Research Paper: Direct and Indirect Timing Functions in Unilateral Hemispheric Lesions

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ABSTRACT

Introduction: The neural substrates of temporal processing are not still fully known. The majority of interval timing studies have dealt with this subject in the context of "Explicit timing" (computing the time intervals explicitly). The hypothesis "Implicit timing" (implicitly using temporal processing to improve function) has also proposed. This lesion study addressed explicit and implicit timing paradigms simultaneously using identical experimental tasks.

Methods: In this case-control study, 15 patients with Right Hemisphere Damage (RHD) and 15 patients with Left Hemisphere Damage (LHD) and 15 age-matched normal subjects were included. Participants performed a temporal reproduction task (assessing explicit timing) and a temporal prediction task (assessing implicit timing) in two sub- and supra-second intervals.

Results: Our results showed that RHD can lead to significantly lower accuracy in the temporal reproduction task in sub-second (P=0.005) and supra-second (P=0.001) intervals, compared with the normal subjects. Also, LHD led to perturbation in temporal prediction task by an increase in reaction time (lower accuracy) in sub- (P=0.011) and supra-second (P=0.006) time intervals than the normal subjects.

Conclusion: Overall, our findings suggested that there is a right hemispheric bias in the neural substrate of explicit timing, in both sub- and supra-second intervals. Furthermore, for the first time in a lesion study, we showed the evidence of left-hemispheric bias in neural substrates of implicit timing.

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Highlights

- Different anatomical regions have been proposed responsible implicit and explicit timing in different studies.

- Right hemisphere damage can lead to significantly lower accuracy in the temporal reproduction task (neural substrates of explicit timing).

- Left hemisphere damage can lead to perturbation in temporal prediction task -(neural substrates of implicit timing).

Plain Language Summary

No precise brain processes have yet been found responsible for the perception of time. Different anatomical regions have been proposed responsible for the phenomenon of timing and its explicit and implicit components. The present study addressed this phenomenon by psychophysical tests and assessing direct and indirect timing in right and left-hemisphere brain damage and normal subjects. This study concluded that right hemisphere damage can lead to significantly lower accuracy in the temporal reproduction task (neural substrates of explicit timing) and left hemisphere damage can lead to perturbation in temporal prediction task -(neural substrates of implicit timing).

1. Introduction

No precise brain processes and receptors have yet been found responsible for the perception of time (Coull, Cheng, & Meck, 2011). The perception of time obeys the characteristics of other perceptions (Gibbon 1991; Grondin 2010) and the Weber-Fechner law and Scalar variability, and is based on the Scalar Expectancy Theory (Gibbon 1991; Wearden 2003). Explicit or direct timing and implicit or indirect timing have been proposed as the main time paradigms (Coull, Cheng, & Meck, 2011; Coull & Nobre, 2008). One component of timing is hazard function that refers to the predictive nature of time (the foreperiod effect); if the target does not emerge at the expected time, the probability of its emergence in the consecutive moments to come constantly increases, whereas the Reaction Time (RT) decreases. The unidirectionality of time acts as a guide and increases the response speed. Hazard function seems to potentially have common neuronal substrates with explicit timing (MacDonald & Meck, 2004).

Different anatomical regions have been proposed responsible for the phenomenon of timing and its direct and indirect paradigms (Harrington, Haaland, & Knight, 1998; Branch Coslett, Shenton, Dyer, & Wiener, 2009). The present study addressed this phenomenon by investigating different damaged regions of the brain and aimed at assessing the paradigm of explicit timing and hazard function in addition to assessing the implicit timing paradigm, which has been addressed in most studies. The results of psychophysical tests assessing direct and indirect timing were compared in patients with right- and left-hemisphere brain damage and normal subjects, and also the two groups were compared in terms of their mean short and long "response accuracy", "raw responses" and "time efficiency". Finally, the correlation between response accuracy in direct and indirect timing tests in the sub- and supra-second range (in addition to neutral condition; when the subject receives no temporal cues) was obtained. Questions to be answered through the study:

- Does hemispheric damage have a significant effect on psychophysical tests of direct and indirect timing?

