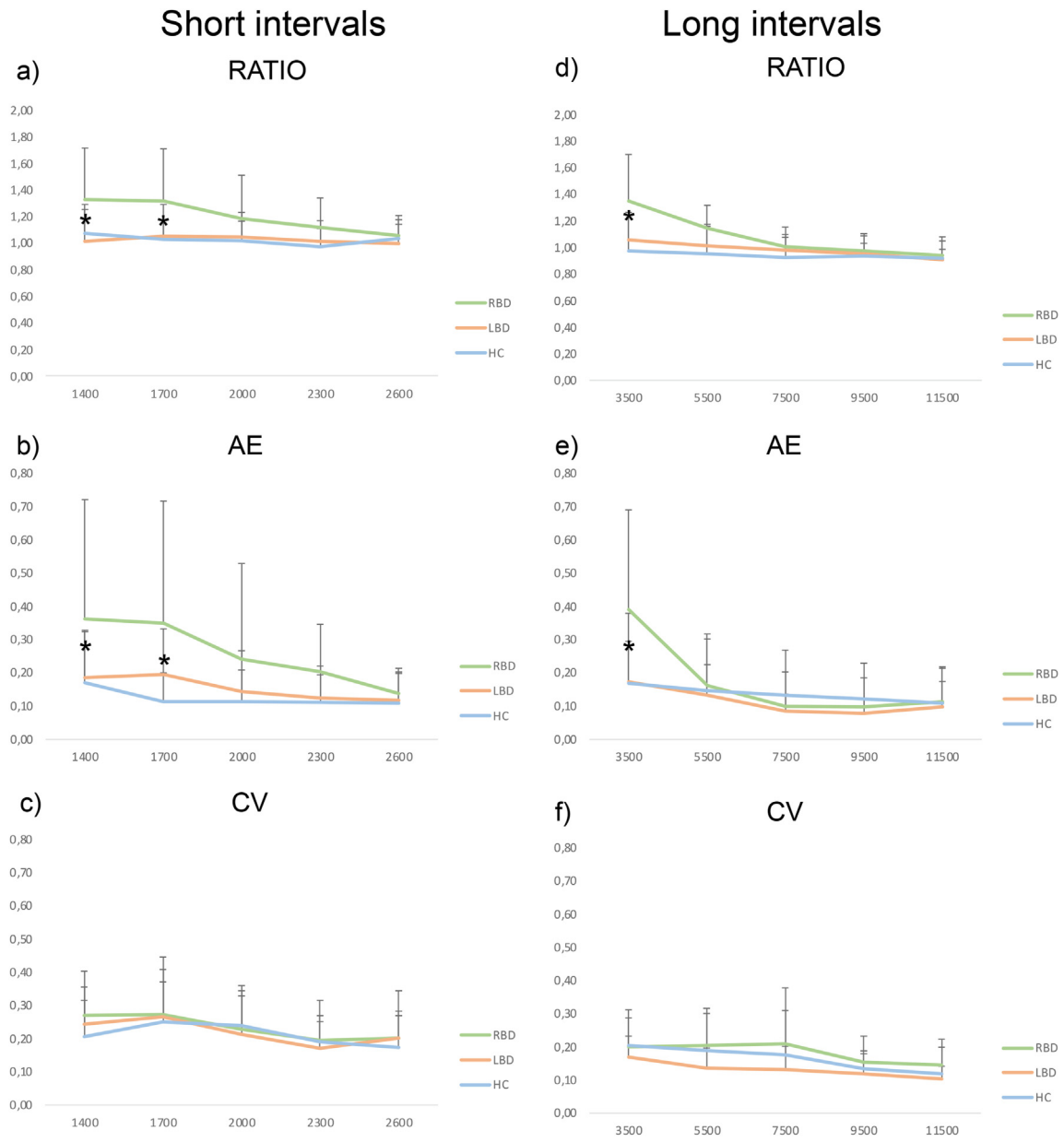

Fig. 3 – Time reproduction task. Panel a–d: RATIO (i.e., the estimated-to-target duration ratio) by stimulus length (in msec), participant group, and condition. Panel b–e: AE (i.e., a measure of accuracy) by stimulus length (in msec), participant group and condition. Panel c–f: CV (i.e., a measure of variability in performances) by stimulus length (in msec), participant group, and condition. HC = healthy controls, LBD = patients with left brain damage; RBD = patients with right brain damage. Error bars indicate standard deviation from the mean.

