



### Cortical Relay Time Shortens in Parkinson's Disease with Apraxia

Ayşegül GÜNDÜZ<sup>1</sup>, Meral E. KIZILTAN<sup>1</sup>, Hatice KUMRU<sup>2</sup>, Semra OĞUZ<sup>5</sup>, Günes KIZILTAN<sup>1</sup>, Sibel ERTAN<sup>1</sup>, Hülya APAYDIN<sup>1</sup>

<sup>1</sup>Department of Neurology, Cerrahpasa School of Medicine, Istanbul University <sup>2</sup>Institut Guttmann, Institut Universitari de Neurorehabilitació adscrit a la UAB, Badalona, Barcelona, Spain <sup>3</sup>Institut Guttmann, Institut Universitari de Neurorehabilitació adscrit a la UAB, Badalona, Barcelona, Spain <sup>4</sup>Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain <sup>5</sup>Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Marmara University

#### Summary

Cortical relay time (CRT) is a neurophysiologic method that measures transmission between sensory and motor cortices. In this study, we calculated CRT to evaluate intrahemispheric transmission in idiopathic Parkinson's disease (PD). We recorded the following parameters: 1) long latency reflexes (LLRs), 2) motor-evoked potentials (MEPs), and 3) somatosensory-evoked potentials (SEPs) according to previously published reports, and cortical relay time was calculated using the following formula: Latency of LLR II - (onset latency of MEP response + latency of N20 response of SEP). CRT was shorter in patients with apraxia compared with patients without apraxia. The findings may raise the possibility of intrahemispheric aberrant conduction or abnormal synaptic reorganization in the presence of apraxia in PD.

**Key words:** Apraxia, Parkinson's disease, Cortical relay time

### Parkinson Hastalığı'nda Kortikal Röle Zamanı Kısalır

#### Özet

Kortikal röle zamanı (KRZ), duyuşsal ve motor korteksler arasındaki iletişimi ölçen nörofizyolojik yöntemdir. Bu çalışmada, hemisfer içindeki iletişimi değerlendirmek amacıyla idiopatik Parkinson hastalığıında (PH) KRZ ölçüldü. Uzun latanslı refleşler (LLR), motor uyandırılmış potansiyel (MEP) ve somatosensoryel uyandırılmış potansiyel (SEP) incelemeleri daha önce bildirilen yazılara uygun olarak yapıldı ve KRZ aşğıdaki formül kullanılarak hesaplandı: LLR II latansı- (MEP başlangıç latansı + SEP N20 latansı). KRZ, apraksi olan hastalarda olmayan hastalara oranla daha kısaydı. Bulgularımız, PH'da apraksi varlığıında hemisfer içinde anormal iletişim olasılığı veya anormal sinaptik organizasyon varlığını akla getirmektedir.

**Anahtar Kelimeler:** Apraksi, Parkinson hastalığı, Kortikal röle zamanı

#### INTRODUCTION

Cortical relay time (CRT) is a known neurophysiologic method that measures transmission between sensory and motor cortices(1). It reflects the difference

between latencies of long latency reflex (LLR) and the sum of somatosensory- and motor-evoked potential (SEP and MEP) latencies, and gives the transmission time between motor and somatosensory cortices(1). Prolonged CRT was reported

in multiple sclerosis, whereas it was extremely brief in progressive myoclonic epilepsies such as Unverricht-Lundborg disease(2,3). CRT has not been studied in PD or other parkinsonian syndromes.

Limb kinetic apraxia is typical in Parkinson's disease (PD); however, the development of ideomotor apraxia and ideational apraxia has been published in PD(4-6).

Here, we hypothesized that if CRT may reflect intrahemispheric transmission, which could be altered in PD because of the motor symptoms and/or apraxia.

## MATERIAL AND METHODS

**Patients:** We included consecutive patients with idiopathic PD who exhibited apraxia between January 2011 and January 2013. Eight patients with idiopathic PD with ideational/ideomotor apraxia (apraxia group), 11 age- and sex-matched patients with idiopathic PD without apraxia (nonapraxia group), and eight age- and sex-matched healthy subjects (control group) were included in the study. The nonapraxia group was formed by including one in every five patients with PD who were admitted during the study period and had no apraxia on clinical examination. Presence of apraxia was determined using the Mayo Clinic praxis assessment test, which has been validated for the Turkish population(7). Clinical characteristics were gathered from medical records. The features of PD were scored and cognitive performance was evaluated. None of the patients had dementia.

