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Original Article

Striatal Beat Frequency Model in Multiple Sclerosis: Evidence for the Role of Thalamus

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Abstract

Background and Objective: According to the Striatal Beat Frequency model, timing behavior is associated with subcortical structures. Substantial study of timing behavior necessitates encompassing more parameters, including reaction time.

Materials and Methods: The present study aimed to assess the timing function of patients with multiple sclerosis (MS) according to the Striatal Beat Frequency (SBF) model of timing behavior, with particular regard to reaction time. A total of 45 MS patients were recruited from Poursina Hospital in Rasht. The patients' magnetic resonance imaging scans were examined by a neurologist to inspect and specify the number and location of MS plaques. The simple and selective reaction time of 31 patients was evaluated. Both parametric and non-parametric tests were used to analyze the data via SPSS software (version 26).

Results: Both simple and selective reaction time was significantly correlated with age, education, body mass index, number of symptoms, and score of disability. After controlling the gender variable, it was revealed that the thalamus was the most affected part of the brain in MS patients; nonetheless, the lesions in other areas were less related to the reaction time in patients.

Conclusions: Simple and selective reaction time was correlated with the function of the thalamus and subthalamic nuclei in MS patients. This study provided valuable insights regarding the usefulness of reaction time as a relevant index of timing behavior in modeling and comprehending timing behavior.

Keywords: Meck's model, Multiple sclerosis, Neuroanatomical, Reaction time

Background

From a voluminous perspective, all forms of animal and human behaviors are associated with time, and the capacity to measure time in seconds to minutes and hours is a cornerstone to delineate different forms of behavior. Accordingly, all aspects of human behavior, including talking, memorizing, remembering, thinking, perception, and reaction time, are somehow interwoven with the ability to mentally manipulate, predict, and alter time. Timing behavior, in turn, is interrelated to the cortical and subcortical parts of the brain, which have been extensively investigated in recent decades. One of the most compelling theories in characterizing timing behavior was proposed by Matell and Meck. It is based on the notion that timing is an emergent activity arising from thalamo-cortico-striatal loops; therefore, it has become famous as striatal beat frequency (SBF) model of timing behavior [1-2]. The theoretical framework of our study is generally based on the presumptions of SBF model; nonetheless, detailed discussion of the model is beyond the scope of this paper.

Multiple sclerosis (MS) is described as the most common disorder of the nervous system in young adults and is thought to be associated with a defect of the autoimmune system, in which neural tissue is targeted by two important types of immune cells, mainly T cells and B cells [3]. The symptoms of MS range from fatigue to bladder and bowel control, depression, pain, and cognitive dysfunctions. Mild cognitive impairment was reported in 40% of patients during the first stage of their disease; nonetheless, it may become more profound as the disease progresses into its severe stages [4-5-6]. A wide array of studies have pointed to the speed of information processing as one of the most affected aspects of cognition in MS. In recent years, reaction time has been proposed and utilized as a marker for cognitive impairments following neurological conditions, and some recent

studies suggested that it may serve as a beneficial alternative in the assessment of information processing [7-8-9].

The current study aimed to assess the possible effects of MS on simple and selective reaction time. It was hypothesized that MS lesions in cortical and subcortical areas may have a role in estimating and responding to visual stimuli through simple and selective forms of reaction time. The author's purpose was to explore the SBF model as a framework for interpreting MS lesions in relation to time estimation and defects in reaction time response. A considerable body of research in recent years has examined different aspects of timing processes, including timing differentiation and discrimination both in animals and humans; nevertheless, some other important issues remained to be explored, among which reaction time merited further investigation. Our argument is based on the ground that there might be a relationship between lesions in different parts of the brain, according to the SBF model, and the ability of MS patients to respond correctly to visual stimuli.

Objectives

The present study aimed to assess the timing function of patients with multiple sclerosis (MS) according to the Striatal Beat Frequency (SBF) model of timing behavior, with particular regard to reaction time.

Materials and Methods

Subjects

This was a retrospective study in which 44 patients were recruited from the MS Society of Pursina Hospital in Guilan province, Rasht, through a purposive sampling method from December 2021 to June 2022. The inclusion criteria were: diagnosis of MS by a specialist in neurology, reading literacy, and basic ability to work with computers. On the other hand, the exclusion criterion was having another neurological or psychiatric disorder other than MS. Demographic data of the patients was gathered, their disability was measured, and their MRIs were inspected by a neurologist in order to find the location of the lesions. The patients were requested to give written consent for their participation in the study, and the design of the study was approved by the Ethics Committee of Isfahan University in accordance with the Helsinki Declaration (IR.UI.REC.1401.123).