η^2_p = .16]: post hoc comparisons revealed that RBD patients exhibited a worse performance (mean = .26; SD = .246) compared to LBD patients (.15; SD = .115) and HC (.12; SD = .102), with no difference between LBD and HC (p = .52). A significant effect of **Interval** [F(4,200) = 7.42, p = .00001, η^2_p = .13] was also found, such that AEs were higher in 1400 msec (.24) and 1700 msec (.22) intervals compared to 2000 msec (.17), 2300 msec (.15) and 2600 msec (.12) intervals (all ps < .044). These main effects were qualified by a **Group** × **Interval** interaction [F(8,200) = 2.022, p = .045, η^2_p = .07]: AEs for stimuli lasting 1400 msec were higher in RBD (.36) than LBD patients (.18; p = .045) and HC (.17; p = .029). Similarly, AEs for stimuli lasting 1700 msec were higher in RBD patients (.35) compared to HC (.11; p = .007), and, though only numerically, LBD patients (p = .06). In both cases, no difference was found between HC and LBD patients (all ps > .80). No significant group difference emerged for other intervals (all ps > .53) (Fig. 3b).

The repeated measures ANOVA on CVs yielded a significant effect of **Interval** [F(4,200) = 6.46, p = .00007, η^2_p = .11]: in 2300 msec (.19) and 2600 msec (.19) intervals, the CVs were significantly lower than in 1400 msec (.24), 1700 msec (.26) and 2000 msec (.23) intervals (all ps < .046). The factor Group [F(2,50) = .297, p = .744, η^2_p = .01] and the interaction Group X

Interval [F(8,200) = .626, p = .755, η^2_p = .02] were not significant (Fig. 3c).

3.4. Time reproduction task – long intervals

The repeated measures ANOVA on RATIO values revealed a significant effect of **Group** [F(2,50) = 4.76, p = .0128, η^2_p = .16], which was due to RBD patients exhibiting higher RATIOs (1.08) compared to HC (.94, p = .014) and LBD patients (.98, p = .04), and a main effect of **Interval** [F(4,200) = 22.04, p = .0001, η^2_p = .31], such that RATIOs decreased as the interval to-be-reproduced increased (3500 = 1.12, 5500 = 1.03, 7500 = .97, 9500 = .95 and 11,500 = .92). These main effects were qualified by a significant **Group** × **Interval** interaction [F(8,200) = 6.959, p = .00001, η^2_p = .22], revealing that only RATIOs for stimuli lasting 3500 were higher in RBD patients (1.35), compared to HC (.98; p < .0001) and LBD patients (1.05; p = .0001), possibly because these were the shortest of the long intervals, whereas no group differences emerged for the other intervals (p > .05 in all cases) (Fig. 3d).

The repeated measures ANOVA on AEs revealed a significant effect of **Interval** [F(4,200) = 18.02, p = .0001, η^2_p = .26]: AEs for intervals lasting 3500 msec (.24) were significantly higher than for the other intervals (5500 msec = .15; 7500 msec = .11; 9500 msec = .10; 11,500 msec = .11). The **Group** × **Interval** interaction was also significant [F(8,200) = 5.41, p = .0003, η^2_p = .18], indicating that AEs for intervals lasting 3500 msec were significantly higher in RBD patients (.39) than in HC (.17; p = .000028) and in LBD patients (.17; p = .000012), with no difference between HC and LBD patients (p > .95), or for other interval durations across groups (all ps > .73) (Fig. 3e). There was no effect of Group [F(2,50) = 1.44, p = .247, η^2_p = .05].

