Basal Ganglia 4 (2014) 95–99

Contents lists available at ScienceDirect

Basal Ganglia

journal homepage: www.elsevier.com/locate/baga

Alterations in time estimation in multiple system atrophy

Birgit Högl [a], Patricia V. Agostino [b], María Cecilia Peralta [c], Oscar Gershanik [d], Diego A. Golombek [b,*]

[a] Department of Neurology, Innsbruck Medical University, Anichstr. 35, 6020 Innsbruck, Austria
[b] Laboratorio de Cronobiología, Universidad Nacional de Quilmes/CONICET, R.S. Peña 352, B1876BXD Bernal, Buenos Aires, Argentina
[c] Departamento de Neurología, Hospital Universitario CEMIC, Galván 4102, C1425DQK Buenos Aires, Argentina
[d] Instituto de Neurociencias, Fundación Favaloro, Solís 461, C1078AAI Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 5 April 2014
Received in revised form 28 June 2014
Accepted 29 June 2014
Available online 19 July 2014

Keywords:
Basal ganglia
Dopamine
Multiple system atrophy
Parkinson's disease
Time estimation

ABSTRACT

Precise spatiotemporal performance is required by many common tasks and represents a basic aspect of cognition. Time estimation in the second-to-minutes range – known as interval timing – involves the interaction of the basal ganglia and the prefrontal cortex via dopaminergic–glutamatergic pathways. Neurodegenerative disorders such as Parkinson's disease (PD) and multiple system atrophy (MSA) are characterized by basal ganglia dysfunction due to dopamine loss. Although interval timing in PD has been studied, little is known about temporal processing in MSA. In the present work, control, PD and MSA subjects ($n = 8$ for each group) were tested for interval timing in short (<5 s), medium (5–15 s) and long (>15 s) duration stimuli. MSA differed significantly from controls and PD patients in terms of decreased accuracy in the timing task. Differences between PD and MSA patients (as well as between MSA and controls) were lost after levodopa treatment. We show that time estimation for time bins between 5 and 20 s is affected in subjects with MSA, who had a significant tendency to underestimate time intervals as compared to controls or PD patients. Recordings of cognitive performance related to timing could be considered useful measurements of the progression of movement disorder-related pathologies.

Introduction

Timing is crucial to all aspects of our lives. Indeed, biological timing includes diverse time-related mechanisms that encompass several orders of magnitude [1]. More specifically, short perception in the seconds-to minutes range, known as interval timing, is crucial to learning, memory, decision making and other cognitive tasks. Time perception is often thought to depend on cognitive processing of events, as well as on an internal pacemaker–counter mechanism. Recent findings argue for the involvement of cortico-striatal circuits, controlled by dopaminergic modulation of oscillatory activity and lateral connectivity. Indeed, striatal medium spiny neurons are able to detect the coincident activity of specific beat patterns of cortical oscillations [2]. A consistent approach used for studying interval timing in human and animals is a reproduction procedure, in which the subject is presented with a given criterion duration and then required to reproduce this duration. Typically, the participant's responses follow a normal distribution around the criterion duration, and the width of this response distribution is proportional to the target length [3]. Interval timing is altered in several disorders associated with pathological dopaminergic function, including schizophrenia, Parkinson's disease (PD), Huntington's disease and attention deficit disorder [4–6].

PD patients experience specific problems with timing of motor responses, such as increased reaction time, movement time, and speech production time, as well as deficits in programming and synchronizing motor responses. These motor deficits may add a constant variance in timing performance, particularly in tasks with substantial motor requirements such as repetitive tapping [7]. Other cognitive deficits have also been recognized in PD, involving attention, memory, temporal discrimination, frontal lobe function, conceptual ability and visuospatial function [8].

Multiple system atrophy (MSA) is a clinically and pathologically distinctive neurodegenerative disease. MSA is characterized

* Corresponding author at: Departamento de Ciencia y Tecnología, Universidad Nacional de Quilmes, Roque Sáenz Peña 352, Bernal B1876BXD, Buenos Aires, Argentina. Tel.: +54 11 43657100x5626; fax: +54 11 43657132.
E-mail addresses: birgit.ho@i-med.ac.at (B. Högl), pagostino@unq.edu.ar (P.V. Agostino), ceciliaperalta@yahoo.com.ar (M.C. Peralta), gersha@gmail.com (O. Gershanik), dgolombek@unq.edu.ar (D.A. Golombek).

http://dx.doi.org/10.1016/j.baga.2014.06.004
2210-5336/

clinically by symptoms that can be subdivided into pyramidal, extrapyramidal, cerebellar and autonomic categories. Extrapyramidal motor abnormalities such as bradykinesia, rigidity and postural instability are classed as either parkinsonian-type (MSA-P) or cerebellar (MSA-C) and reflect damage to the basal ganglia or cerebellum, respectively [9]. In patients with MSA, the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores correlate with the amount of nigrostriatal dopaminergic neuronal loss and damage to the striatal neurons [10]. Moreover, a more pronounced decline in dopamine transporter (DAT) signal was observed in the caudate and anterior putamen of patients with MSA-P as compared to that in patients with PD [11]. In PD, dopaminergic degeneration is presynaptic, while in MSA it is not only presynaptic but also postsynaptic, showing dopamine 2 (D2) receptor downregulation [12]. In addition, cognitive impairments have been reported in MSA patients, in some cases with higher deficits in MSA-P compared to PD [13,14].

