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Research report

# The brain and the subjective experience of time. A voxel based symptom-lesion mapping study

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ABSTRACT

The aim of the study was to identify the anatomical bases involved in the subjective experience of time, by means of a voxel based symptom-lesion mapping (VLSM) study on patients with focal brain damage. Thirty-three patients (nineteen with right-hemisphere lesions −RBD, and fourteen with left lesion- LBD) and twenty-eight non-neurological controls (NNC) underwent the semi-structured QUEstionnaire for the Subjective experience of Time (QUEST) requiring retrospective and prospective judgements on self-relevant time intervals. All participants also completed tests to assess general cognitive functioning and two questionnaires to evaluate their emotional state. Both groups of brain-damaged patients achieved significantly different scores from NNC on the time performance, without differences between RBD and LBD. VLSM showed a cluster of voxels located in the right inferior parietal lobule significantly related to errors in the prospective items. The lesion subtraction analysis revealed two different patterns possibly associated with errors in the prospective items (the right inferior parietal cortex, rolandic operculum and posterior middle temporal gyrus) and in the retrospective items (superior middle temporal gyrus, white matter posterior to the insula).

## 1. Introduction

Time is a peculiar object of investigation: it is intangible, no body organ is known to be responsible for its perception, subjective experience of time is extremely variable and is not isometric to physical time, yet it is essential for daily behaviour [1]. Time cognition can encompass quite heterogeneous facets, among which are those involved in time perception, estimation and judgement tasks, but operationalization of time cognition remains challenging [2]. Factors such as attention, memory, emotion and subjective mental states can modulate time cognition [3,4], and several theoretical frameworks have been put forward to account for such effects. Some models highlight the role of attentional factors [5], whereas others stress the importance of emotional and bodily states [6,7]. All multiple cognitive and neural mechanisms related to time cognition converge to warrant the existence of the sense of self across time, thus allowing the phenomenologic experience of subjective time [8–10], for which no simple and generally accepted definitions are available [11]. In the present paper we will operatively address the "subjective experience of time" involved in evaluation of events commonly occurring in daily life, and typically ranging from minutes to hours, days or months [12].

Adopting different experimental settings, several neuroimaging studies investigated the neural correlates of time cognition, emphasizing the role of the basal ganglia [13,14], cerebellum [15,16], right prefrontal cortex [17], right inferior parietal lobe [18], and insular cortex [19]. The basal ganglia might be selectively activated during the coding phase of temporal perception tasks, that is, in the initial phase in which a representation of stimulus duration is formed for later recall [20–22]. Koch et al. [23] underlined that cerebellum may be involved in processing short intervals (in the sub-second range), whereas basal ganglia and frontal-parietal areas may be involved in processing longer intervals (in the second range) and in more complex cognitive functions. The prefrontal cortex seems to be critical for perception and comparison of time intervals.

In a comprehensive review, Macar et al. [24] suggested that basal ganglia (caudate and putamen), supplementary motor area, cerebellum, dorsolateral prefrontal cortex (DLPFC, BA 9/46), anterior cingulate and right inferior parietal lobule (IPL, BA 40) were often active across all time-related tasks and suggest that these regions form the core network of time cognition in the brain. However, literature on time processing in healthy individuals provided a quite heterogeneous picture, likely related to substantial differences in the procedures, tasks, duration of

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the stimuli and type of subjects' response [25,26].

The different aspects of time cognition have been less investigated in brain-damaged individuals. Koch et al. [27] reported a patient with an ischemic lesion of the right dorsolateral prefrontal cortex (BA 46/9) and impaired perception of duration of long intervals (seconds), thus suggesting that the right prefrontal cortex could work as an accumulator of an internal clock, receiving information from the basal ganglia and cerebellum in order to form a conscious representation of the time intervals. In a study on patients with focal left or right hemisphere lesions compared with healthy controls, Harrington et al. [28] observed defective performance on two time perception tasks in patients with right lesions, suggesting that time perception would entail a prefrontal-inferior parietal network in the right hemisphere. Other authors assessed timing processes in patients with cerebellar damage. In particular, Ivry et al. [29] suggested that lateral lesions of the cerebellum could be linked to a deficit in the central timing process. In a related study on patients with different brain lesions, Ivry and Keele [30] confirmed that cerebellum has a central role in timing functions, since only lesions in the cerebellum could determine deficit in both production and perception of time intervals. Later, Spencer et al. [31,32] indicated that the specific role of cerebellum could be related to tasks requiring an explicit timing of behaviorally meaningful events.

All previous studies on both healthy individuals and brain-damaged patients investigated very short time intervals, quite disparate from time intervals relevant for common daily life, usually referring to periods of minutes or hours, or longer. Moreover, all previous studies employed experimental tasks in which participants had to judge time intervals without any reference to personal life and events, but the subjective experience of time has strong relationships with emotional states and situational information [9,33–35]. The neural bases of subjective experience of time have not been specifically explored. Craig [19], in a theoretical essay, suggested that the neural substrate for awareness across time might be located in the anterior insular cortex, but also in this case the model addressed aspects quite far from the ecologically relevant construct of the sense of time. In fact, as recently pointed by Riemer [36], empirical research on time highlighted methodological problems mainly related to the lack of correspondence between psychological and physical time.