The repeated measures ANOVA on CVs yielded a significant effect of **Interval** [F(4,200) = 9.53, p = .00001, η^2_p = .16]: CVs were significantly lower in 9500 msec (.14) and 11,500 msec (.12) intervals than in 3500 msec (.19), 5500 msec (.18) and 7500 msec (.17) intervals (all ps < .0005). The factor Group [F(2,50) = 2.20, p = .12, η^2_p = .08] and the interaction Group and Interval [F(8,200) = .54; p = .82, η^2_p = .02] were not significant (Fig. 3f).

3.5. Correlation analyses

To investigate the hypothesized relation between time underestimation and over-reproduction in RBD patients, we performed a Pearson correlation analysis between the proportion of "long" responses in the Time bisection task and mean reproduction values in the Time reproduction task, separately for short and long intervals.

3.5.1. Short intervals

We found a significant negative correlation (r = −.735; p = .001): the lower the proportion of "long" responses (time underestimation), the higher the mean values of reproduction (over-reproduction).

3.5.2. Long intervals

The analysis failed to reveal a significant correlation (r = .195; p = .438).

3.5.3. Interim discussion

This second set of analyses shows again that time interval durations were correctly differentiated since reproduced time increased with the actual length of target intervals across groups and timescales, indicating compliance with task instructions and preserved time discrimination. Moreover, we found time over-reproduction in RBD patients compared to LBD patients and controls, again mostly affecting the reproduction of intervals varying in the timescale of milliseconds. Time over-reproduction was related to time underestimation in RBD patients, suggesting a common underlying mechanism.

3.6. Lesion mapping

The area of maximal overlap of brain lesions in LBD patients covered the insula, putamen, caudate and pallidum, and in RBD patients it covered the insula, putamen, caudate, superior corona radiata, external and internal capsule (see Fig. 4). RBD and LBD patients did not differ in total lesion volume (t_{31} = .05; p = .96).

3.6.1. Time bisection task – short intervals

Voxel-based lesion-symptom mapping (VLSM) showed a significant association (threshold z = 3.389, permutation-based cluster size corrected, p < .05) between time underestimation for short intervals and lesions in the right inferior frontal gyrus (34; 23; −5; z = 3.72, p < .05), superior temporal gyrus (44; −19; 8; z = 4.06, p < .05), insula (37; −24; 11; z = 3.89, p < .05), claustrum (30; 0; 16; z = 3.79, p < .05), caudate (24; −1; 20; z = 3.79, p < .05), inferior parietal lobule (47; −35; 26; z = 3.89, p < .05) anterior portion of the internal capsule (22; −4; 18; z = 3.79, p < .05), external capsule (30; −11; 12; z = 3.58, p < .05), and corona radiata (29; −24; 23; z = 3.89, p < .05) (see Fig. 5a).

3.6.2. Time bisection task – long intervals

No lesion site was significantly associated with performance in the Time bisection task.

3.6.3. Time reproduction task – short intervals

VLSM showed a significant association (threshold z = 3.45, permutation-based cluster size corrected, p < .05) between time over-reproduction for short intervals and lesions in a subset of brain regions also associated with time underestimation in the Time bisection task (see section 3.6.1), including the right superior temporal gyrus (47; −16; 9; z = −3.54, p < .05), insula (45; −16; 14; z = −3.54, p < .05) and postcentral gyrus (56; −24; 14; z = −3.54, p < .05) (see Fig. 5b).

3.6.4. Time reproduction task – long intervals

No lesion site was significantly associated with performance in the Time reproduction task.