In PD patients there are time estimation deficits compatible with the alteration of an internal clock and partially reversed by levodopa [7]. Although the efficacy of levodopa has been documented in several cases of MSA [15], there is almost no information about time estimation impediments and its treatment in MSA patients.

The objective of this work is to assess putative time estimation deficits in MSA patients, compared to PD patients and a control group. Because dopaminergic degeneration is more severe in MSA compared to PD patients, with these sets of experiments we are testing the hypothesis of more serious deficits in time estimation in MSA patients, which could be partially reversed by levodopa treatment.

Materials and methods

Subjects

Eight patients with MSA (parkinsonian-type) and eight matching (age, sex and progression of disease) patients with PD were examined. A matched control group ($n = 8$) was also included. Patients with cognitive impairment (mini-mental state by Folstein below 27) were excluded [16]. Matching criteria were gender, age (±5 years), and the Unified Parkinson's Disease Rating Scale (UPDRS) motor score [17] ±15%. Patients were examined (a) after an overnight medication fast and (b) after intake of their usual levodopa (L-DOPA) dose. NMDA antagonists, monoamine oxidase-B inhibitors, sedatives, selective serotonin reuptake inhibitors, anxiolytics, and other CNS medications were permitted if dose was stable for the 28 days prior to baseline and likely to remain so for the duration of the experiment. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All subjects (or their families) provided informed consent before study participation.

Protocol

Patients were seated comfortably in a chair with the computer screen before them. Wheelchair-bound MSA patients were examined in their homes. An examination session consisted of 2 parts: before medication intake after an overnight fast, and 1 h after the usual levodopa dose. At each examination, the time estimation program and a UPDRS motor part was performed, in order to analyze the relationship between changes in time estimation and changes in motor performance. Control subjects were examined only once.

Since most patients cannot operate the computer program properly by pressing the keyboard keys in response to the temporal signals due to their motor impairments – which would produce quite variable, and therefore unreliable, results – in this protocol both MSA and PD patients as well as the control group communicated the examiner via hand grip when to press the computer key. Although the examiners were not blind to patient group, they were randomly assigned to each patient. This procedure was validated in an informal pre-protocol and has been used previously in the literature [18].

Time estimation assessment was performed with a special software that we have developed specifically for this purpose. The procedure was compiled with visual basic and run on a portable PC. The methodology is similar to other time production protocols [19] in which the subjects had to match a variable duration tone to the exact duration of the previous tone that had been presented. This program offered a set of different durations of auditory stimuli (600 Hz, 50 dB tone), which the participant had to estimate and then reproduce. Twenty stimuli were presented per trial, so that an equal proportion of short (<5 s), medium (5–15 s) and long (>15 s) stimuli were presented in each trial. The target duration was presented with an uninterrupted tone that lasted between 1 and 20 s. Session duration was of approximately 30 min. No feedback was given to the participants. The computer stored the real and estimated time values, and further analysis characterized the different ratios between these two sets of data, including stratification in short-, medium- and long-duration stimuli.

Mini-mental tests were done before study entry and the Montgomery–Asberg Depression Scale [20] was performed to control for depression-induced impairment of time estimation.

Data analysis

For each subject, a subjective/real time ratio was calculated. One-way analysis of variance (ANOVA) was applied, followed by a post hoc least significance difference test. All data sets passed the Kolmogorov–Smirnov (KS) normality test.

Results

Table 1 shows the clinical motor and neuropsychological profiles of both samples of patients. MSA and PD subjects were comparable in all of the variables considered. The mini-mental state examination (MMSE) scores confirmed that patients were free of symptoms of dementia. Most of the patients were undergoing treatment with additional medication other than levodopa.

Fig. 1 summarizes the resulting behavioral performance during the timing task. When all target durations were analyzed together, MSA subjects had a significant tendency to underestimate real time as compared to controls and PD patients ($F_{4,35} = 6.78$, $p = 0.0004$, one-way ANOVA followed by Tukey's test), while PD

Table 1
Clinical motor and neuropsychological profiles of PD and MSA patients[a].

Patients	Age[b]	Mini-mental	Montgomery	UPDRS before	UPDRS after[c]
PD	60.62 ± 7.34	28.11 ± 2.08	8.0 ± 5.09	36.88 ± 11.75	21.11 ± 11.12
MSA	60.50 ± 7.38	28.0 ± 1.15	10.57 ± 7.20	32.71 ± 13.51	31.86 ± 13.13

[a] Data are expressed as mean ± S.D., $n = 8$/group.
[b] Expressed in years.
[c] Corresponding to 1 h after treatment.