- Do neuronal infrastructures associated with direct and indirect timing overlap?

- Do neuronal infrastructures associated with hazard function and direct timing overlap?

2. Methods

2.1. Participants

This case-control pilot study was conducted over three months in an academic hospital affiliated to the Guilan University of Medical Sciences in the north of Iran. The subjects were the patients admitted to the neurology and neurosurgery wards with Left Hemisphere Brain Damage (LHD) and Right Hemisphere Brain Damage (RHD) and Normal Subjects (NS) in groups of 15 subjects. The patients were in the acute (6-48 h) and subacute (48 h-1 w) phase of the brain damage. The cases in the NS

group were age-education matched with case groups. The brain lesions included trauma and ischemic or hemorrhagic stroke or tumor/tumor resection confirmed by brain imaging (brain computed tomography or magnetic resonance imaging).

2.2. Exclusion criteria

The exclusion criteria were as follows: a history of underlying neurological diseases before the incidence of the studied lesion, a concurrent lesion in the cerebellum or the opposite hemisphere (in patients) and a history of overt neurological disorders, opium use, and head trauma leading to a loss of consciousness (except for the considered lesion), overt psychiatric disorders based on the DSM-IV-TR, being under treatment with antipsychotics or stimulants, impaired memory or vision, abnormal or uncorrectable visual accuracy, perception disorders, and motor impairment preventing performance of the tasks.

2.3. Data collection tools

2.3.1. Checklist

A researcher-made checklist was used to record participant's data, including gender, age, education, handedness, the time elapsed since the lesion, the neurological examination results, the nature of the lesion, and the history of previous disorders.

2.3.2. Software

Software was designed in C^{++} and running on MS Windows OS (XP, service pack 2 and higher). Using this software, the psychophysical test and the main tasks, including Temporal Reproduction and Temporal Prediction were assessed. The output was a Microsoft Office spreadsheet for each participant. The following variables were assessed:

The mean response accuracy in the direct timing test: this is the difference between the time spent by the participant in the test and the target duration (long or short), which is calculated as the absolute mean of values obtained in the four test sessions. Lower numerical values indicate a higher accuracy.

The mean response accuracy in the indirect timing test: it signifies a faster response to the stimulus that is measured in milliseconds. In the indirect timing test, the numbers in the short and long durations and the neutral condition of the short, middle, and long durations and the numerical mean of these three were obtained. Their means were calculated based on the values obtained from the four test sessions indicating the mean response accuracy. Lower values indicated a faster and more accurate response.

The mean raw response in the direct timing test: It is the mean value obtained in the direct timing test in the four test sessions.

Time efficiency: Time efficiency is the difference between the mean response accuracy in the indirect timing test in the long or short durations and their corresponding mode in the neutral condition (e.g. T.Pre.L and T.Pre.N.L).

2.4. Methods

Through the three months of sampling and performing the tests, 30 out of about 400 eligible patients performed the tests completely (the examinations, the checklist, and the main tests). These tests were also performed on 15 normal subjects. Informed consent was obtained from all participants before the study.

The examinations and tests were performed between 6 and 8 pm in a room at the patient's ward with adequate peace and quietude to facilitate concentration. The light was dimmed to the degree that the only noticeable object was the laptop screen. The participants were positioned in a chair at the right distance from the screen of a laptop (Dell Inspiron 1505).

Participants' interaction was enabled by pressing the space key on a keyboard. All the participants used their dominant hand to take the test or used the opposite hand for hemiplegia/hemiparesis. The tests were carried out by an examiner familiar with the software and behavioral data. Practical explanations were given and the main trial was carried out only after proper participants' understanding of its stages.

No quantitative ceilings were determined for ensuring that the participants are informed about how to perform the tasks; therefore, given that ill patients were also examined as a part of the samples, having a limiting assumption and eliminating the test results, merely based on the "possible non-comprehension of the test", can in practice result in the elimination of some of the results for impaired timing. Consequently, participants' "comprehension of how to perform the tasks" was assessed objectively through a question and answer and by comparing the results after several practices by the examiner.