4. Discussion

The present study investigated the contribution of the right hemisphere in time processing, by studying performance in time bisection and time reproduction tasks in RBD patients,

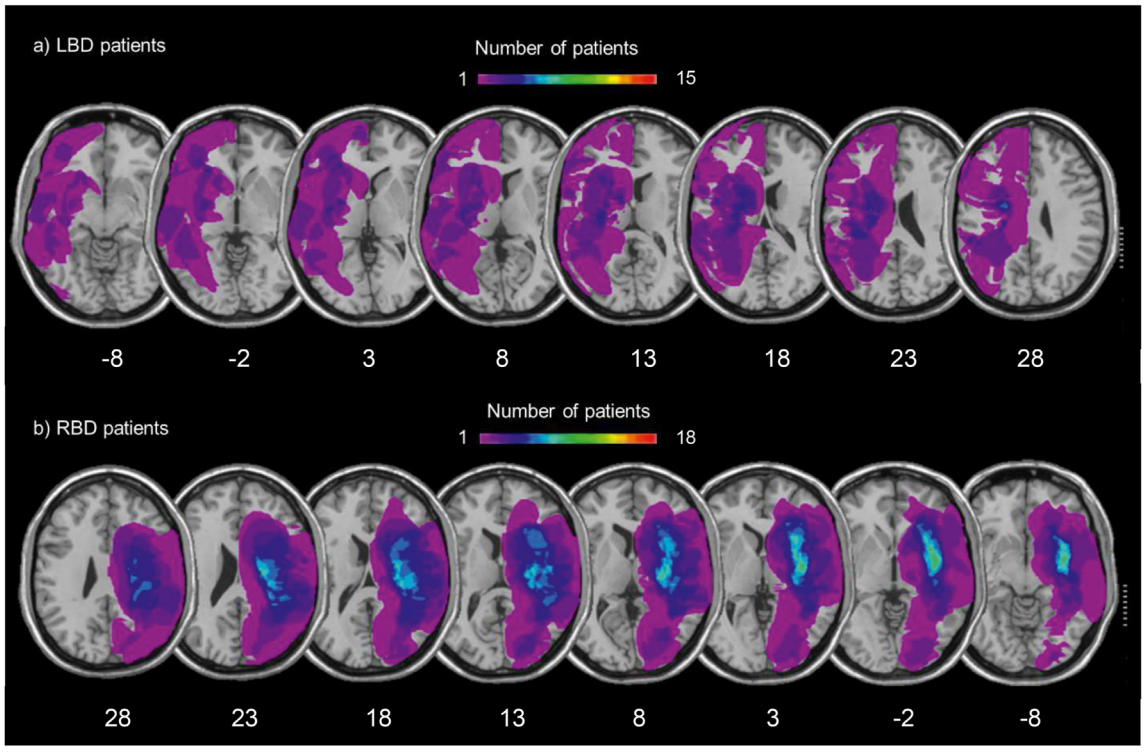

Fig. 4 – Overlay lesion plots for LBD and RBD patients.

LBD patients, and healthy controls. Our results showed that RBD patients perceive time intervals as shorter and reproduce them as longer than they are. This applied consistently to time intervals varying in the range of milliseconds (short intervals), and not seconds (long intervals). Time underestimation and over-reproduction in RBD patients were not a general consequence of brain damage or cognitive impairment, because they were not present in LBD patients. Moreover, RBD patients performed similar to LBD patients at the standardized neuropsychological evaluation. It is also worth noting that RBD patients' performance in time reproduction was not more variable than that of LBD patients and controls,