Some tests of time estimation about 'long' time intervals are indeed available, but they have been devised to tap the ability of making general cognitive inferences (e.g., by questions such as 'In how long time will an egg become solid?' [37]), or the individual psychological time perspective [9,38], rather than estimation of the subjective time experience. To the best of our knowledge, one questionnaire has been specifically devised to evaluate self-relevant, ecological time intervals in clinical samples [12]. In particular, the questionnaire included items assessing minute to month periods and implied both retrospective and prospective judgements; participants' responses are checked by an informed caregiver or by clinical records. By this questionnaire Crisci et al. [12] observed that accuracy in subjective time estimation did not differ in young-old vs. old–old individuals and was higher on prospective than on retrospective items. Such results confirmed that the emotional state modulates the sense of time and that use of ecologically valid tools is the best choice for assessment of time cognition in older people.

In the present study we aimed at evaluating the subjective experience of time and its anatomical substrates in a sample of focal brain damaged individuals. In particular we aimed to investigate if defects in prospective or retrospective judgements about self-relevant time intervals may have specific and differentiated neuro-anatomical correlates.

## 2. Materials and methods

### 2.1. Participants

Thirty-three inpatients (17 females; mean age = 67.7 years, SD = 12.1; mean education = 8.4 years, SD = 4.1) suffering from a single focal ischemic or hemorrhagic lesion were recruited from the Clinic Center, Rehabilitation Institute, Naples. Nineteen patients had right-hemisphere lesion (RBD), and the remaining 14 participants had lesion in the left hemisphere (LBD). None of them had a history of previous neurological or psychiatric disease or presented severe pathological organ insufficiency at time of the study. Patients left-handed or with impairments in language comprehension (see below) or severe cognitive deterioration (see below) were also excluded from the study, whereas presence of unilateral neglect (detected in 7/19 RBD by means of clinical tests, see below) was not considered as an exclusion criterion. Mean time from stroke was 3.4 months (range: 1–48): in 26 patients time from stroke ranged 1–3 months, in 6 patients it ranged 4–6, and only 1 patient was evaluated at 48 months post-onset.

Twenty-eight individuals (25 females; mean age = 73,2, SD = 5,1; mean education = 7.7, SD = 4.6) admitted to the same institute for the purpose of motor rehabilitation after orthopedic surgical interventions, and matched for age and education with the patient sample, were evaluated as non-neurological controls. Participants were enrolled if they were right-handed, had no history of previous neurological or psychiatric disease and did not present severe pathological organ insufficiency at time of the study.

All participants provided their written informed consent. The study was conducted in accordance with the declaration of Helsinki and approved by the local ethics committee.

### 2.2. Neuropsychological evaluation

All patients completed a short screening battery for general cognitive abilities, including Mini Mental State Examination [39], Frontal Assessment Battery [40], and Clock Drawing Test [41]. Only patients who did not show impairment in language comprehension or severe mental deterioration during testing sessions and clinical interviews were included in the study. Unilateral spatial neglect was assessed by commonly used paper and pencil tests (Albert's cancellation test, star cancellation test, sentence reading test) and clinical observation.

Two standardized questionnaires for assessment of anxiety and depressive symptoms were also administered to enrolled patients, the Hospital Anxiety and Depression Scale (HADS) [42], and the Apathy Evaluation Scale (AES) [43].

The same neuropsychological assessment was administered to the control participants. All tests and questionnaires were administered according to Italian standardized procedures.

### 2.3. QUEstionnaire for Subjective Experience of Time-Revised (QUEST-R)

We used an extended version of the QUEST questionnaire, devised to assess the subjective experience of time in hospitalized elderly people [12]. The original version of the QUEST included 8 open-ended items requiring retrospective or prospective time estimations for short (minutes) or long (days) time intervals referring to self-relevant life situations [35,44,45]. In the present paper we included 4 additional items for a total of 12 items balanced for assessing past or future intervals on self-relevant events with a larger item set (see Appendix A).

All participants, both brain-lesioned and control individuals, were required to provide estimations as accurate as possible for all items, and their responses were checked against reference ('correct') values gathered by means of an interview with an informed caregiver or referring to clinical records. For scoring purposes, for each item we computed the difference between participant's response and the

**Table 1**
Demographic data, neuropsychological and QUEST-R scores, and summary of MANOVA results in brain damaged patients and non-neurological controls.

| Variable | RBD (n = 19) | | LBD (n = 14) | | NNC (n = 28) | | F | Sig | Partial $\eta^2$ |
|---|---|---|---|---|---|---|---|---|---|
| | M | SD | M | SD | M | SD | | | |
| Age | 66.74 | 12.90 | 69.21 | 11.29 | 73.21 | 5.14 | 2.677 | 0.077 | 0.084 |
| Edu. | 8.12 | 4.02 | 8 | 3.21 | 7.71 | 4.64 | 0.55 | 0.947 | 0.002 |
| MMSE | 23.7 | 5.67 | 22.86 | 5.37 | 26.79 | 2.74 | 4.657 | 0.013 | 0.138 |
| CDT | 4.47 | 3.80 | 4,99 | 2.90 | 8.35 | 1.67 | 13.338 | < 0.001 | 0.315 |
| FAB | 10.79 | 3.79 | 11.29 | 3.53 | 12.79 | 3.31 | 2.029 | 0.141 | 0.065 |
| AES | 35.47 | 6.22 | 38.71 | 9.80 | 31.50 | 5.58 | 5.383 | 0.007 | 0.157 |
| HADS:A | 6.26 | 5.37 | 9.36 | 5.37 | 5.93 | 3.61 | 2.755 | 0.072 | 0.087 |
| HADS:D | 7.63 | 3.90 | 9.79 | 5.20 | 2.43 | 2.09 | 23.498 | 0.000 | 0.448 |
| CEI | 0.66 | 0.44 | 0.77 | 0.44 | 0.36 | 0.14 | 7.930 | 0.001 | 0.215 |
| Ret-EI | 0.56 | 0.34 | 0.67 | 0.75 | 0.34 | 0.12 | 4.641 | 0.013 | 0.138 |
| Pro-EI | 0.75 | 0.87 | 0.65 | 0.36 | 0.37 | 0.18 | 3.449 | 0.038 | 0.106 |