Table 1. An example of a block of different tasks assigned by a quantity

Trial	Quantity
1. Temporal Pro. Long (T. Pro. L)	1
2. Temporal Pro. Short (T. Pro. S)	0
3. Temporal Pre. Long. (T. Pre. L)	2
4. Temporal Pre. Short (T. Pre. S)	0
5. Neutral Condition. Long (NC.L)	0
6. Neutral Condition. Short (NC.S)	2
7. Neutral Condition. Middle (NC.M)	1

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In the main trial, the participants performed the temporal reproduction (for direct timing assessment) and temporal prediction (for indirect timing assessment) tests.

2.5. Meta design

The Meta design of the trials was carried out by the experimenter. Given the possibility of adjusting the values in the software, it was possible to form blocks of different tasks by assigning a quantity to them from 0-99 as listed in Table 1.

Accordingly, one block of the trials, in which T.Pro.L is performed once, T.Pre.L is performed twice, N.C.S twice, and N.C.M once, continuously and without interruptions. Each time a block was adjusted, an ID was assigned to that block enabling practice runs on specific trials.

The final trials were performed as a block included both assessments concurrently. Ultimately, each participant performed each temporal reproduction (long), the temporal reproduction (short), the temporal prediction (long), and the temporal prediction (short) for four times, as well as the neutral conditions (long/mid/short), twice each and six times in total. The neutral conditions were considered as the benefit and assessing randomly between the long/short temporal prediction tests. The participants were asked to use the counting strategy to have the same method for all participants for performing the temporal reproduction tests. Participants who counted out loud were asked to count covertly. To assess the hazard function, a neutral condition was included in the tests. Both the implicit and explicit timing paradigms were measured in the sub- and supra-second range.

2.6. Statistical analysis

The data obtained were processed in SPSS V. 20 using the independent t-test and the one-way ANOVA. Levene's test was used to ensure the accuracy of the parametric assumptions, especially the homogeneity of the variances assumption between the groups. The Brown-Forsythe test was used to determine the significance of the F-ratio in the one-way ANOVA, since the data of all three groups had been collected from several trials, converted into milliseconds, and then compared. When the F-ratio was significant, the Games-Howell post-hoc test was used to determine the significance of the pair means, if the variance between the groups was significantly unequal for each dependent variable ($P<0.05$), and Bonferroni's post-hoc test was used for the pairwise comparisons if the variance of the groups was equal. Finally, Welch's t-test was used when both sample size and variance were unequal between the groups in the comparison of the means.

3. Results

Eight participants in the NS group and 7 cases in each patient group were female. There was no significant age difference between the RHD (46.5±8.7), LHD (47.9±13.3) and NS (43.5±10.4) groups (P=NS, F (2.42)=0.626), as well as no significant difference in the number of years of education (an indirect index for measuring the ntelligence quotient (IQ)) between the NS (10.2±3.5), LHD (9±3.4) and RHD (8.5±4.1) groups (P=NS, $F_{2.42}$=0.876). Table 2 shows no significant difference in groups in terms of age, gender, and other demographic details, and also the defects, types of lesions, and the time spent since the lesion development. A relatively similar distribution of damaged regions was observed in the two groups of patients.

Table 2. The demographic details of the three groups and the brain lesions of the case groups