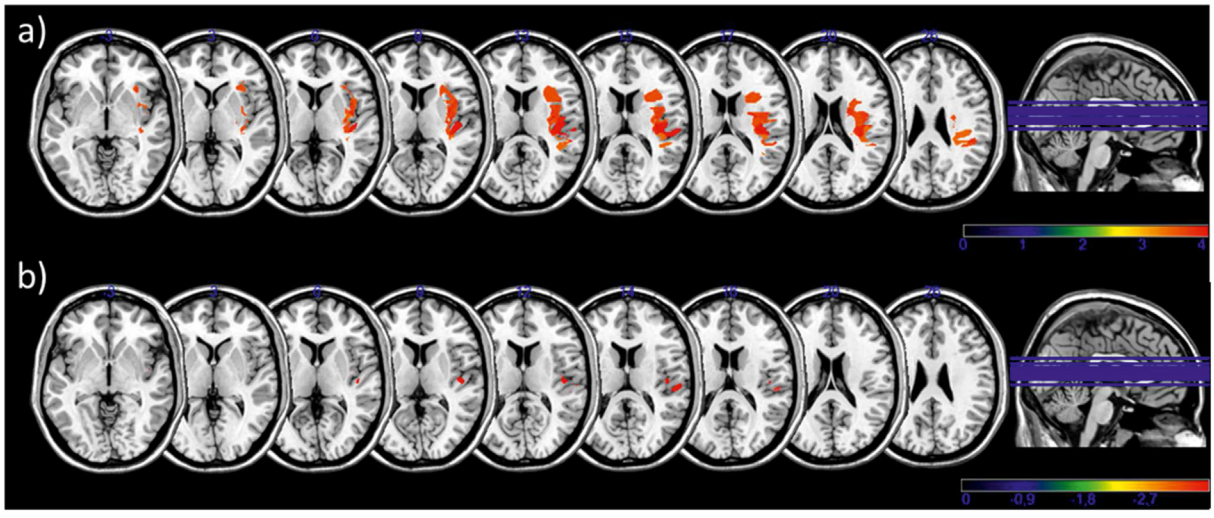

Fig. 5 – VLSM results. Brain regions significantly associated with time underestimation and over-reproduction. Panel a) High z-scores (red) indicate that lesions to these voxels are significantly associated with the underestimation of time intervals in the range of milliseconds (Time bisection task). Panel b) High z-scores (red) indicate that lesions to these voxels are significantly associated with the over-reproduction of time intervals in the range of milliseconds (Time reproduction task). Only voxels that were significant at $p = .01$ are shown. Axial slices are numbered according to Montreal Neurological Institute z coordinates.

suggesting that time over-reproduction is consistently observed in RBD patients. Thus, our results point to a crucial role of the right hemisphere in temporal processing.

The time underestimation observed in RBD patients in the time bisection task aligns with previous neuropsychological and TMS evidence (Harrington et al., 1998; Koch et al., 2002, 2003; Danckert et al., 2007, Oliveri et al., 2009; Calabria et al., 2011; Magnani et al., 2011) of time underestimation following right brain damage or inhibition. These findings suggest that a right hemisphere lesion (or functional lesion) induces a slowdown of the encoding rate from the internal clock (Gibbon et al., 1984). As a consequence, the time flow in the perceived interval would be slower than that in the real interval, leading to fewer clock pulses stored in the accumulator and altered time length representation. On this view, in RBD patients, the tendency to underestimate time would depend on a pure deficit of timing mechanisms while keeping the flow of time (Wiener, Turkeltaub, & Coslett, 2010).

A novel finding of this study is that, in addition to time underestimation, RBD patients showed a tendency to reproduce time intervals as longer than they are, confirming the findings reported by Magnani et al. (2011) (see also Hosseini, Rezaei, & Saberi, 2020 for time reproduction impairments in patients in the acute phase of RBD). Again, the finding applied to short but not long time intervals. Interestingly, performance in the time bisection and time reproduction tasks were related in our sample, such that the more patients underestimated time intervals during time bisection the more they elongated their duration during reproduction, suggesting that time underestimation and time over-reproduction are linked in RBD patients. We propose that both deficits are reflective of a slowdown of the internal clock (Gibbon et al., 1984). Such impairment, indeed, would cause a deficit in timing apparent in the underestimation of time intervals during the time bisection task, and also in the underestimation of the passage of time while reproducing time intervals, and a consequent tendency to prolong their duration. An alternative possibility is that time underestimation and over-reproduction in RBD patients are due to deficits in monitoring mechanisms tracking the passage of time (Stuss et al., 2005; Vallesi, 2021). Were this the case, however, one would not necessarily expect the systematic time underestimation (and corresponding over-reproduction) we observed following right brain damage, but a more erratic pattern of impairment. Moreover, time-based monitoring has been mainly ascribed to the right dorsolateral prefrontal cortex (Vallesi et al., 2009), while our patients had lesions mainly affecting the ventral aspects of prefrontal cortex. Clearly, this also limits our capacity to detect timing deficits related to dorsolateral prefrontal damage (see also Coull, Frith, Büchel, & Nobre, 2000; Stuss et al., 2005; Vallesi, 2021; Vallesi et al., 2009; Vallesi et al., 2007), which will need to be addressed in future studies with a more complete lesion coverage.