*Note:* RBD = Right Brain Damaged participants; LBD = Left Brain Damaged participants; NNC = Non-Neurological Controls. Edu. = education; MMSE = Mini Mental State Examination; CDT = Clock Drawing Test; FAB = Frontal Assessment Battery; AES = Apathy Evaluation Scale; HADS:A = Hospital Anxiety and Depression Scale: Anxiety; HADS:D = Hospital Anxiety and Depression Scale: Depression; CEI = Cumulative Error Index; Ret-EI = Retrospective estimation Error Index; Pro-EI = Prospective estimation Error Index. Bonferroni's corrected post hoc comparisons revealed that RBD and LBD participants did not differ between each other on any demographic or behavioural measure (all $p > 0.05$).

'correct' time interval (positive values meaning an overestimation, negative values an underestimation with respect to the 'correct' interval), and then error was expressed as percentage of the 'correct' response. A cumulative error index (CEI) was computed, as the mean of absolute errors (i.e. regardless of their arithmetic sign) to avoid that magnitude of the index was masked by direction of errors; for each individual the number of over- and under-estimations was also recorded to assess directionality of errors.

Moreover, we computed separate Error Indexes for Retrospective (Ret-EI) and Prospective (Pro-EI) items with the same procedure used for CEI. For Ret-EI and Pro-EI we performed a Crawford's analysis in order to assess whether error scores in retrospective or prospective estimations of individual patients were significantly higher than those of non-neurological controls. For this purpose we used SINGLIMS_ES.exe software [46,47], which allows a direct comparison between performance of each patient (treated as a sample of $N = 1$) and performance of a small control group ($N < 50$ individuals) using the t-student distribution.

### 2.4. Lesion mapping

Brain CT scans without contrast (30 slice, 5–8 mm slice thickness) were acquired by a Siemens Somatom Spirit scanner. Lesions were manually drawn directly on patients' CT scans using MRIcron software (www.mccauslandcenter.sc.edu/crnl/tools). Using Clinical Toolbox [48] running with SPM8 (www.fil.ion.ucl.ac.uk/spm/), all structural scans and lesion maps were registered to the standard (MNI space) stroke-control CT template provided with Clinical Toolbox. The total brain lesion volume (cubic centimeters) was calculated for each patient with MRIcron. Spearman rank correlation analyses were run to assess the relationships between total lesion volume and patients' scores on neuropsychological tests and on CEI and the other indexes of the QUEST-R (Ret-EI and Pro-EI). To identify brain lesions significantly predicting differences in behavioural measures, Voxel-based lesion Symptom Mapping (VLSM) analyses were separately conducted on each index of the QUEST-R (i.e., CEI, Ret-EI and Pro-EI) using Non Parametric Mapping (NPM) software (included with MRIcron). In each analysis a *t*-test (converted into Z scores) was calculated at each voxel lesioned at least in five patients (30423 voxels out of 715902 total damaged voxels), to compare the error scores of patients with and without damage in that voxel. The alpha-level was set to a $p < 0.05$ corrected for multiple comparisons with false discovery rate (FDR) threshold.

To confirm the data from VLSM and to check for different lesion patterns possibly linked to errors in prospective (Pro-EI) or retrospective estimations (Ret-EI), two separated subtraction analyses were performed by subtracting lesion overlay of RBD patients who performed comparably to controls from superimposed lesions of RBD patients who exhibited significantly lower accuracy than controls (at $p < 0.01$), as assessed by Crawford's analysis. Subtraction plots reflect the difference between the percentage of lesion at each voxel in the two patient groups, showing the brain areas most frequently damaged in the group of patients with lower accuracy and most frequently spared in the other group.

Finally, to better characterize lesion mostly associated with specific deficits in prospective or retrospective estimations, lesion overlay of RBD patients with a selective impairment in prospective estimation (i.e., with normal accuracy in retrospective estimations) was subtracted from lesion overlay of RBD patients with a selective impairment in retrospective estimation (i.e. with normal accuracy in prospective estimations), and vice-versa. We limited subtraction analyses to RBD participants based on our sample size and on results of VLSM analyses (see below).

## 3. Results

### 3.1. Behavioral data

#### 3.1.1. Group analysis

Table 1 shows participants' demographic and neuropsychological data and scores on QUEST-R. A multivariate ANOVA with Group (RBD, LBD, NNC) as the fixed factor was conducted on demographic data, neuropsychological scores (i.e., MMSE, FAB, Clock Drawing Test, AES, HADS) and QUEST-R error indexes (i.e., CEI, Ret-EI, Pro-EI). The groups did not significantly differ for demographic features, whereas between-group differences were significant for all dependent measures but FAB and Anxiety subscale of HADS (Table 1). Bonferroni's corrected post-hoc comparisons revealed that RBD and LBD groups did not differ on any demographic or behavioural measure (all $p > 0.05$).