Patients' ID	Groups	SEX	AGE	Level of Education	Opium Addiction	Head Trauma	Handedness	Time Post Incident	Deficits	Lesion Type
01	LHD	F	34	10	N	P	R	30	NHP	ISC
02	RHD	F	46	8	P	N	R	20	LHP	ISC
03	RHD	F	47	14	N	N	R	10	LHP	ISC
04	RHD	M	52	14	N	N	R	7	NHP	BT
05	RHD	M	30	8	P	N	R	4	NHP-D	SDH
06	RHD	M	61	3	P	N	R	4	LHP	ISC
07	RHD	M	52	16	N	N	R	4	LHP	ISC
08	RHD	F	46	5	N	N	R	3	LHP	ISC
09	LHD	F	52	12	N	N	R	3	RHP-A	ISC
10	LHD	M	63	12	N	N	R	4	RHP	ISC
11	RHD	F	28	8	N	N	R	10	LHP	BT
12	LHD	F	33	12	N	P	R	14	RHP	ISC
13	RHD	F	44	6	N	P	L	4	LHP	ISC
14	LHD	M	24	14	N	P	L	3	NHP	TR
15	LHD	F	53	3	N	N	R	3	NHP-D	ISC
16	RHD	M	51	14	N	N	R	3	LHP	ISC
17	RHD	F	44	6	N	P	R	2	LHP	ISC
18	RHD	M	42	3	P	N	L	8	LHP	ISC
19	LHD	M	50	9	N	N	R	2	NHP	BT
20	LHD	M	68	5	N	N	R	3	RHP-A	ISC
21	RHD	M	57	8	P	N	R	1	NHP-A	ISC
22	RHD	M	50	7	N	P	R	14	NHP	SDH
23	RHD	F	48	8	N	N	R	5	LHP	ISC
24	LHD	M	59	8	N	N	R	6	RHP	ISC
25	LHD	F	35	12	N	P	R	9	RHP	ISC
26	LHD	M	34	10	N	P	L	3	NHP	TR
27	LHD	F	50	5	N	N	R	4	NHP	ISC
28	LHD	M	49	6	N	N	R	4	NHP	BT
29	LHD	M	66	5	N	N	R	5	RHP-A	ISC
30	LHD	F	49	12	N	N	R	4	RHP-A	ISC
31	NS	F	38	7	N	N	R	-	NHP	-
32	NS	M	57	3	N	N	R	-	NHP	-
33	NS	F	29	10	N	N	R	-	NHP	-
34	NS	F	58	10	N	N	R	-	NHP	-
35	NS	F	46	13	N	P	R	-	NHP	-
36	NS	F	32	10	N	N	R	-	NHP	-
37	NS	F	38	12	N	N	R	-	NHP	-
38	NS	M	27	16	N	N	R	-	NHP	-
39	NS	M	48	16	N	N	R	-	NHP	-
40	NS	F	38	11	N	N	R	-	NHP	-

Patients' ID	Groups	SEX	AGE	Level of Education	Opium Addiction	Head Trauma	Handedness	Time Post Incident	Deficits	Lesion Type
41	NS	M	35	11	N	N	R	-	NHP	-
42	NS	M	50	8	N	N	R	-	NHP	-
43	NS	M	48	13	N	N	R	-	NHP	-
44	NS	F	59	8	N	N	R	-	NHP	-
45	NS	M	50	6	N	N	R	-	NHP	-

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RHD: Right Hemisphere Damage, LHD: Left Hemisphere Damage NS: Normal Subjects, M: Male F: Female N: Negative P: Positive R: Right L: Left NHP: No Hemiplegia/paresis LHP: Left Hemiplegia/paresis RHP: Right Hemiplegia/paresis A: Aphasia D: Diplopia ISC: Ischemic Stroke SDH: Sub Doral Hematoma BT: Brain Tumor TR: Tumor Resection

Table 3. The mean response accuracy, raw responses and time efficiency in the long and short direct and indirect timing tests