Experimentation and Instrument

In order to measure simple and selective reaction time, we used a reaction timer apparatus, which was designed and developed at the Department of Physics at Sharif University and manufactured by Sina Psychological Corporation. The software is able to measure reaction time in a range of 1-3000 milliseconds. The test-retest reliability of the measures was obtained at 0.84 in previous studies [10].

At the commencement of the experiment, the task was explained to each patient, and he/she was then asked to press certain buttons on the keyboard following the onset of visual stimuli. There were 10 trials for each patient, elapsed time after the exposure of stimuli was measured by the computer in milliseconds, and the number of errors was calculated as well. Each patient's task lasted for eight minutes.

Data analysis

The data were analyzed in SPSS software (version 26) using the Mann-Whitney U test, analysis of variance (ANOVA), analysis of covariance (ANCOVA), student's t-test, and logistic regression.

Transparency and open

Table 1. Mean and Standard Deviation of the sample

Dependent variable	N	male	Female	mean	Std. Deviation	Age Mean
simple	28	15	13	560.30	340.42	37.75
reaction	16	3	13	587.82	268.28	39.00
time	44			570.30	313.13	
selective	28			718.93	272.31	
reaction	16			1322.50	2445.46	
time	44			938.41	1489.62	

Results

Based on the ANCOVA test, after controlling the gender variable, there was a statistically significant difference between patients with and without lesions in the thalamus and basal ganglia in their selective reaction time; however, there was not a significant difference in patients' simple reaction time.

Descriptive statistics are illustrated in Table 1. As depicted in Table 2, MS plaques were remarkably observed in the parietal and frontal lobes, respectively. The lesions were both cortical and subcortical, located in the frontal, occipital, and parietal lobes and in the thalamus as well. Table 3 demonstrates the statistical frequency of lesions in different parts of patients' brains.

Table 2. Percentage and locations of MS plaques

Location of plaque	No		Cortical		Subcortical		both	
	N	Percent	N	Percent	N	Percent	N	Percent
Right Frontal Lobe	28	65.1	0	0.0	13	30.2	2	4.7
Left Frontal Lobe	26	59.1	0	0.0	15	34.1	3	6.8
Right Parietal Lobe	11	25.0	0	0.0	30	68.2	3	6.8
Left Parietal Lobe	4	9.1	1	2.3	35	79.5	4	9.1
Right Temporal Lobe	33	75.0	3	6.8	6	13.6	2	4.5
Left Temporal Lobe	35	79.5	4	9.1	4	9.1	1	2.3
Right Occipital Lobe	39	88.6	0	0.0	5	11.4	0	0.0
Left Occipital Lobe	41	93.2	0	0.0	3	6.8	0	0.0
	no		yes					
	N	Percent	N	Percent				
Left Thalamus	40	90.9	4	9.1				
Right Thalamus	44	100.0	0	0.0				

Table 3. Statistical frequency of lesions in different parts of the patient's brains

variable	Regression with Simple RT	P-value	Regression with Selective RT	P-value
Age	.405**	.006	.397**	.008
Education	-.507**	<.001	-.536**	<.001
Age of onset	.226	.141	.228	.137
Duration of MS	.191	.215	.226	.140
EDSS	.503**	.001	.546**	<.001
Brain plaqes	-.059	.705	-.061	.694
symptom	.496**	.001	.442**	.003
BMI	.366*	.014	.329*	.029

Table 4. Statistical values of the relationship between reaction time and individual and clinical characteristics of the patients

Dependent Variable	Independent variable	group	N	Mn	interquartile range	Mean Rank	z statistic	P-value
Simple RT	Gender	male	18	441.40	649.53	25.17	-1.146	.252
		female	26	399.20	261.53	20.65		
	Location	Town/city	38	403.20	436.33	22.37	-.171	.864
		Village	6	432.10	293.35	23.33		
	Family History	no	37	421.10	457.80	23.84	-1.588	.112
		yes	7	386.10	111.60	15.43		
	Hospitalization History	no	11	344.60	83.70	13.27	-2.751	.006
		yes	33	439.20	550.55	25.58		
Selective RT	Gender	male	18	665.0	352.50	24.06	-1.365	.172
		female	26	610.0	232.50	21.42		
	Location	town/city	38	645.0	247.50	21.70	-1.241	.214
		village	6	755.0	273.00	27.58		
	Family History	no	37	710.00	365.00	23.72	84.50	.148
		yes	7	610.00	100.0	16.07		
	Hospitalization History	no	11	550.00	230.0	17.50	-1.492	.136
		yes	33	710.00	315.0	24.17		

Table 4 displays the statistical values of the relationship of reaction time with the individual and clinical characteristics of the patients. Table 5 illustrates the results of the Man Whitney-U test for the difference between simple and selective reaction time of patients.

