Published in final edited form as:

Parkinsonism Relat Disord. 2011 September ; 17(8): 642–644. doi:10.1016/j.parkreldis.2011.06.021.

Basal Ganglia and Kinematics Modulation: Insights from Parkinson's and Huntington's diseases

Clara Moisello¹, Bernardo Perfetti¹, Lucio Marinelli², Vittorio Sanguineti³, Marco Bove⁴, Andrew Feigin⁵, Alessandro Di Rocco⁶, David Eidelberg⁵, and M. Felice Ghilardi¹

¹ Dept. of Physiology and Pharmacology, CUNY Medical School, New York, NY

² Dept. of Neurosciences, Ophthalmology and Genetics, University of Genova, Italy

³ Department of Informatics, Systems and Telecommunications, University of Genova, Italy

⁴ Department of Experimental Medicine, University of Genova, Italy

⁵ North Shore University Hospital, Manhasset, NY

⁶ Department of Neurology, New York University, New York, NY

Abstract

Movement kinematic variables related to force production can be modulated to respond appropriately to different contexts. We previously showed that in a choice-reaction time and a predictable timed-response task, normal subjects perform reaching movements to the same targets with two different kinematic patterns, a marker of flexibility. Here, we used the two tasks to determine whether basal ganglia are involved in the selection and modulation of movement kinematics and therefore in flexible force production.

We tested seventeen patients in the early stages of Parkinson's disease, eleven pre-symptomatic Huntington's disease carriers and sixteen age-matched normal controls with the above-mentioned motor tasks.

In both patient groups, the difference in kinematics (movement duration, peak velocity and acceleration) between the two tasks was significantly reduced compared to controls, indicating a limited range of choices or flexibility. However, this reduction was skewed in opposite directions in the two disorders, with force production being generally higher in Huntington's carriers and lower in Parkinson's patients compared to controls.

We conclude that basal ganglia are involved in adapting movement to different contexts and selecting the appropriate movement force. The opposite trends in Parkinson's and Huntington's disease suggest that such regulation might depend on the balance between the outputs of direct and indirect pathways.

Keywords

Force; Reaching Movements; Regulation; Flexibility; Motor Control

© 2011 Elsevier Ltd. All rights reserved.

Corresponding author: M. Felice Ghilardi, Dept. of Physiology & Pharmacology, CUNY Medical School, 160 Convent Avenue, New York, NY, 10031, USA, Tel: +1 212 650 7487, Fax: +1 212 650 7726, lice.mg79@gmail.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

The kinematic characteristics of movements are determined by contextual demands: the flexibility of a healthy motor system allows to switch and select the strategy more suitable to the specific situation, to produce efficient movements and, ultimately, to save either time or energy [1].

Recently, we have designed two arm-reaching tasks requiring movements with equal geometric characteristics both directed to temporally predictable targets, but with different contextual attributes: in one, targets appear in unpredictable order and subjects are instructed to react as soon as possible, avoiding anticipation (reaction time paradigm, RAN). In the other one, targets appear in a repeating predictable counterclockwise order, and subjects are instructed to anticipate them and reach the target in synchrony with its appearance (timed-response paradigm, CCW). We found that movements to unpredictable targets are faster, with shorter movement times and higher peak velocity and accelerations, than movements to the exact same locations performed when advanced information about the spatial location of target occurrence are available [2]. Interestingly, we found that the kinematic variables derived from the hand trajectories in these tasks (movement time, peak velocity and acceleration) reflect significantly the amount of muscle energy expense or effort for a given movement [3]. The differences in performance between the two experimental contexts reflect a range of available choices and thus, can be used as a marker of kinematic flexibility in the adaptation to different contexts.

The selection of the movement kinematics, as well as the flexible regulation of muscle force, might depend on the proper functioning of the basal ganglia [4-10]. However, how the basal ganglia circuitry contributes to the selection of appropriate movement kinematics is still a matter of debate.

Here, we hypothesized that different basal ganglia disorders might reduce the flexibility of the healthy motor system in the selection of movement kinematics and thus muscle force. For this purpose, we tested two populations with basal ganglia involvement but minimal or no motor impairment: a group of patients in the early stage of Parkinson's Disease (PD) and a group of pre-symptomatic carriers of Huntington's disease (pHD). We used our two reaching tasks and measured the kinematic and spatial characteristics of movements to unpredictable and predictable targets. In this way, we ascertained whether: 1. basal ganglia are involved in the selection of the movement kinematics; 2. different pathologies of the basal ganglia produce different types of disregulation.