QUEST-R indices were not correlated to time post-onset in enrolled brain-damaged patients (all $p > 0.05$). To ascertain whether between-group differences on QUEST-R indices could be ascribed to concomitant differences on cognitive and psychological measures, we run a MANCOVA on QUEST-R error indices (i.e., CEI, Ret-EI, Pro-EI) in which the group (RBD, LBD, NNC) was considered as the fixed factor, and scores achieved on MMSE, clock drawing test and Depression subscale of HADS as covariates. The results confirmed the significant effect of the group factor on the QUEST-R indices; none of the covariates exerted a significant multivariate effect on QUEST-R indices.

The proportion of overestimation and underestimation errors did

**Table 2**
Summary of Crawford's analysis showing brain damaged patients with significantly larger errors than non-neurological controls in retrospective and prospective time estimations.

| Patient | Group | Ret-EI | t-value | p | Pro-EI | t-value | p |
|---|---|---|---|---|---|---|---|
| Pt 1 | RBD | 0.285 | −0.45 | 0.328 | 0.485 | 0.622 | 0.269 |
| Pt 2 | RBD | 0.676 | 2.702 | 0.005 | 0.520 | 0.813 | 0.211 |
| Pt 3 | RBD | 0.230 | −0.901 | 0.188 | 0.405 | 0.186 | 0.427 |
| Pt 4 | RBD | 0.413 | 0.59 | 0.280 | 0.932 | 2.976 | 0.002 |
| Pt 5 | RBD | 0.587 | 2023 | 0.027 | 0.552 | 0.994 | 0.164 |
| Pt 6 | RBD | 0.439 | 0.811 | 0.212 | 4.034 | 20.002 | < 0.001 |
| Pt 7 | RBD | 1.495 | 9.449 | < 0.001 | 0.469 | 0.54 | 0.296 |
| Pt 8 | RBD | 0.876 | 4.389 | < 0.001 | 0.392 | 0.12 | 0.45 |
| Pt 9 | RBD | 0.561 | 1.81 | 0.041 | 0.426 | 0.306 | 0.38 |
| Pt 10 | RBD | 0.446 | 0.868 | 0.197 | 0.547 | 0.966 | 0.171 |
| Pt 11 | RBD | 0.742 | 3.284 | 0.001 | 1671 | 7.1 | < 0.001 |
| Pt 12 | RBD | 0.250 | −0.735 | 0.234 | 1266 | 4.89 | < 0.001 |
| Pt 13 | RBD | 1.110 | 6.305 | < 0.001 | 0.230 | −0.762 | 0.226 |
| Pt 14 | RBD | 0.550 | 1.711 | 0.049 | 0.397 | 0.146 | 0.442 |
| Pt 15 | RBD | 0.219 | −0.999 | 0.163 | 0.494 | 0.704 | 0.245 |
| Pt 16 | RBD | 0.227 | −0.925 | 0.181 | 0.425 | 0.3 | 0.83 |
| Pt 17 | RBD | 0.190 | −1.114 | 0.114 | 0.252 | −0.681 | 0.252 |
| Pt 18 | RBD | 0.672 | 2.719 | 0.005 | 0.911 | 2.953 | 0.003 |
| Pt 19 | RBD | 0.857 | 4.233 | < 0.001 | 0.225 | −0.792 | 0.217 |
| Pt 20 | LBD | 0.403 | 0.508 | 0.308 | 1.088 | 3.914 | < 0.001 |
| Pt 21 | LBD | 0.330 | −0.09 | 0.464 | 0.609 | 1.305 | 0.101 |
| Pt 22 | LBD | 1.849 | 12.348 | < 0.001 | 1015 | 3.516 | < 0.001 |
| Pt 23 | LBD | 0.314 | −0.221 | 0.413 | 1441 | 5.847 | < 0.001 |
| Pt 24 | LBD | 0.406 | 0.532 | 0.299 | 0.782 | 2.238 | 0.016 |
| Pt 25 | LBD | 0.192 | −1212 | 0.118 | 0.470 | 0.546 | 0.295 |
| Pt 26 | LBD | 0.412 | 0.581 | 0.283 | 0.655 | 1.555 | 0.066 |
| Pt 27 | LBD | 0.338 | −0.025 | 0.490 | 0.530 | 0.868 | 0.197 |
| Pt 28 | LBD | 0.643 | 2.293 | 0.014 | 0.359 | −0.066 | 0.474 |
| Pt 29 | LBD | 0.538 | 1.619 | 0.059 | 0.447 | 0.42 | 0.339 |
| Pt 30 | LBD | 2.886 | 20.839 | < 0.001 | 0.345 | −0.142 | 0.444 |
| Pt 31 | LBD | 0.609 | 2.203 | 0.018 | 0.297 | −0.399 | 0.347 |
| Pt 32 | LBD | 0.175 | −1.351 | 0.094 | 1.006 | 3.466 | < 0.001 |
| Pt 33 | LBD | 0.414 | 0.598 | 0.277 | 0.188 | −0.999 | 0.163 |

*Note*: RBD = Right Brain Damaged participants; LBD = Left Brain Damaged participants; Ret-EI = Retrospective estimation Error Index; Pro-EI = Prospective estimation Error Index.

not differ among the three groups of participants (proportion of overestimations was 0.42 in RBD, 0.38 in LBD, and 0.39 in NNC; chi-square = 0.67; df = 2; p = 0.72). The proportion of over- and under-estimations did not differ in RBD with (proportion of overestimations: 0.42) or without unilateral spatial neglect (0.43; chi-square = 0.02; df = 1; p = 0.89).