Timing	Test	Duration	Groups	N	M±SD	Range	95%CI for mean		F†	P
							lower	Upper		
Direct for Accuracy	Temporal reproduction	Short (600 ms)	NS	15	895.00±550.25	251-20785	590.28	1199.72	8.08	0.001
			LHD	12*	728.33±210.25	856-2918	960.32	1885.84		
			RHD	15	1501.05±387.57	453-5308	1561.28	3223.78		
Direct for Accuracy	Temporal reproduction	Long (1500 ms)	NS	15	720.67±325.90	130-1322	540.19	901.15	11.77	0.0001
			LHD	13*	1063.92±406.24	515-1817	818.43	1309.42		
			RHD	15	1587±666.94	598-2789	1218.06	1956.74		
Indirect for Accuracy	Temporal prediction	Short (600 ms)	NS	15	273.23±57.07	202.50-385.50	241.63	304.84	5.14	0.010
			LHD	14*	359.21±76.20	257.50-440.25	315.22	403.21		
			RHD	15	335.33±88.27	225.75-514	286.45	384.21		
Indirect for Accuracy	Temporal prediction	Long (1500 ms)	NS	15	299.35±63.01	218-440.50	264.46	334.24	3.68	0.034
			LHD	14*	364.98±38.12	315-420-75	342.97	386.99		
			RHD	15	326.50±84.60	239.25-498.75	279.65	373.35		
Direct for raw responses	Temporal reproduction	Short (600 ms)	NS	15	783.38±162.63	549.50-1118.75	693.32	873.45	7.306	0.002
			LHD	12*	271.74±78.44	438.25-1329.50	704.86	1050.18		
			RHD	15	387.99±100.18	486.75-1843.50	959.23	1388.96		
Direct for raw responses	Temporal reproduction	Long (1500 ms)	NS	15	1456.10±182.67	1169.50-1805.25	1354.93	1557.26	3.189	0.052
			LHD	13*	1646.75±192.77	1384.75-1954.25	1530.26	1763.23		
			RHD	15	325.96±84.16	802.75-2086.50	1548.87	1609.89		
Indirect for benefit from cued	Temporal prediction	Short (600 ms)	NS	15	-86.13±108.09	-312.25-81.50	-145.99	-26.27	5.470	0.008
			LHD	14*	6.03±47.32	-31.00-113.25	-21.28	33.36		
			RHD	15	-9.76±73.43	-136.25-116.50	-50.43	30.90		
Indirect for benefit from cued	Temporal prediction	Long (1500 ms)	NS	15	17.95±46.39	-75-105	-43.64	7.74	0.64	0.531
			LHD	14*	2.94±51.79	-89.75-72	-26.96	32.85		
			RHD	15	30.26±87.64	-214-140	-78.80	18.27		

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* Fewer than 15 patients in these units, indicating missing values; Participants with missing data were thus excluded from the analysis.

Table 3 presents a comparison of the mean response accuracy, the raw responses, and the time efficiency in the direct and indirect timing tests for short and long intervals in the RHD, LHD and NS groups. The homogeneity of the variance between the groups was verified by Levene's test, which showed significantly unequal variances between groups in their mean response accuracy in the short indirect timing test, the mean raw responses in the long timing test, and the mean time efficiency in the long indirect timing test (P<0.05). Accordingly, the Games-Howell post-hoc test was used for the pairwise comparisons and Bonferroni's post-hoc test for the remaining pairwise comparisons in groups with equal variances.

The ANOVA results based on the Brown-Forsythe test showed significant differences between the three groups in the mean response accuracy in the short direct timing test ($F_{2, 24.68}$=8.08, P=0.001). The planed contrasts showed significant differences between the NS group and the two case groups in the mean response accuracy ($t_{33.6}$=3.86, P=0.005), and also significant differences between the RHD and LHD groups in the mean response accuracy in the short direct timing test ($t_{21.1}$=2.2, P=0.039). The post-hoc comparison using the Games-Howell test showed a significant difference between the NS group (M=895, 95%CI [590, 1199] and the RHD group (M=2392, 95%CI [1561, 3223] in the mean response accuracy in the short direct timing test (P=0.005).

The ANOVA results based on the Brown-Forsythe test also showed significant differences between the three groups in the mean response accuracy in the long direct timing test ($F_{2, 30.2}$=12.04, P<0.005). The planed contrast showed significant differences between the NS group and the two case groups in the mean response accuracy ($t_{37.4}$=4.5, P<0.005), and also significant differences between the RHD and LHD groups in the mean response accuracy in the long direct timing test ($t_{23.5}$=2.5, P=0.018). The post-hoc comparison using the Games-Howell test showed a significant difference in the mean response accuracy in the long direct timing test between the NS group (M=720, 95% CI [540, 901] and the RHD group (M=1587, 95% CI [1218, 1956]) (P=0.001) and also between the RHD and LHD groups (P=0.046).