Methods

We tested 44 subjects

Seventeen patients with PD (12 men, mean age: 59.3 ± 8.0 years; age range: 46-72; Hoehn-Yahr Stage 1-2). Eleven patients were drug naïve. Treated patients were tested 12-hour off-drug. UPDRS motor scores (mean 8.5 ± 1.6) were assessed in each patient while off medication.

Eleven pHD subjects (5 men, mean age: 45.6 ± 10.9 years; range: 25-61; CAG>40). Neuropsychological tests of general cognition and visuo-spatial abilities were in the normal range [5].

Sixteen neurologically normal controls, which were subdivided in two partially overlapping groups, age-matched to the two patient populations, respectively. The controls for PD were

11 subjects (5 men, mean age 54.1 ± 10.0 years; range: 43-70); the controls for pHD were 12 subjects (6 men, mean age: 44.3 ± 12.5 years; range 23-67). Written informed consent was obtained from all participants under a protocol approved by the institutional review board of the participating institutions.

Motor task—Subjects performed two motor tasks (RAN and CCW) described in details previously [2, 5, 11]. Briefly, in both, subjects performed out-and-back movements on a digitizing tablet (sampling rate 200Hz) by moving as fast as possible a cursor with their right hand from a common starting point to one of eight targets (distance = 1.6 cm, radius = 0.5 cm) that appeared, with a tone, at a regular 1-second interval. In RAN, targets were presented in an unpredictable order; instructions were to reach the target as soon as possible. In CCW, targets appeared in a predictable, counterclockwise order; instructions were to reach the target in synchrony with the tone. In both tasks, subjects were required to reach for the target without specific instructions about spatial accuracy. All subjects were able to follow instructions and to perform the motor tasks; they practiced the two tasks before testing, and, by the end of training, their performance was stable in both tasks (more than 95% target hits). There were no differences in hit rate between tasks or groups.

Subjects then performed a total of 176 movements for each task

For each response, we computed: movement onset time -the time between stimulus appearance and movement onset; movement time (MT) -the time between the movement onset and reversal; amplitudes of peak velocity and acceleration; path length -the distance between the onset and the reversal point; symmetry index of the velocity profile – the ratio between the time from onset to peak velocity, and total movement time, expressed in percentage. As we found that peak velocity and peak acceleration were highly correlated with MT ($r=0.87$ and 0.78 respectively, $p<0.0001$), here, for the sake of brevity and clarity, we report the results for MT.

We computed the mean MT for the RAN and CCW blocks separately. To capture the difference between the two conditions, -and thus the degree of the system flexibility for each subject,- we computed the delta MT (CCW-RAN). In addition, to assess the mean duration for each subject, we then averaged the MTs of the two tasks (combined mean MT).

In the statistical analysis, each patient group was compared with the respective age-matched control group. A mixed model RM-ANOVA ($\alpha=0.05$) was performed on MT with Group (patient, control) as between-subject factor and Task (RAN, CCW) as within-subject factor. A one-way ANOVA with main effect Group was performed on delta-MT and combined-MT. Significant effects and interactions were further explored with Bonferroni corrected post-hoc tests. We computed Pearson's correlations indices between MT-related variables and disease markers (UPDRS in PD and CAG repeats in pHD group, respectively). In addition, a stepwise binary logistic regression was used to estimate predictors of group membership based on the values of delta MT and combined mean MT.

Results

The trajectory of all patients and controls had a bell-shaped velocity profile, without difference in symmetry index between groups or tasks (Group: $F(1,41)=1.5$; $p=0.23$; Task ($F(1,41)=2.4$; $p=0.15$; Group $\times$ Task: $F(1,2)=0.04$, $p=0.95$). We found that both peak velocity and peak acceleration were highly correlated with the movement time (MT, $r=0.87$ and 0.78 respectively, $p<0.0001$), as expected in case of rapid, ballistic movements. Thus, for the sake of brevity and clarity, we only report the results for MT. However, similar results (not shown) were obtained using both peak velocity and acceleration.