#### 3.1.2. Single-case analysis

Results of Crawford's analyses are reported in Table 2. Seven patients in RBD group (pt 2, 7, 8, 11, 13, 18 and 19) and 2 patients in LBD group (pt 22 and 30) showed significantly greater error-scores than controls in retrospective estimations (at $p < 0.01$), whereas 5 patients in RBD group (pt 4, 6, 11, 12 and 18) and 4 patients in LBD group (pt 20, 22, 23 and 32) made significantly greater errors than controls in prospective estimations (at $p < 0.01$). Crawford's analysis allowed to detect double dissociations between prospective and retrospective estimation, since 5 RBD patients (pt 2, 7, 8, 13 and 19) and 1 LBD patient (pt 30) were significantly less accurate (at $p < 0.01$) than controls in retrospective estimations, while performed equally to controls in prospective estimations; conversely, 3 RBD (pt 4, 6 and 12) and 3 LBD patients (pt 20, 23 and 32) were as accurate as controls in retrospective estimations, but made significantly greater errors than controls on prospective estimations (at $p < 0.01$).

### 3.2. Lesion data

The overlay of brain lesions in our sample mainly covered the brain territory supplied by the middle cerebral artery (Fig. 1). RBD and LBD did not significantly differ in mean overall lesion volume (48,56 vs 27,5 cm3; Mann-Whitney U = 87.0; Z = −1.676; p = 0.094). Overall lesion volume was not significantly correlated with any clinical neuropsychological measure, but a negative correlation between lesion volume and MMSE scores approached the significance (rs = − 0.311, p = 0.083). Total lesion volume was significantly and positively correlated with CEI (rs = 0.351, p = 0.045). No other correlation between lesion volume and QUEST-R measures was significant.

VLSM analyses on Ret-EI revealed no voxel surviving the FDR-corrected threshold for significance, while for Pro-EI voxels exceeding the critical value of Z = −2.71 (ranging −2.71 to −3.19) were found in white matter underlying the right parietal lobe, mainly corresponding to the right superior longitudinal fasciculus (see Fig. 2 and Table 3).

Lesion subtractions of RBD patients with or without deficits in prospective or retrospective time estimations (as assessed by Crawford's analysis) revealed distinct patterns of lesions possibly associated with Pro-EI or Ret-EI (Fig. 3, panels A-C). Lesion subtraction of RBD performing similarly to controls (n = 14) from RBD with significantly lower accuracy than controls (n = 5) on prospective estimations revealed that patients with larger errors showed greater percentage of lesion in the angular gyrus and in the underlying white matter, mainly involving the superior longitudinal fasciculus, thus confirming the findings of VLSM analysis. Besides this cluster, additional areas with a sufficiently large percentage of lesion included the rolandic operculum extending medially into anterior insula, and the middle temporal gyrus. In most of these areas the percentage of lesion exceeded the minimal percentage difference between groups yielding a significant Fisher's exact test at p < 0.05 at each voxel (for our group size such difference was 50%), meaning that in these regions percentage of lesion significantly differed between patients with or without impairments in prospective estimations. Additional clusters of voxel with lesion overlap below 50% were found in the ventro-medial portion of postcentral gyrus, in the supramarginal gyrus and in the posterior portion of inferior temporal gyrus, medially involving posterior corona radiata and posterior thalamic radiation.

Subtraction of lesion of RBD performing similar to controls (n = 12) from lesion of RBD with significantly lower accuracy than controls (n = 7) in retrospective estimations revealed that patients with significantly larger errors showed lesions located more inferiorly and anteriorly, and mainly including the superior temporal gyrus, the white matter posterior to the insula (posterior portion of the external capsula and retrolenticular part of internal capsula, with a marginal involvement of posterior putamen), as well as in the posterior insula. Other small clusters of voxels were deeply located in the supramarginal gyrus, as well. However, maximum lesion density (about 35%) in such regions did not reach the threshold for a significant difference between groups at p < 0.05 (50%).

When subtracting lesion overlays of RBD patients with selective impairment in prospective estimations (n = 3) from RBD patients with selective impairment in retrospective estimations (n = 5), we observed that the maximum percentage of lesions (about 60%) associated with larger errors in retrospective estimations were located in the white matter posterior to the insula and in the superior temporal gyrus. The reverse analysis revealed that maximum percentage of lesion (about 80%) associated with selectively impaired prospective estimations was within the superior longitudinal fasciculus (Fig. 3, panel D), thus confirming both VLSM and previous subtraction analysis.

We did not perform subtraction analyses on Pro-EI and Ret-EI of LBD patients because of the small number of patients having significant deficit in prospective or retrospective estimations (as assessed by Crawford's analysis) and because VLSM did not reveal any voxel significantly associated to such types of estimations.

## 4. Discussion

In the present study we aimed at assessing subjective experience of time in focal brain damaged patients, and at identifying its possible

