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Cognitive correlates of prospective memory in dystonia

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ABSTRACT

Introduction: Executive dysfunctions are observed in focal dystonia (i.e., blepharospasm and cervical dystonia). Prospective memory (PM) is the ability to remember to carry out intended actions in the future and plays a relevant role in everyday living and quality of life. Although alterations of prefrontal cortex occur in focal dystonia, until now, no study has yet investigated the occurrence of deficit of PM in focal dystonia. Therefore, the aim of the study was to explore PM and its cognitive correlates in cervical dystonia and blepharospasm.
Methods: Twenty-seven patients with blepharospasm, 26 patients with cervical dystonia and 30 healthy subjects, matched for demographic features, underwent neuropsychological tests assessing PM, verbal memory, executive functions, and questionnaires assessing subjective prospective and retrospective memory failures, and apathy.
Results: The three groups did not differ on tests assessing verbal memory, executive functions, but they significantly differed on PM tests. In detail, patients with blepharospasm and cervical dystonia performed worse on time-based and recognition tasks than healthy subjects, while no difference on event-based task was found. Regression analysis showed a relationship between a lower score on Modified Card Sorting Test and a reduced performance on time-based, event-based and recognition tasks within focal dystonia group.
Conclusion: The results indicated a selective deficit of time-based PM in focal dystonia, supporting previous evidence of cognitive dysfunctions in dystonic patients. The relationship between impaired time-based PM and poor performance on cognitive flexibility tests might suggest that difficulty in managing two concurrent cognitive demands contributes to impaired time-based PM.

1. Introduction

Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both [1]. A recent classification of dystonia has been proposed by Albanese et al. [1] and identifies several forms of the disease according to two main axes: clinical characteristics, including age at onset, body distribution, temporal pattern and associated features; and etiology, which includes nervous system pathology and inheritance. As for the axis of clinical characteristics focal forms of dystonia can be distinguished on the base of body distribution in blepharospasm (BSP), oro-mandibular dystonia (OMD), cervical dystonia (CD), laryngeal dystonia (LD), and limb dystonia. Although the etiology and pathophysiology of primary dystonia are still not completely defined [2], they are related to basal ganglia dysfunction, which is closely related to altered motor and cognitive control [3]. Some neuropsychological studies focusing on cognitive deficits related to focal dystonia found mild executive dysfunctions including deficits of set-shifting, verbal learning, category fluency in patients with CD and BSP, when compared to healthy subjects (HCs) [4–7]. The prospective memory (PM) is a cognitive function defined as the ability to remember to carry out intended actions in the future [8] and is mediated mainly by frontal cortex [9]. However, the PM ability has not yet been investigated in focal dystonia although executive deficits were reported in previous studies [4–7]. Einstein and McDaniel [10] proposed an important distinction between two different components of PM: event-based and time-based prospective memory. Event-based prospective memory consists in remembering to perform an action when some external event occurs, whereas time-based prospective memory consists in remembering to perform an action at a certain time. Until now, no study has yet explored the two forms of PM in dystonic patients. The evaluation of the PM ability may be clinically relevant since it plays a pivotal role in everyday life autonomy. In fact, deficits of the PM may lead to severe reduction of patients' quality of life and functional

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autonomy [11] and it may increase caregiver's burden. Therefore, the assessment of the possible deficit of PM abilities could help to identify dystonic patients at higher risk of reduced functional autonomy.

Considering the abovementioned assumptions, the present study was performed to identify possible dysfunctions of PM abilities (i.e. event-based and time-based PM) in patients with focal dystonia, particularly in patients with CD and with BSP, compared to HCs. Moreover, the second aim of the study was to identify neuropsychological correlates underpinning event-based and time-based PM abilities within dystonic patients.

2. Methods

2.1. Participants

In the present study, consecutive dystonic outpatients referred to the clinic of movement disorders of Neuroscience Department, Federico II University of Naples, Italy, were included in the study if they met the following inclusion criteria: 1) a diagnosis of idiopathic focal dystonia according to clinical diagnostic criteria; 2) absence of cognitive decline defined by an age-and education- adjusted score on the Italian version of the Montreal Cognitive Assessment (MoCA > 15.5; for all tests and questionnaires references, see supplementary material 1); 3) neurodegenerative and metabolic diseases causing secondary dystonia were excluded performing MRI scan [12] and evoked potentials [13] only when patients were presenting atypical clinical features; 4) absence of major depression according to DSM-5 diagnostic criteria and absence of severe depressive symptomatology evaluated by means of an Italian version of the Beck Depression Inventory-II (BDI-II < 16).