The ANOVA results based on the Brown-Forsythe test also showed significant differences between the three groups in the mean response accuracy in the short indirect timing test ($F_{2, 41}$=5.14, P=.010). The planed contrast showed significant differences between the NS group and the two case groups in the mean response accuracy (t_{41}=3.1, P=0.003); however, no significant differences were observed between the RHD and LHD groups in the mean response accuracy in the short indirect timing test (t_{41}=-0.858, P=0.396). The post-hoc comparison using Bonferroni's test showed a significant difference between the NS and LHD groups (M=359, 95% CI [315, 403] in the mean response accuracy in the short indirect timing test (P=0.011).

The ANOVA results based on the Brown-Forsythe test showed significant differences between the three groups in the mean response accuracy in the long indirect timing test ($F_{2,25.32}$=6.04, P=0.007). The planed contrast showed significant differences between the NS group and the two case groups in the mean response accuracy ($t_{27.6}$=2.3, P=0.030). The post-hoc comparison using the Games-Howell test showed a significant difference between the NS and LHD groups (M=365, 95% CI [343, 387]) (P=0.006).

The ANOVA results based on the Brown-Forsythe test showed significant differences between the three groups in the mean raw responses in the short direct timing test ($F_{2,29.4}$=7.4, P=0.002). The planed contrast showed significant differences between the NS group and the two case groups in the mean raw responses ($t_{33.6}$=3.86, P<0.005) and also a significant difference between the RHD and LHD groups in the mean raw responses in the short direct timing test ($t_{24.6}$=2.33, P=0.028). The post-hoc comparison using the Games-Howell test showed a significant difference between the NS group (M=783, 95% CI [693, 873] and the RHD group (M=1174, 95%CI [959, 1389] in the mean raw responses in the short direct timing test (P=0.005). Dunnett's t-test showed a significant difference between the RHD and LHD groups (P=0.011) that confirmed the planed contrast results.

The ANOVA results based on Welch's test showed significant differences between the three groups in the mean of time efficiency in the short indirect timing test ($F_{2, 25.4}$=4.4, P=0.023). The planed contrast showed significant differences between the NS group and the two case groups in the mean of time efficiency ($t_{18.7}$=2.8, P=0.012). The post-hoc comparison using the Games-Howell test showed a significant difference between the NS and LHD groups (M=6.03, 95% CI [-21.28, 33.35] in the mean of time efficiency in the short indirect timing test (P=0.019). The non-significant cases were not explained to avoid a tedious results section.

To answer the second question, Pearson's correlation analysis (r) showed a significant relationship between the response accuracy in the direct and indirect timing tests in the sub-second range (r=0.617, P<0.05) and also between the response accuracy in the direct and indirect timing tests in the supra-second range (r=0.539, P<0.05). These results suggested duration-dependent infrastructure overlap between the two paradigms.

Finally, to answer the third question, Pearson's correlation analysis (r) showed a significant relationship between the response accuracy in the direct timing test in the sub-second range and the neutral condition in the indirect timing test in the supra-second range ($r=0.724$, $P<0.01$) and also a negative relationship with time efficiency in the indirect timing test in the supra-second range ($r=-0.517$, $P<0.05$), which suggested an overlap between the neuronal infrastructures in the hazard function and the direct timing test in the sub-second range.