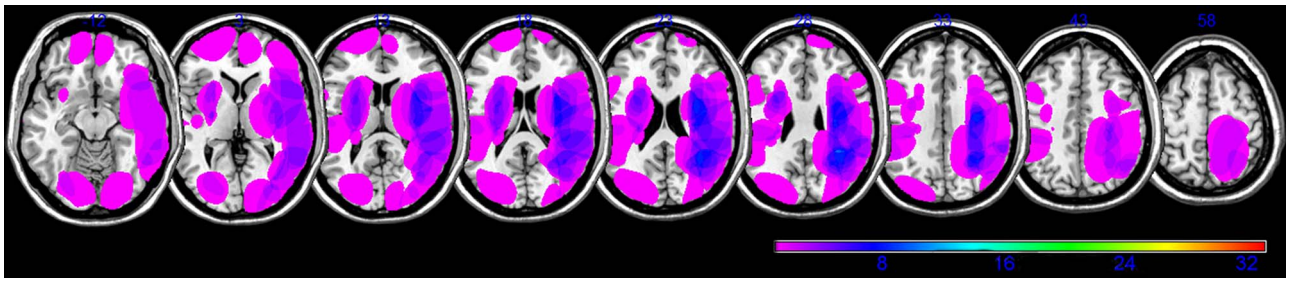


**Fig. 1.** Lesion overlay of 33 brain-damaged participants rendered on the Montreal Neurological Institute–space ch2bet template. Colours represent number of patients having a lesion at each voxel (from lilac = 1 to red = 32). Maximum lesion density was found in the right angular gyrus (x = 38, y = −51, z = 27; n = 8) and in the underlying white matter (x = 33, y = −45, z = 28; n = 10); in the left hemisphere, maximum lesion overlap occurred in the superior corona radiata (x = −25, y = −1, z = 20; n = 6). MNI coordinates are specified for each axial slice. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

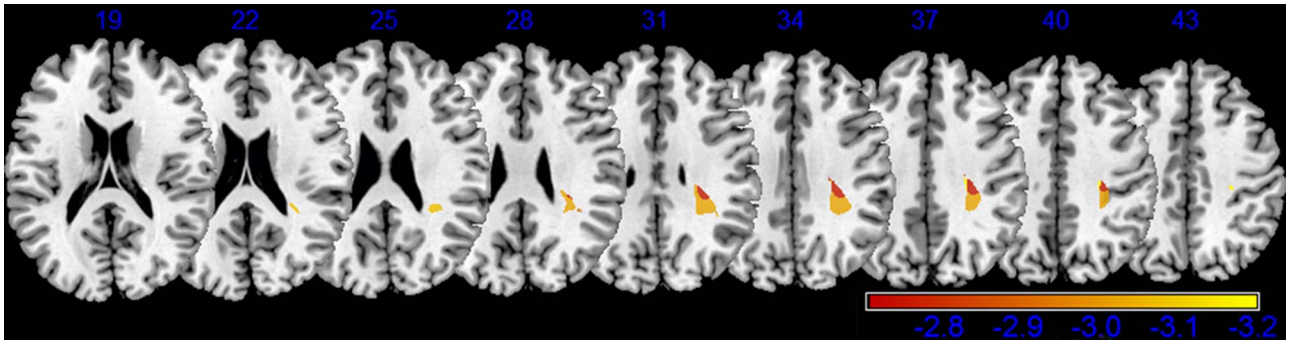


**Fig. 2.** Results of VLSM analysis on error index in prospective estimations. Statistical map shows voxels wherein comparison of error scores of patients with and without lesion yielded a significant *t*-test (converted into Z-scores) at p < 0.05 with FDR correction. Significant voxels are rendered in red (Z = −2.71) to bright yellow (Z = 3.199) scale. Z coordinates of axial slices refer to MNI standardized space. (For interpretation of the references to colour in legends to Figures 1 and 2, the reader is referred to the web version of this article.)

**Table 3**
Voxel-based Lesion Symptom Mapping: Regions with their number/proportion of damaged voxels significantly associated with lower accuracy in Prospective Estimations (PRO-EI score).

| Regions | Voxel | | Peak voxel | | | |
|---|---|---|---|---|---|---|
| | *N* | *N%* | *Z-score* | *X* | *Y* | *Z* |
| Right Superior Corona Radiata | 42 | 0.6 | −3.200 | 25 | −24 | 35 |
| Right Posterior Corona Radiata | 365 | 9.8 | −3.078 | 28 | −38 | 22 |
| Right Superior Longitudinal Fasciculus | 931 | 14.1 | −3.200 | 28 | −23 | 40 |
| Right Postcentral Gyrus | 513 | 0.6 | −3.200 | 31 | −28 | 42 |
| Right Supramarginal Gyrus | 420 | 1.3 | −3.058 | 39 | −44 | 31 |

*Note*: Voxels significant at p < 0.05 (FDR-corrected). Peak voxels coordinates are in MNI space.

neural correlates. Our behavioural data showed that both groups of brain-damaged patients achieved significantly different scores from NNC on the overall performance on QUEST-R questionnaire, as assessed by the CEI index. This finding suggests that the subjective experience of time tended to be less efficient after a brain lesion, irrespective of the lesion side. The significant correlation of CEI index with total lesion volume would add to the idea that the subjective sense of time is an emergent property of the brain [49], and would be in keeping with recent theoretical models considering the subjective experience of time as an epiphenomenon of different factors including emotional and bodily states [6,7,9]. After Merchant et al. [50], we could suggest that it seems highly improbable that a focal unilateral brain lesion could hamper such a deeply rooted function, also in reason of redundancy from the opposite hemisphere contributing to recovery [51–54].