In agreement with previous results [2], in the control groups, MT in RAN was significantly lower than in CCW (Figure 1A). This was true also for the PD and pHD groups. However, in PD, MT was significantly prolonged in RAN ($p=0.05$) but not in CCW ($p=0.96$) compared to controls. This effect was reflected in a significant Task $\times$ Group interaction ($F(1,26)=9.15$, $p=0.006$; Task: $F(1,25)=105.56$, $p<0.00001$; Group: $F(1,26)=1.99$, $p=0.17$). Consequently, delta MT was significantly smaller in PD compared to controls ($F(1,26)=9.14$, $p=0.006$). We verified that the group differences in RAN MT were not due to differences of path length (mean $\pm$ S.E.: PD: 1.67 ± 0.03 cm; controls: 1.82 ± 0.04 cm; $p=0.27$). Interestingly, UPDRS motor score significantly correlated with delta MT ($r=-0.55$, $p<0.05$), but not with RAN MT, CCW MT, nor with combined mean MT ($r=0.16$, -0.26 , and 0.05 , respectively).

The pHD group showed a difference between tasks and, on average, shorter MTs compared to controls (Effect of Group: $F(1,21)=11.76$, $p=0.003$; Task: $F(1,21)=98.75$, $p<0.000001$). As indicated by the significant Task $\times$ Group interaction ($F(1,21)=11.34$, $p=0.003$), MT in CCW was significantly decreased in pHD compared to controls (post-hoc $p=0.02$), whereas the performance in RAN was comparable ($p=0.98$). Therefore, as for PD patients, delta MTs were significantly smaller compared to controls ($F(1,21)=11.33$, $p=0.002$). Again, we verified that the differences observed in the CCW MT were not due to path length changes (pHD: 1.77 ± 0.03 ; controls: 1.79 ± 0.03 , $p=0.99$). We found a significant correlation between the number of CAG repeats and delta MTs ($r=-0.49$, $p<0.05$), but not with the other MT-derived measurements. Estimated age of onset showed only a trend with delta MT ($r=-0.40$, $p=0.08$).

Finally, we verified whether the joint information provided by the combined mean MT and the delta MT correctly predicted the association to the specific disorder (Figure 1B). Therefore, we performed a stepwise binary logistic regression with these variables as covariates. Overall, the model classified correctly the 89.3% of the patients. As shown in Table 1, the only variable that entered the model was the combined mean MT, indicating that, while modulation of MT (delta) is similar in the two patient populations, the combined mean MT can discriminate between PD and pHD.

Discussion

Our results show that in basal ganglia disorders, even when motor symptoms are minimal, as in our PD group, or clinically absent, as in our pHD subjects, the flexibility of kinematics selection is reduced compared to controls, as indicated by the patients' reduced range of movement time (delta MTs) between the predictable and unpredictable conditions. Further, the pattern of impairment is different in the two disorders: compared to normal controls, combined MT is shorter in pHD and longer in PD. Although we did not measure directly the muscle effort in the present experiment, we have shown, with the appropriate experimental setup for muscle torque measurement, that kinematic variables in our tasks are significantly correlated with the amount of muscle effort (see also Supplemental Material and [3]). Specifically, movements in the RAN condition, with shorter duration and higher peak velocity and acceleration, require higher effort than movements of longer duration but lower peak velocity and acceleration, as in CCW. Thus, our results support the idea that basal ganglia are involved in the appropriate selection and regulation of movement force. Indeed, basal ganglia involvement in force and effort regulation has been already suggested by the results of recent studies in normal subjects using either grip [9, 10] or reaching tasks [8].

Both our patient groups show a reduced range of force selection as reflected by lower values of delta MT compared to controls. This could be part of an abnormal sensitivity to contextual demands that manifests differently in the two diseases. In PD patients, the choice

reaction time task failed to elicit the higher force levels that instead, were found in normal controls, while their performance in the predictable condition, when lower effort is required, was normal. This finding supports the idea that, when possible, patients with PD opt for less effortful movements. On the other hand, pHD subjects did not exploit the option of reducing muscle effort in the predictable condition to the same degree of normal controls. Altogether, these results suggest that basal ganglia are involved in adapting movements to different contexts. This conclusion is also supported by recent imaging studies showing that basal ganglia play a role in “selecting” the appropriate force amplitude [10] or effort levels [4].

It is not clear which could be the sources of the different results that we obtained in PD and pHD groups. In general, dopaminergic deficit in the substantia nigra occurs early on in PD [12], while atrophy of the caudate is already present in the presymptomatic stages of HD [13]. It is possible this differential involvement of the basal ganglia is responsible for the different kinematic regulation. Based upon the current knowledge [14], it is likely that the main pathophysiological difference between the two disorders, at least at the basal ganglia level, resides in the involvement of the direct pathway in PD and of the indirect pathway in pHD. Thus, we hypothesize that only the normal equilibrium between the two pathways might allow for a wider range of choice and, ultimately, for a balanced, appropriate force selection. This type of balance is likely needed for the correct functioning of all the cortico-striato-cortical loops and might be reflected also in domains other than the motor [4]. Further studies are needed to test this hypothesis in patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grants

This work was supported by grants from: the McDonnell Foundation (MFG), National Parkinson Foundation (MFG), NIH NS054864 (MFG).