VLSM showed that in our RBD sample the selective underestimation of short intervals observed in the time bisection task was associated with lesions in the insula, caudate body, claustrum, inferior frontal gyrus, and a subcortical periventricular portion of the inferior parietal region, a finding closely aligned with a recent meta-analysis of functional imaging studies on time processing in healthy participants (Nani et al., 2019) and with previous lesion studies on time underestimation (Oliveri et al., 2013). This finding provides causal evidence for the role of this distributed network in time processing, highlighting the importance of an interplay between cortical and subcortical components in performing temporal tasks (Wittmann, Simmons, Aron, & Paulus, 2010). The brain lesions in RBD patients associated with the over-reproduction of short time intervals were the insula and post–central gyrus, a subset of those was also associated with the time perception deficits observed in the time bisection task. The overlap in the brain regions associated with the time processing impairments observed in time bisection and reproduction tasks reinforces our view that both depend on a slowdown of the internal clock that follows right brain damage, and puts the insula and post–central gyrus at the core of the timing network. The fact that the VLSM focused on time reproduction deficits only evinced a subset of the brain regions associated with time bisection deficits is likely to reflect the fact that time estimation is but one component process of time reproduction, for which other sources of variation exist (e.g., motor preparation; Mioni et al., 2014), diluting brain-behavior associations.

The right insula has been previously associated with time perception (Craig, 2009; Cromer et al., 2010; Hashiguchi et al., 2022; Hayashi et al., 2013; Jiang et al., 2007; Mella et al., 2019; Monfort et al., 2014; Mottaghy, Gangitano, Krause, & Pascual-Leone, 2003; Wittmann, 2013). The involvement of the right insula is consistent with the role played by this region in the integration of information from the external world with subjective experience of time that is related to interoceptive information (e.g., sequential bodily states; Craig, 2009). This activity has been associated with encoding, but also with reproduction of time representations (Wittmann, 2013). Previous lesion studies have indeed indicated the functional relevance of the right insula in time reproduction (Mella et al., 2019; Monfort et al., 2014). Monfort et al. (2014), for example, reported the case of a patient with a focal lesion in the right anterior insula, showing global over-reproduction of time intervals.

The right inferior frontal gyrus is related instead to categorical decisions (Cromer et al., 2010; Jiang et al., 2007) and has been found to be particularly involved in the decision stage of tasks requiring comparison between two intervals (Hayashi et al., 2013; Mottaghy et al., 2003; Gibbon, et al., 1984; Hayashi et al., 2013). In the present study, the time bisection task - but not time reproduction task - required a categorical decision, which may explain why we detected a selective involvement of the right inferior frontal gyrus in the former. The insula and inferior frontal gyrus, therefore, may support distinct levels of temporal processing: the accumulation of pulses and the decision stage, respectively (see also Hashiguchi et al., 2022).

The basal ganglia and the right part of the caudate nucleus seem to be involved in the early stages of timing – that is, in the encoding of time intervals (Jueptner et al., 1995; Pouthas et al., 2005; Rao, Mayer, & Harrington, 2001). By virtue of its many connections with cortical regions, the caudate nucleus would play the role of an “internal clock” capable of integrating the oscillatory cortical activity (Nani et al., 2019). The claustrum is a structure hidden beneath the inner surface of the insula,

strongly connected with prefrontal regions. A meta-analysis (Schulz, 2016) emphasized the role of the claustrum in orchestrating top-down attention deployment and processing of interoceptive information. Damage to these subcortical regions may therefore affect the encoding stage of durations, by altering the time code for temporal representations.