4. Discussion

This lesion study used sensorimotor-homogeneous timing tests to examine explicit and implicit timing paradigms. We assessed the acute and subacute lesions. Behavioral studies using brain damage models often examine patients with chronic damage. One scientific reason for this tendency is that, typically, no further evolutions occur in the lesion after one month (Gaudinski, Henning, Miracle, Luby, Warach, & Latour, 2008). The best method to prepare a brain map is using both acute and chronic lesions since each has its advantages and disadvantages. After an acute lesion, an extensive dysfunction develops immediately and sometimes intact regions become dysfunctional due to their dependence on the damaged regions. In chronic lesion mapping, the degree to which the damaged region is responsible for behavioral problems cannot be easily determined because of neural plasticity (Kleim & Jones, 2008). A specific advantage of these two mappings is that acute lesions have higher clinical relevance, whereas chronic lesions are more stable and show irrecoverable defects in a better way (Rorden 2014).

The present study found different variability/accuracy in the subjects with brain lesions compared with the normal subjects similar to other studies that used different tasks (Melgire, Ragot, Samson, Penney, Meck, & Pouthas, 2005; Pouthas & Perbal, 2004).

The main hypothesis in this study was that "implicit and explicit timing paradigms have hemispheric bias and the neuronal infrastructures of these two paradigms possibly overlap", which was confirmed; the left hemisphere is mainly responsible for indirect or implicit timing, whereas the right hemisphere is mainly responsible for direct or explicit timing. The results obtained are separately interpreted in this section.

Hemispheric bias – Direct timing – Right hemisphere:

Reduced response accuracy in the direct timing test was only significant in the RHD group in both the sub- and supra-second range, which is consistent with the results of many previous studies (Wiener, Hamilton, Turkeltaub, Matell, & Coslett, 2010; Melgire, et al., 2005). Harrington et al. (1998) and Kagerer, Wittmann, Szelag, & Steinbüchel (2002) showed that explicit temporal processing defects are associated with right hemisphere lesions. Nonetheless, Branch et al., (2009) could not achieve these results. In assessing patients with hemispheric lesions through task reproduction (explicit timing), Kagerer et al. showed that in addition to damage, all participants provided accurate mean responses in one to two seconds, which is in line with our findings in terms of the mean raw responses in supra-second range. Besides, they showed that in ranges longer than two seconds, right hemisphere damage significantly impairs responses; however, they did not assess responses in the sub-second range (Kagerer et al., 2002).

Very few studies have assessed the sub- and supra-second range concurrently with controversy (Gooch, Wiener, Wencil, & Branch Coslett, 2011). A fundamental difference has been reported between short (sub-second) and long (often supra-second) timing in involved structures and neurotransmitters (Mangels 1998-Ivry 1988). Two studies emphasized the potential role of the right prefrontal cortex in sub- and supra-second timing. Melgire et al. (2005) used a temporal bisection test in patients under medial temporal lobe resection in the right or left hemispheres and showed that right hemispheric damage generally produces responses with a greater variability compared with the normal subjects or those with left hemispheric damage. It was concluded that the right temporal region plays a role in the temporal processing of long and short intervals in the millisecond range.

In a study conducted by Picton, Stuss, Shallice, Alexander, & Gillingham (2006) on patients with frontal lesions, the Brodmann area 45 and Brodmann area 6 regions on the right hemisphere were found to be responsible for timing disorders. Some imaging studies have confirmed the hemispheric bias (Melgire et al., 2005; Rao, Harrington, Haaland, Bobholz, Cox, & Binder, 1997), whereas others have rejected it (Brunia, de Jong, van den Berg-Lenssen, & Paans 2000, Shih, Kuo, Yeh, Tzeng, & Hsieh, 2009). Weiner et al. conducted a voxel-wise meta-analysis of functional imaging (Wiener, Hamilton, Turkeltaub, Matell, & Coslett, 2010) and showed a significant asymmetry in inferior frontal gyrus activation (exacerbated activity in the right hemisphere) in both sub- and supra-second range. In a Voxel-based Lesion Symptom Mapping (VLSM) study using a temporal discrimination test at 600 and 2000 ms intervals, Gooch et al., (2011) demonstrated lateralization associated with

explicit timing, and damage in the right medial and superior frontal gyrus caused impaired timing in the sub- and supra-second range.

The results of rTMS studies also have confirmed these findings. The stimulation of the right dorsolateral prefrontal cortex region underestimates the intervals up to two seconds (Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004) and up to several seconds (Koch, Oliveri, Torriero, & Caltagirone, 2003).