Our VLSM analysis, however, revealed a cluster of voxels significantly related to errors in prospective judgments in white matter underlying the right IPL. Subtraction analysis provided convergent results since patients with selective defect in prospective time estimations showed maximum lesion density in the same subcortical region evidenced by VLSM analysis, thus suggesting the clinical relevance of lesions in the right inferior parietal lobe for subjective time experience. The IPL plays a role in judging sub-second time intervals [13,18,55], and transcranial magnetic stimulation of the right IPL disrupts performance on a supra-second task too [56]. Unlike the above studies, QUEST-R investigated intervals on very different time scales and nonetheless we could observe for the first time that IPL might be involved in prospective judgements on ecologically valid time intervals. However, our VLSM analysis revealed that the specific cluster associated with lower performance on the prospective judgements was located in the white matter underlying the right IPL. This region, corresponding to the superior longitudinal fasciculus (SLF), has been recently associated with spatial attention [57–59] and spatial orientation [60,61], and is involved in the genesis of unilateral neglect in focal brain damaged patients [62]. Previous findings in neglect patients supported the idea that mental representation of time would follow a spatially-oriented “mental time line” accessible by spatial attention mechanisms [16,63,64], linking left spatial neglect with temporal errors [65]. However, seven of our patients had clinical evidence of left spatial neglect, as it could be predicted on the basis of the lesion pattern, but we did not observe differences in the distribution of over- or under-estimation in RBD patients with or without spatial neglect, or even in patients with right or left hemisphere lesions. Therefore, we cannot suggest that the subjective experience of time is strictly related to spatial-attention mechanisms, at least as far as the subjective experience of time is concerned. The well-known difficulty in comparing findings from time cognition literature [25,26], the peculiarities of questionnaire used in the present study, and the lack of other empirical evidence on the neural bases of the sense of time, however, limit interpretation of the present data. The possible role of the white matter tracts underlying the IPL in the prospective judgement should be investigated in further studies.

Our lesion subtraction analysis, combined with the observation of double dissociations in our patient sample, suggests that prospective