Finally, a subcortical periventricular area within the right inferior temporo-parietal region was significantly associated with time underestimation in the time bisection task, consistent with previous lesion (Harrington et al., 1998) and fMRI evidence (Lewis & Miall, 2003; Coull, Vidal, Nazarian, & Macar, 2004; Livesey, Wall, & Smith, 2007; Morillon et al., 2009; Wiener et al., 2010) of an involvement of this region in time perception. The auditory system may be implicated in representing the temporal duration of stimuli presented across modalities (Morillon et al., 2009). In addition, the lateral parietal cortex (post–central gyrus) was associated with time reproduction. Several evidence support a role of the posterior parietal cortex, in particular the right inferior parietal lobe, in time processing (see Nani et al., 2019 for a review). For example, cathodal tDCS to the right posterior parietal cortex causes time over-reproduction (Vicario, Martino, & Koch, 2013). The right inferior parietal cortex is deemed involved in interfacing the sensory and motor processes required in time reproduction, by connecting the central clock and peripheral motor effectors (Bueti et al., 2008; Morillon et al., 2009). A lesion to the parietal cortex might therefore impair the translation of perceived durations into the appropriate action (output stage).

A final note pertains to the association of white matter tracts (e.g., internal and external capsules, corona radiata) connecting basal ganglia to frontal motor areas of the brain with the underestimation of intervals in the range of milliseconds in the time bisection task revealed by our VSLM analysis. Previous research had provided evidence for a role of brain connectivity in time processing. Kotz, Brown, and Schwartze (2016), for example, pointed out that reciprocal (afferent and efferent) pathways between cortical and striatal regions of the brain are engaged during temporal discrimination tasks (see also Akkal, Dum, & Strick, 2007; Buhusi & Meck, 2005; Kotz, Anwander, Axer, & Knösche, 2013; Merchant, Harrington, & Meck, 2013). Together, these findings hint at a possible role of damaged connectivity within motor related areas in timing deficits that deserves future inquiry.

5. Conclusion

In summary, we confirmed a systematic tendency in RBD patients to perceive time intervals in the range of milliseconds as shorter than they are. Additionally, we showed that in RBD patients time underestimation was associated (perhaps causally) with a concomitant tendency to reproduce time intervals as longer than they are, and with lesions in the insula, basal ganglia, parieto-temporal cortices, and the inferior frontal gyrus. Both deficits in temporal processing are compatible with a slowdown of time encoding in an 'internal clock' following right brain damage. Additional investigation on the ecological impact of temporal deficits in RBD patients would be necessary to quantify the effects of the timing impairment on daily activities and inform novel, tailored rehabilitation protocols and compensatory strategies.

Open practices section

The study in this article earned Open Material badge for transparent practices. The material used for this study are publicly accessible on Zenodo at the following link: https://doi.org/10.5281/zenodo.8138286.

Data availability statement

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. No part of the study or analyses procedures were pre-registered prior to the research being conducted. The behavioral and lesion data as well as the research materials (e.g., task, including stimuli and code) for this study are publicly accessible on Zenodo at the following link: https://doi.org/10.5281/zenodo.8138286. The ethics approval prevent us from disseminating behavioral data at individual level. No specific permissions/conditions will be considered.

Ethics statement

The studies involving human participants were reviewed and approved by University of Bologna and by Istituti Clinici Scientifici Meugeri IRCCS. The participants provided their written informed consent to participate in this study.

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Credit author statement

GVi, MC, and FF developed the study concept and contributed to the study design. GVi and GVe recruited patients and GVi carried out data collection. GC, GVi, MC conducted data and lesion analyses. All authors contributed to the interpretation of the findings. GC drafted the manuscript. EC and FF revised the manuscript and all authors approved its final version.

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This paper is dedicated to the memory of our dear colleague -and friend- Francesca Frassinetti, who passed away while this paper was being peer-reviewed. She will be remembered not only for her insightfulness and creativity in science, but also for the extraordinary and generous mentor she was.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2023.05.024.

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