Demographic features (i.e. gender, age, years of schooling) were recorded for each participant.

In addition, we enrolled HCs matched with patients for demographic features. HCs were recruited among patients' friends and employees at the university centers. HCs had to meet the following selection criteria: lack of any neurodegenerative or cerebrovascular disorders according to clinical criteria; lack of previous or current psychiatric diseases (e.g. major depression, or psychosis according to DSM-V criteria); absence of cognitive decline defined by an age-and education- adjusted score on the Italian version of the Montreal Cognitive Assessment (MoCA > 15.5). Hospital employees were naïve about the hypotheses of the study.

All participants gave their written informed consent to participate to the study, which was approved by the local ethics committee.

2.2. Neuropsychological and behavioral evaluation

All participants underwent the Italian version of the Memory for Intentions Screening Test (MIST), a neuropsychological test which assesses prospective memory (PM). The MIST is composed of 8 trials consisting of a number of goals, which the subject must keep in mind. Test procedures provide specific instructions to form a conscious intention that must be executed after a delay from the encoding phase. This delay must be filled with a secondary ongoing task (a word search puzzle). Furthermore, the MIST allows to evaluate several variables as the type of cue (time-based and event-based tasks). At the end of the testing session, participants undergo a multiple-choice recognition test. Finally, the MIST contains a 24-hour delayed (24-hr) item to try to approximate the time-span of memory for intentions in daily life.

All participants also underwent a neuropsychological battery to assess verbal memory by immediate and delayed recall of prose memory test and executive functions, by the Trail Making Test (TMT) and the Modified Card Sorting Test (MCST).

Moreover, we also investigated the frequency of prospective memory and retrospective memory failures in all participants by the Italian version of Prospective and Retrospective Memory Questionnaire (PMRQ) and the subjective memory complaints by the Italian version of the multifactorial memory questionnaire (MMQ).

Finally, all the participants completed the Dimensional Apathy Scale (DAS), a questionnaire assessing severity of apathy.

All patients underwent cognitive evaluation 12–16 weeks after the last treatment when botulinum toxin efficacy was almost wore off so they would have been experiencing their symptoms at their most.

2.3. Statistical analysis

To verify the distribution of the variables, we applied Kolmogorov-Smirnov test which revealed the non-normal distribution of the PM variables (Supplemental material 2); thus, statistical analysis was based on non-parametric tests.

Demographic, behavioral, cognitive variables were compared between patients with CD, patients with BSP and HCs by Kruskal-Wallis test. The two-tailed Mann-Whitney *U* test was used to assess the paired difference between two groups.

To investigate the possible influence of neuropsychological variables on PM abilities within patients with focal dystonia as whole group, we performed a logistic binary regression analysis (by stepwise method) where age and education-adjusted score on part B-A of TMT, prose memory test and number of categories of MCST were entered as independent variables and performance on time-based, event-based, recognition and 24-hr tasks of the MIST were entered as dependent variables dichotomized according to their median.

The critical alpha level for all analyses was set < 0.05. Moreover, Bonferroni post-hoc test was performed to control for the type I error. All analyses were performed with IBM SPSS-20.

3. Results

In the present study, we enrolled 26 patients with CD, 27 patients with BSP, according to the classification based on the affected region of the body [1].

Focal dystonia was treated in each patient with botulinum toxin injections. Only few of them (5/27 with BSP and 3/26 with CD) were taking clonazepam at the occurrence when spasms were more severe. Moreover, none were chronically under benzodiazepine.

Moreover, we enrolled 30 healthy subjects.

The comparison between patients with CD, patients with BSP and HCs showed no significant difference on demographic, cognitive and behavioral aspects (Table 1).

As for PM abilities, whereas no significant difference among the three groups was found on event-based PM task and on 24-hr task, the three groups differed significantly on the time-based PM task and the recognition task of MIST (Table 2).

In detail, post-hoc comparisons (by Mann-Whitney *U* test) showed that both patients with BSP and patients with CD scored significantly worse than HCs (Table 2).

3.1. Neuropsychological correlates of the PM abilities in focal dystonia

Taking into account previous neuropsychological studies where patients with BSP and ones with CD were considered as one single group [5,6], we performed a logistic binary regression analysis showing a significant relationship between a lower score on categories of MCST and a reduced performance on time-based PM task (Odds ratio = 1.479, 95%CI: 1.085–2.015, p = 0.013), event-based PM task (Odds ratio = 1.560, 95%CI: 1.128–2.157, p = 0.007) and recognition task (Odds ratio = 1.372, 95%CI: 1.018–1.849, p = 0.038) of the MIST within focal dystonia group (n = 53).