The study was approved by the local ethics committee of Cerrahpasa Medical Faculty and all participants gave informed consent.

### *Electrophysiologic recordings*

We used surface silver-silver chloride recording electrodes placed over the abductor policis brevis (APB) muscle bilaterally. All examinations were performed with a Neuropack Sigma MEB-5504k (Nihon Kohden Medical, Tokyo,

Japan). All recordings were made under optimum dopaminergic treatment for patients with PD.

We recorded the following parameters: 1) long latency reflexes (LLRs), 2) motor-evoked potentials (MEPs), and 3) somatosensory-evoked potentials (SEPs).

1. LLRs: The recording electrodes were placed over the belly of the APB muscle with the ground electrode over the palm. The electrical stimulus (0.2 ms in duration) was randomly applied on the median nerve at the wrist with the stimulus intensity between 5-15 mA. The recording was repeated 20 times. The gain was predetermined at 100 mV/division with a sweep ranging from 20 ms per division, and the band-pass filters were 2 to 2000 Hz. LLRs were recorded during rest and while subjects were performing a slight (approximately 10-25% of maximum) contraction of the APB muscle.

2. MEPs: We used a MagStim single-pulse magnetic stimulator (Magstim, Whitland, Wales, UK) equipped with a commercially available circular coil (90 mm in diameter), which was held over the vertex. MEP recordings were made using pairs of Ag-AgCl surface electromyography (EMG) electrodes, which were placed over the APB muscles. To maintain attention during transcranial magnetic stimulation sessions, the patients and healthy volunteers were asked to keep their eyes open and to count the stimuli. At the end of each session, we recorded the number of stimuli counted by patients and healthy subjects.

3. SEPs: The recording electrodes were placed over the parietal cortex "C3" and "C4" with reference electrodes over Cz and Pz areas. An electrical stimulus was applied with surface electrodes on the median nerve at wrist level. Stimulus duration was 0.2 ms and stimulus intensity was maintained at 3 times the sensory threshold. EMG was amplified (10  $\mu$ V) and filtered at 10 and 100 Hz. Recordings

were averaged 200 times and repeated twice.

### **Data and Statistical analysis:**

We measured latency of LLR as distance from electrical stimulus artifact until negative deflection after F-wave. LLRs were classified as I, II, and III according to onset latencies(8). Presence ratios were calculated as number of participants with LLRx100 / total number of participants in the specific group.

The MEP latency was measured as duration from electrical stimulus artifact until negative deflection.

In SEPs, we measured latencies of the N20 component and peak-to-peak amplitudes of N20 responses.

Cortical relay time was calculated using the following formula: Latency of LLR II - (onset latency of MEP response + latency of N20 response of SEP)(8).

First, we grouped the data from dominant vs. non-dominant hands and compared electrophysiologic findings from dominant hands between the three groups. In the next analysis, we grouped data according to the more affected side from patients with PD and compared these electrophysiologic findings between the more affected side of patients with PD with and without apraxia. In this comparison, we considered electrophysiologic findings over dominant hand in healthy subjects.

Data are presented as mean  $\pm$  standard deviation (SD). The three groups were compared using the Kruskal-Wallis and Mann-Whitney U tests for post-hoc comparisons. The Chi-square test was used to compare qualitative data. The data analyses were performed using SPSS version 15.0 and P values  $< 0.05$  were accepted as significant.

## **RESULTS**

The demographic and clinical findings of participants are presented in Table 1.

1. LLRs: We could only obtain LLRs during slight contraction of APB muscle. LLRs II and LLRs III were recorded, but there was no LLR I. LLRs were absent during rest in all groups.

Mean LLR II latency of the dominant extremity was significantly different between three groups ( $P = 0.031$ , Kruskal-Wallis test) (Table 2). Posthoc analysis showed significant longer LLR II latency in the PD group without apraxia than in healthy subjects ( $P = 0.005$ ). LLR II was recorded in all participants. The probability of LLR III was higher in non-apraxia (63.6%) than healthy subjects (12.5%) ( $P = 0.050$ , Chi-square test). Pairwise analysis demonstrated that the mean LLR II latency of the more affected extremity was significantly shorter in the group with apraxia than in the group with no apraxia ( $P = 0.037$ , Mann-Whitney U).