References

1. Schmidt, RA.; Lee, TD. Motor Control and Learning - A Behavioral Emphasis. Third ed.. Human Kinetics; 1999.
2. Moisello C, Crupi D, Tunik E, Quartarone A, Bove M, Tononi G, et al. The serial reaction time task revisited: a study on motor sequence learning with an arm-reaching task. *Exp Brain Res*. Mar; 2009 194(1):143–55. [PubMed: 19104787]
3. Moisello, C.; Pruski, A.; Sanguineti, V.; Bove, M.; Crupi, D.; Perfetti, B., et al., editors. Selection of motor strategy: I. Effects of task demands Society for Neuroscience Annual Meeting. Washington, DC: 2008.
4. Croxson PL, Walton ME, O'Reilly JX, Behrens TE, Rushworth MF. Effort-based cost-benefit valuation and the human brain. *J Neurosci*. Apr 8; 2009 29(14):4531–41. [PubMed: 19357278]
5. Ghilardi MF, Silvestri G, Feigin A, Mattis P, Zgaljardic D, Moisello C, et al. Implicit and explicit aspects of sequence learning in pre-symptomatic Huntington's disease. *Parkinsonism Relat Disord*. Aug; 2008 14(6):457–64. [PubMed: 18316233]
6. Kurniawan IT, Seymour B, Talmi D, Yoshida W, Chater N, Dolan RJ. Choosing to make an effort: the role of striatum in signaling physical effort of a chosen action. *J Neurophysiol*. Jul; 2010 104(1): 313–21. [PubMed: 20463204]
7. Mazzoni P, Hristova A, Krakauer JW. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. *J Neurosci*. Jul 4; 2007 27(27):7105–16. [PubMed: 17611263]

8. Grafton ST, Tunik E. Human Basal Ganglia and the Dynamic Control of Force during On-Line Corrections. *J Neurosci*. Feb 2; 2011 31(5):1600–5. [PubMed: 21289168]
9. Spraker MB, Yu H, Corcos DM, Vaillancourt DE. Role of individual basal ganglia nuclei in force amplitude generation. *J Neurophysiol*. Aug; 2007 98(2):821–34. [PubMed: 17567775]
10. Vaillancourt DE, Yu H, Mayka MA, Corcos DM. Role of the basal ganglia and frontal cortex in selecting and producing internally guided force pulses. *Neuroimage*. Jul 1; 2007 36(3):793–803. [PubMed: 17451971]
11. Ghilardi MF, Eidelberg D, Silvestri G, Ghez C. The differential effect of PD and normal aging on early explicit sequence learning. *Neurology*. Apr 22; 2003 60(8):1313–9. [PubMed: 12707435]
12. Braak H, Müller CM, Rüb U, Ackermann H, Bratzke H, de Vos RA, Del Tredici K. Pathology associated with sporadic Parkinson's disease--where does it end? *J Neural Transm Suppl*. 2006; (70):89–97. [PubMed: 17017514]
13. Tabrizi SJ, Scahill RI, Durr A, Roos RA, Leavitt BR, Jones R, Landwehrmeyer GB, Fox NC, Johnson H, Hicks SL, Kennard C, Craufurd D, Frost C, Langbehn DR, Reilmann R, Stout JC. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol*. Jan; 2011 10(1):31–42. Epub 2010 Dec 2. [PubMed: 21130037]
14. DeLong M, Wichmann T. Update on models of basal ganglia function and dysfunction. *Parkinsonism Relat Disord*. Dec; 2009 15(Suppl 3):S237–40. [PubMed: 20082999]

Figure 1.

A) Mean RAN and CCW MT for patient and control groups. Bars represent standard errors. The dashed lines indicate the Combined mean MT. B) Delta MTs plotted against Combined mean MTs for each PD (black) and pHD (white) patient. Larger dots represent the group means and standard errors. The gray area indicates the normal controls' range.

Table 1

Results of the stepwise binary logistic regression.

Chi-Square	df	P	Cox & Snell R ²	Nagelkerke R ²
23.289	1	.000	0.565	0.765

	B	SE	Wald	p	95% CI		Odds Ratio
					Lower	Upper	
Mean MT	-.047	.018	6.635	.010	.920	.989	.954
constant	15.226	6.143	6.143	.013			