Table 5. Results of Man Whitney-U test for difference between simple and selective reaction time of patients

variable	Correlation Coefficient	P-value
number of Hospitalization	.398 **	<.001
Age of onset	.07	.653
Duration of MS	.296	.051
Selective R T	.546**	.001
Simple R T	.503 **	.001
Number of Brain plaques	.065	.677
number of symptoms	.58**	.001
BMI	.092	.554

Table 6. Relationship between physical disability and clinical features of patients

variable	group	mn	interquartile range	Mean Rank	z statistic	P-value
Gender	male	3.5	2.25	23.5	-0۴۳۳.	.66۵
	female	3	2.	21.81		
Hospitalization History	no	2	1.5	15.64	-2.0۶۱	.039
	yes	3	1.5	24.79		

Table 6 presents the relationship between physical disability and clinical features of patients.

Discussion

The current study aimed to assess the neuropathological lesions following MS and their effect on reaction time with a glance at the SBF neuroanatomical model of timing behavior. In this section, we first discuss the findings regarding the simple and selective reaction time, and we will then consider the implication of our findings in regard to the SBF model. The reaction time speed was lower in older patients; nonetheless, this finding seems insignificant since both patients and normal people may become slower in reacting to stimuli with increasing age [11]. This finding is concordant with a study by Turgeon, Lustig, and Meck (2016), [12] which emphasized that age difference is crucial in interpreting the findings of timing experiments on neurological and psychiatric disorders.

Inconsistent with the report of Martola et al. (2008) [13], we found no relationship between the number of lesions, age of onset, duration of illness, and reaction time in patients. However, it is in line with a study by Matell and Meck (2004) [2], which reported that while cortico-striatal circuits are the most sensitive part of neural networks in timing behavior, age-related differences may be compensated by "degeneracy," which help the organism to protect itself against loss of a vital function. According to the SBF model [2-14], cortical damage is expected to alter the network input to coincidence detectors, which in turn may lead to the disruption of their capacity to respond appropriately during reaction time. In agreement with the findings of the studies by Khanlarzadeh et al. (2015), Loerding et al. (2016), and Chiaravalloti and Deluca (2008) [10-15-16], the simple reaction time was negatively correlated with total number of symptoms, body mass index, disability, and academic level of patients. In line with a study by Vanessa et al. (2018) [17], we found no relationship between family history of MS and reaction time. Nevertheless, in accordance with the studies by Amato et al. (2001, 2006) and Król et al. (2015) [4-5-18], the relationship of reaction time with a history of illness and hospitalization was found to be significant.

In agreement with a study by Rogers et al. (2007) [19], the speed of selective reaction time was significantly related to the age of patients; however, it was related neither to gender nor living in rural and urban areas. Moreover, in line with the findings of Bisecco et al. (2018) [20], selective reaction time was not related to the total number of lesions; instead, it was correlated with the location of lesions, including the thalamus. This finding is basically congruent with the theoretical role of the thalamus in Meck's neuroanatomical model of timing. As stated by Meck, thalamus glutamatergic pathways to the cortex provide a main substrate for differential responses toward stimuli [21].

Another important factor in relation to selective reaction time was the level of disability. The more disabled patients had an increased reaction time toward selective stimuli. Feuillet et al. (2007) [3] reported similar results in MS patients. In the present study, the locations of MS plaques were found to be more related to reaction time in comparison with the total number of lesions. That may be due to different underlying mechanisms which are thought to be responsible for those effects. For instance, Paton and Buonomano (2018) [22] argue that there might be different substrates for subsecond versus suprasecond timing in the brain areas. In the same line, in their study on the pathogenesis of demyelination, Lucchnetti et al. (2000) [23] stated that autoimmune reactions through B-cells may lead to an increase in the plaques, while inflammatory reactions through T-cells correspond to the location of lesions [23] [18]. The same findings were reported by Gioia et al. (2007) and Bisecco et al. (2018) [24, 19].

Conclusions

In conclusion, we found that the simple and selective reaction time of MS patients seems to be affected differently by the disease. This finding suggests that there may be different pathways or substrates for the simple versus selective reaction time, which is consistent with some other reports suggesting different networks for diverse forms of timing behavior in other neurological disorders, including dementia and Alzheimer's disease [25]. Furthermore, we found that the thalamus and parts of basal ganglia were the most important structures related to reaction time in MS. This is concordant with the SBF model regarding the role of subcortical nuclei as the vital underlying parts of timing behavior. Among the notable limitations of this study are the inaccessibility of patients from other parts of the country and the sampling during the COVID-19 pandemic. Therefore, great caution should be exercised when generalizing the results of other populations. Furthermore, we were not able to have an encompassing overview of the SBF model of timing due to project limitations.

Compliance with ethical guidelines

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Authors' contributions
All authors contributed equally to the preparation of all parts of the research.

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Conflicts of Interest
The authors declare no conflict of interest in this study.

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