2. MEPs: Between three groups, there were no significant differences in MEP latency ( $P = 0.08$ , Kruskal-Wallis test) or MEP amplitudes ( $P = 0.804$ , Kruskal-Wallis test).

3. SEPs: There were no statistical differences regarding latencies or amplitudes of SEP responses ( $P = 0.060$  and  $P = 0.083$ , respectively, Kruskal-Wallis test) (Table 2).

4. CRT: The dominant extremity was the right hand in all participants. The affected upper extremity was the left side in 37.5% of patients with PD with apraxia and 36.4% of patients of PD without apraxia. The CRT of the dominant extremity was shorter in the apraxia group compared with the non-apraxia group ( $P = 0.031$ , Mann-Whitney U), but not in comparison with healthy subjects. The CRT of the more affected extremity was also significantly shorter in the apraxia group compared with the non-apraxia group ( $P = 0.005$ , Mann-Whitney U) (Table 3), but there were no differences compared with the healthy subjects.

**Table 1.** Clinical and demographic findings of all participants

	PD Apraxia(+) (n=8)	PD Apraxia(-) (n=11)	Healthy Subjects (n=8)	<i>P</i>
Mean age ( $\pm$ SD, year)	62.7 $\pm$ 13.4	55.2 $\pm$ 9.6	55.2 $\pm$ 8.6	0.160
Sex (F/M)	3/5	1/10	2/6	0.331
Dominant hand (right/left)	8/0	11/0	7/1	0.291
Affected side at onset (right/left)	5/3	7/4	-	0.906
Symptom at onset (tremor/bradykinesia)	6/2	9/2	-	0.829
PD type (A-R/Tr)	6/2	4/7	-	0.138
PD duration (y, mean $\pm$ SD)	5.6 $\pm$ 5.4	5.9 $\pm$ 3.6	-	0.915
PD duration (y, range)	2-16	4-15	-	
UPDRS motor score (mean $\pm$ SD)	13.8 $\pm$ 7.3	9.5 $\pm$ 3.5	-	0.128
Hoehn-Yahr stage (mean $\pm$ SD)	1.9 $\pm$ 0.3	1.6 $\pm$ 0.5	-	0.218
MMSE (mean $\pm$ SD)	27.7 $\pm$ 1.5	28.3 $\pm$ 1.1	30	0.450

PD, Parkinson's disease, SD, standard deviation; A-R, akinetic-rigid; Tr, tremor dominant; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination

**Table 2.** Electrophysiologic findings recorded over the dominant upper extremity in patients with PD and healthy subjects.

	PD Apraxia+ (n=8)	PD Apraxia- (n=11)	Healthy Subjects (n=8)	<i>P</i>
<b>CRT (ms)</b>	10.9 $\pm$ 4.5	15.3 $\pm$ 0.9	10.1 $\pm$ 4.1	0.031***
<b>LLR II n (%)</b>	8 (100)	11 (100)	8 (100)	0.999**
<b>LLR III n (%)</b>	2 (25.0)	7 (63.6)	1 (12.5)	0.050**
<b>LLR II latency</b>				
(mean $\pm$ SD, ms)	57.1 $\pm$ 6.3	60.4 $\pm$ 4.2	53.4 $\pm$ 3.9	0.031*
<b>MEP latency (ms)</b>	23.7 $\pm$ 1.2	23.9 $\pm$ 1.1	22.1 $\pm$ 2.1	0.080*
<b>MEP amplitude (mV)</b>	2.2 $\pm$ 1.7	1.9 $\pm$ 1.8	2.5 $\pm$ 0.2	0.804*
<b>SEP latency (ms)</b>	22.5 $\pm$ 1.6	23.1 $\pm$ 2.8	20.8 $\pm$ 0.8	0.060*
<b>SEP amplitude (<math>\mu</math>V)</b>	2.7 $\pm$ 2.9	2.1 $\pm$ 1.6	5.5 $\pm$ 3.0	0.083*

PD, Parkinson's disease; LLR, long latency reflex; MEP, motor-evoked potential; SEP, somatosensory-evoked potential; CRT, cortical relay time

\*\*\*According to Mann-Whitney U between PD with and without apraxia

\*Data analysis performed using Kruskal-Wallis test (Mann-Whitney U for LLRII latency, nonapraxia group vs. control group  $P = 0.005$ )

\*\*Chi-square test

**Table 3.** Electrophysiologic findings recorded over the more affected upper extremity in patients with PD and healthy subjects.