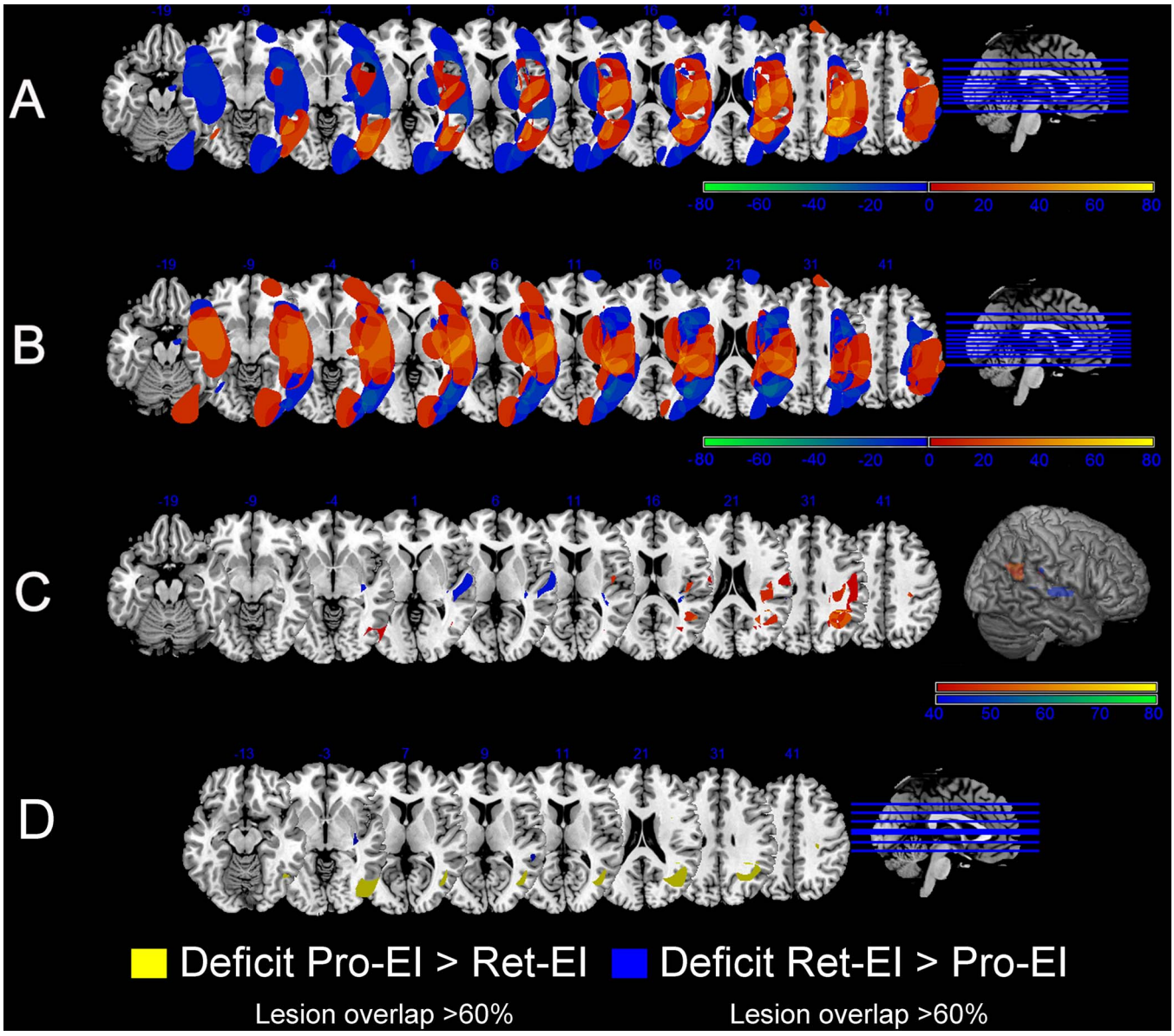


**Fig. 3.** Panels A and B show subtraction of lesion overlay of RBD patients with impaired performance from lesion overlay of RBD patients with normal performance in prospective estimations (Panel A) and in retrospective estimations (Panel B). Each colour represents 20% increments in lesion percentage. Colours from red to yellow indicate brain regions more frequently damaged in the group of patients with low accuracy; colours from dark blue to green represent regions more frequently damaged in the group with high accuracy. Panel C shows brain regions more frequently damaged in patients with low accuracy in prospective estimations (red to yellow) or in retrospective estimations (dark blue to green) superimposed on the same Montreal Neurological Institute–space ch2bet template, and rendered in 3D at a search depth of 16 mm. Colours represents 10% increments in lesion percentage. Panel D shows subtraction plot of lesion overlays of patients with a selective impairment for prospective estimations vs retrospective estimations and vice-versa. Coordinates of axial slices are reported. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and retrospective time judgements lay on partially distinct networks in the right hemisphere: prospective judgements seem to be based on a network involving the inferior parietal cortex, rolandic operculum and posterior middle temporal gyrus, whereas retrospective judgements might depend on connections between superior middle temporal gyrus and the white matter posterior to the insula. Although subctration analysis is less conservative than VLSM, such suggestions are generally consistent with empirical findings [e.g.,66,67] and *meta*-analyses [68] proposing that different timing processes characterize prospective versus retrospective duration judgments. In a *meta*-analysis on healthy individuals, Block et al. [69] suggested that prospective judgements are strongly related to attentional resources and executive control, whereas retrospectives judgements would be linked to memory processes. As underlined by Wearden et al. [70], prospective and retrospective judgments may be very different, since prospective judgments would be based on the operation of some timing-specific mechanisms, like an internal clock [e.g.,71], whereas retrospective judgements would not imply timing-specific mechanisms but other cognitive processes such as memory [72] or sensitivity to contextual changes [3,73].

Lesion subtraction analysis also showed a possible different involvement of the right insular white matter in prospective and retrospective judgements, with a small cluster in the anterior portion of the insula that seems to be related to prospective judgements, and a cluster in the posterior insula that would be linked to retrospective judgements. These findings would provide support to the growing body of literature addressing relevance of the insula in time experience [17,55,74,75]. The insular cortex is indeed considered an interoceptive hub where body signals are acquired and integrated over time [19]. Several recent neuroimaging studies have shown that the anterior insula, besides the striatum, is involved in explicit temporal prediction especially of

emotional situation [6,76]. This result is also consistent with the notion of the right insula as a temporal accumulator independently from a required motor response [55].

Finally, the involvement of subcortical areas (posterior portion of the external capsula and retrolenticular part of internal capsula, with a marginal involvement of posterior putamen) is consistent with models postulating cortico-striatal networks underlying the neural basis of time, although it is worth stressing here that all data about the involvement of the striatum came from studies on short time intervals [55,77,78].

Our study has several limitations. The first main limitation was related to the relatively small number of focal brain damaged patients, and in particular of those with left hemisphere damage, because of the presence of severe cognitive deterioration or of clinically evident language disturbances. Another limitation of our study consisted in the recruitment of a large proportion of patients with lesions within the territory of the middle cerebral artery, leaving relatively unexplored the cerebral territories with different arterial supply. Some limitations are also inherent to the questionnaire used in the present study: i) QUEST-R necessarily included a relatively small number of items that were ecologically valid and easily to be checked for evaluting accuracy of patients' answers; ii) QUEST-R could not assess different ranges of time intervals, that might imply different cognitive processes, to be addressed in future studies. A last limitation of the present study consisted in the fact that the present anatomo-clinical correlation study could not address the cognitive mechanisms contributing to the subjective experience of time, as assessed by the QUEST-R; for this purpose a wider battery of neuropsychological tests would be necessary.

## 5. Conclusions

Notwithstanding the above limitations, our attempt at dealing with "the subjective experience of time" in focal brain damaged patients revealed that time cognition is based on a wide distributed network. The clinical observation did not disclose a clear-cut hemispheric lateralization of the areas implied in subjective time processing, but we could identify some patients with double dissociations between impairment in estimation of prospective or retrospective time intervals. This evidence complemented our voxel-based and subtraction lesion analyses in demonstrating separate neural correlates of prospective versus retrospective time processing in the right hemisphere. Some of the regions involved in the network are specifically related to representing the self, thus underlining that "…We become aware of what is happening to me through memory of what has happened to me and expectations of what might happen to me. Through this temporal structure of consciousness the realization of a self emerges…"[8].

## Compliance with ethical standards

The paper has not been submitted and is not under consideration for publication elsewhere.

## Conflict of interest

No author has any conflict of interest to disclose.

## Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Informed consent

Informed consent was obtained from all individual participants included in the study.

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## Appendix A

A. QUEstionnaire for Subjective experience of Time-Revised (QUEST-R)* including prospective (Pro) and retrospective (Ret) questions.

Item 1 (Ret)- How long have you been staying in this Hospital?

Item 2 (Ret)- How many days ago did you have stroke?

Item 3 (Pro)- How long will you have to wait for your next meal?

Item 4 (Ret)- How long did your physical therapy session last today (yesterday)?

Item 5 (Pro)- Could you tell me how many days there are before next Christmas (Easter)?

Item 6 (Pro)- In how long time will your relatives (friends) come to visit you?

Item 7 (Pro)- Could you drop a hint in 4 min?

Item 8 (Pro)- In how many days will you back home?

Item 9 (Ret)- Could you tell me how many days passed since last Easter (Christmas)

Item 10 (Ret)- How many days ago did you start physical therapy?

Item 11 (Pro)- How long will you have to wait for physical therapy today?

Item 12 (Ret)- How long has this interview lasted?

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