Various reasons have been proposed for this hemispheric superiority. A possible reason might be the role of the cortical structure in the right hemisphere in the frontal region, especially the inferior frontal cortex and the dorsolateral prefrontal cortex in working memory (Pouthas, 2005). Another study showed that Broadman area 6 is associated with working memory load and the right premotor cortex is involved in spatial working memory storage (Lemus, Hernández, & Romo, 2009; Posner, Walker, Friedrich, & Rafal 1984). This role is performed by the online suspension of a short interval and access to it to perform the intended task (comparison or reproduction), which is followed immediately (Gooch et al., 2011). It has suggested that the discharge of the neurons in this region can monitor the duration of the interval.

Hemispheric bias - Indirect timing – Left hemisphere:

The temporal prediction test is a task achieved by combining a temporal cue and the RT task that is followed. Providing a temporal cue before the emergence of the stimulus allowed the participant to use this temporal cue for increasing his response speed (reducing RT). The test of the temporal prediction of neutral condition was a simple RT task to prepare RT type. The preparatory signal used was neutral and offered no cues about the potential time of stimulus emergence. Temporal prediction task is used in the assessment of temporal orienting that is an aspect of indirect timing, in which an exogenous stimulus that implies a temporal meaning improves performing the task. The present findings related to the NS group confirmed their optimal use of temporal cues (the size of a circle in this study) to increase the response speed or reduce RT. For the quantitative assessment of the subjects' benefiting from temporal cues, the variable of temporal benefit was introduced, which is the RT difference between the prediction test and the neutral test. The values obtained suggest that the NS group benefited from temporal cues and could perfectly use structures related to implicit timing and improve the outcomes of the task performed.

The second neutral condition fact was related to the normal hazard function that showed its dysfunction in two patient groups in the pairwise comparisons (Table 3). The LHD group suffered a relative increase in RT (slow responses) in both the short and long intervals compared with the NS group that revealed the role of left hemisphere damage in the temporal prediction dysfunction, especially in indirect timing. Comparing the quantitative variable (optimal use of temporal cues for reducing RT) of temporal benefit showed a significantly lower temporal benefit in the LHD group compared with the other groups. This result confirmed that the slow RT was caused by the inability to benefit from temporal cues. Although the slow RTs in both the short and long intervals were significantly different from the NS group, temporal benefit showed a significant difference with the NS group, only in the short interval. The reason is the interference of the foreperiod effect and the temporal benefit in the long interval. The benefit gained from the temporal cue is so weakened by the hazard function leading to a significant difference between the groups practically.

The findings showed that right hemisphere damage causes significant disorder in the reproduction task in the sub- and supra-second range (explicit timing impairment). Moreover, left hemisphere damage causes disability in using temporal cues to improve motor activity (implicit timing impairment suggesting hemispheric lateralization in the direct (right) and indirect (left) timing paradigms. As the timing has a key role in reactions, decision making, and even avoiding the hazard, this finding and fact help the neurosurgeons to resect abnormal tissues consciously to preserve these functions.

The main limitation of this study was the lack of a quantitative index of IQ (for instance, IQ>85) in the inclusion criteria; however, the number of years of education was included as a relative indicator of IQ. It is recommended to assimilate the study groups in terms of IQ, and the other confounding factors.

Another limitation was the lack of access to an image processing specialist; therefore, the target region was unidentified. Also, future studies should be conducted using more accurate imaging systems, including functional magnetic resonance imaging, diffusion tensor imaging, and other techniques using an image processing specialist.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the Ethical Guidelines of the Declaration of Helsinki 2013.

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Authors' contributions

Conceptualization, methodology: Sajjad Rezaei and Alia Saberi; Data collection: Ali Hosseini; Writing-original draft preparation: Ali Hossein, Sajjad Rezaei; Writing, revision, editing, and final approval of the study: All authors.

Conflict of interest

The authors declared no conflict of interest.

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