	<b>PD Apraxia+ (n=8)</b>	<b>PD Apraxia- (n=11)</b>	<b>Healthy subjects (n=8)</b>	<b>p</b>
<b>CRT</b>	7.6±3.2	13.4±3.7	10.1±4.1	0.005 ***
<b>LLR II n (%)</b>	8 (100)	11 (100)	8 (100)	0.999 **
<b>LLR II latency (mean±SD, ms)</b>	53.2±3.9	58.5±4.9	53.4±3.9	0.078*

*PD, Parkinson's disease; LLR, long latency reflex; CRT, cortical relay time*

\*Data analysis are done by Kruskal-Wallis test

\*\*\*According to Mann-Whitney U between patients with PD with and without apraxia

\*\*Chi-square test

## DISCUSSION

Our study demonstrated the following: 1) Patients with PD who had apraxia showed no differences in LLR, SEPs, MEPs, or in CRT in comparison with healthy subjects, 2) comparing patients with PD with and without apraxia, CRTs of dominant extremities and of upper extremities with symptoms at onset were shorter in patients with PD who had apraxia. CRT has a normal range of 8.5-11.4 ms in healthy subjects(9). Longer CRTs were attributed to the occurrence of conduction velocity slowing and/or synaptic transmission impairment along the sensory-motor intracortical pathway in multiple sclerosis(2,10).

The idea of functional network organization in the brain is gaining importance after the discovery of a default mode network with the evolution of neuroimaging techniques(11). Basal ganglia, specifically substantia nigra pars compacta, have functional connectivity with the supplementary motor area, the default mode network, and dorsolateral prefrontal cortex(12). Functional neuroimaging studies showed functional disruption of the default mode network in cognitively unimpaired patients with PD, in the absence of significant structural differences between patients and healthy

subjects(13,14). The pattern of functional connectivity impairment was partially normalized after dopaminergic treatment(12). On the other hand, patients with limb kinetic apraxia showed impaired primary somatosensory cortex activation, which did not improve after dopaminergic treatment(15). The process seems to be different in ideational/ideomotor apraxia because our patients with PD with and without apraxia were examined under optimum dopaminergic treatment and there were no changes in the CRT pathway in PD in comparison with healthy subjects.

The CRT in our patients was shorter in the presence of apraxia in PD compared with patients with PD who had no apraxia. Functional magnetic resonance imaging (fMRI) studies showed overactivity of precentral gyrus and decreased activity of postcentral gyrus in PD apraxia(16). Although that study included patients with limb-kinetic apraxia, our results in patients with PD with ideomotor and ideational apraxia paralleled their results. fMRI studies during different cognitive functions showed activation of task-irrelevant areas in PD, which was interpreted as the development of aberrant pathways or crosstalk between networks(17). Activity of the default mode increases in PD to optimize movement, which in turn may

lead to impairment of other functions(16). imilarly, we may speculate that an aberrant conduction may operate in PD that compensates for apraxia. However, this hypothesis still needs to be proven because our results failed to show differences between PD with apraxia and healthy subjects.

Second, CRT is known to develop as a function of an oligosynaptic network. Thus, any synaptic dysregulation in this network may change CRT. Alpha-synuclein is known to regulate synaptic function in dopamine neurons and its absence changes the organization of synaptic vesicles(18). Additionally, compensatory reorganization occurs in nigrostriatal pathways and in the sensorimotor cortex, even in early PD(19). Therefore, synaptic changes in the CRT network may be an alternative explanation. However, absence of a similar shortening in the PD group without apraxia under optimum dopaminergic treatment suggests a synaptic dysfunction cause other than alpha-synuclein accumulation in dopamine neurons.

We determined similar findings regarding CRT of the dominant extremity and CRT of the more affected upper extremity. Although praxis is a function of the dominant hemisphere, we indirectly measured CRT and praxis over the upper extremities, both of which are controlled by the dominant hemisphere for praxis function(19).

In conclusion, our data suggests that there is no altered transmission in the CRT pathway in PD with and without apraxia compared to healthy subjects, which may be secondary to optimum dopaminergic treatment. Shorter CRT in PD with apraxia compared with PD without apraxia may raise the possibility of aberrant conduction in the presence of apraxia, which needs further confirmation.

### Correspondence to:

Aysegul Gunduz

E-mail: draysegulgunduz@yahoo.com

Received by: 03 September 2016

Revised by: 09 February 2017

Accepted: 06 April 2017

### The Online Journal of Neurological Sciences (Turkish) 1984-2017

This e-journal is run by Ege University Faculty of Medicine,

Dept. of Neurological Surgery, Bornova, Izmir-35100TR

as part of the Ege Neurological Surgery World Wide Web service.

Comments and feedback:

E-mail: editor@jns.dergisi.org

URL: <http://www.jns.dergisi.org>

Journal of Neurological Sciences (Turkish)

Abbr: J. Neurol. Sci.[Turk]

ISSNe 1302-1664

### REFERENCES

1. Deuschl G, Schenck E, Lücking CH. Long-latency responses in human thenar muscles mediated by fast conducting muscle and cutaneous afferents. *Neurosci Lett* 1985; 55: 361-6.
2. Tataroglu C, Genc A, Idiman E, Cakmur R, Idiman F. Cortical relay time for long latency reflexes in patients with definite multiple sclerosis. *Can J Neurol Sci* 2004; 31: 229-34.
3. Canafoglia L, Ciano C, Panzica F, et al. Sensorimotor cortex excitability in Unverricht-Lundborg disease and Lafora body disease. *Neurology* 2004; 63: 2309-15.
4. Zadikoff C, Lang AE. Apraxia in movement disorders. *Brain* 2005; 128: 1480-97.
5. Leiguarda RC, Pramstaller PP, Merello M, et al. Apraxia in Parkinson's disease, progressive supranuclear palsy, multiple system atrophy and neuroleptic-induced parkinsonism. *Brain* 1997; 120: 75-90.
6. Uluduz D, Ertürk O, Kenangil G, et al. Apraxia in Parkinson's disease and multiple system atrophy. *Eur J Neurol* 2010; 17: 413-8.
7. Kokmen E, Ozekmekci FS, Cha RH, O'Brien PJ. Testing for apraxia in neurological patients: a descriptive study in two diverse cultures. *Eur J Neurol* 1998; 5: 175-80.

8. Valls-Sole J, Deuschl G. Reflex responses, silent period and long-latency responses. In: Kimura J, editor. *Peripheral nerve diseases*, Amsterdam: Elsevier. 2006, p. 237-62.
9. Bonfiglio L, Rossi B, Sartucci F. Prolonged intracortical delay of long-latency reflexes: electrophysiological evidence for a cortical dysfunction in multiple sclerosis. *Brain Res Bull* 2006; 69: 606-13.
10. Iturria-Medina Y. Anatomical brain networks on the prediction of abnormal brain states. *Brain Connect* 2013; 3: 1-21.
11. Wu T, Wang J, Wang C, et al. Basal ganglia circuits changes in Parkinson's disease patients. *Neurosci Lett* 2012; 524: 55-9.
12. Tessitore A, Esposito F, Vitale C, et al. Default-mode network connectivity in cognitively unimpaired patients with Parkinson disease. *Neurology* 2012; 79: 2226-32.
13. van Eimeren T, Monchi O, Ballanger B, et al. Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. *Arch Neurol* 2009; 66: 877-83.
14. Foki T, Pirker W, Geißler A, et al. Finger dexterity deficits in Parkinson's disease and somatosensory cortical dysfunction. *Parkinsonism Relat Disord* 2015; 21: 259-65.
15. Foki T, Pirker W, Klinger N, et al. FMRI correlates of apraxia in Parkinson's disease patients OFF medication. *Exp Neurol* 2010; 225: 416-22.
16. Rottschy C, Kleiman A, Dogan I, et al. Diminished activation of motor working-memory networks in Parkinson's disease. *PLoS One* 2013; 8: e61786.
17. Zaltieri M, Grigoletto J, Longhena F, et al.  $\alpha$ -synuclein and synapsin III cooperatively regulate synaptic function in dopamine neurons. *J Cell Sci* 2015; 128: 2231-43.
18. Kojovic M, Bologna M, Kassavetis P, et al. Functional reorganization of sensorimotor cortex in early Parkinson disease. *Neurology* 2012 1; 78: 1441-8.
19. Heilmann KM, Valenstein E, Rothi LJG, Watson RT. *Intentional Motor Disorders and the Apraxias*. In: Bradley WG, Daroff RB, Fenichel GM, Jankovic J, editors. *Neurology in Clinical Practice. Principles of Diagnosis and Management. Volume 1*. Philadelphia: Butterworth-Heinemann. 2004, p. 117-30.