The relationship between lower score on categories of MCST and a reduced performance on time-based PM task is shown in Fig. 1.

Table 1
Comparison between patients with Blepharospam, Cervical Dystonia and healthy subjects on demographic, cognitive and behavioral variables.

	BSP (n = 27)	CD (n = 26)	HCs (n = 30)	χ2	p
	Mean ± SD	Mean ± SD			
Age (ys)	65.6 ± 8.6	60.5 ± 9.1	61.2 ± 9.8	4.178	0.124
Education (ys)	8.8 ± 4.7	10.0 ± 4.4	9.6 ± 4.4	1.730	0.421
MoCA	20.2 ± 4.0	21.1 ± 4.2	22.3 ± 2.7	3.924	0.141
MCST – Categories	3.3 ± 1.9	4.0 ± 2.0	4.1 ± 1.5	2.450	0.294
MCST – Perseverative errors	7.2 ± 8.4	5.1 ± 5.1	4.7 ± 4.4	1.403	0.496
TMT A	65.7 ± 36.8	50.3 ± 28.8	47.5 ± 26.7	5.714	0.057
TMT B	200.1 ± 114.8	177.6 ± 125.6	144.2 ± 76.7	2.818	0.244
TMT B-A	138.4 ± 88.6	127.2 ± 99.7	94.0 ± 61.7	3.217	0.200
Recall of a short story	11.0 ± 5.7	10.8 ± 4.6	12.1 ± 4.8	0.903	0.637
MMQ total score	113.1 ± 28.2	123.4 ± 21.5	114.4 ± 18.5	3.087	0.214
MMQ - Ability	51.0 ± 18.8	57.4 ± 11.6	50.0 ± 13.9	3.899	0.142
MMQ - Contentment	42.5 ± 13.8	46.3 ± 11.3	42.5 ± 10.6	2.362	0.307
MMQ - Strategy	20.0 ± 10.9	19.6 ± 10.5	21.8 ± 14.9	0.004	0.998
PMRQ - Prospective	29.5 ± 7.9	33.4 ± 10.5	30.6 ± 5.2	2.067	0.356
PMRQ - Retrospective	30.8 ± 7.9	33.3 ± 5.1	33.5 ± 7.2	1.079	0.583
DAS total score	23.4 ± 10.7	22.2 ± 11.1	23.0 ± 7.3	0.966	0.617

BSP, blepharospasm; CD, cervical dystonia; HCs, Healthy controls; SD, Standard deviation; ys, years; MoCA, Montreal Cognitive Assessment; MCST, Modified Card Sorting Test; TMT, Trail Making Test; MMQ, Multifactorial Memory Questionnaire; PMRQ, Prospective and Retrospective Memory Questionnaire; DAS, Dimensional Apathy Scale.
*Significant difference after Bonferroni correction (0.05/16 = 0.0031).

Table 2
Comparison between patients with Blepharospasm, Cervical Dystonia and healthy subjects on prospective memory tests.

MIST subtests	BSP (n = 27)	CD (n = 26)	HCs (n = 30)	χ^2	p
	Mean ± SD	Mean ± SD	Mean ± SD		
Time-based	2.8 ± 1.3 *	3.5 ± 1.7 *	4.9 ± 1.1	22.978	< **0.001**
Event-based	5.2 ± 2.1	5.1 ± 2.2	6.3 ± 1.7	5.447	0.066
Recognition	6.5 ± 1.4°	6.1 ± 1.7°	7.2 ± 0.9	8.764	**0.013**
24-hr item	0.1 ± 0.5	0.7 ± 2.4	0.4 ± 0.8	1.556	0.459

BSP, blepharospasm; CD, cervical dystonia; HCs, Healthy controls; SD, Standard deviation; MIST, Memory for Intentions Screening Test; 24-hr, 24-hour delayed.
* Significant difference between BSP and HCs (U = 116.000; p < 0.001) and between CD and HCs (U = 205.000; p = 0.002).
° Significant difference between BSP and HCs (U = 283.500; p = 0.040) and between CD and HCs (U = 226.000; p = 0.005).

4. Discussion

The present study investigated PM abilities in BSP and CD, two different forms of focal dystonia. The results revealed a selective deficit of time-based PM ability rather than event-based one in both patients with BSP and ones with CD when compared to HCs. Moreover, patients with dystonia performed worse on recognition task of the MIST. As for neuropsychological mechanisms underlying PM abilities, impaired set-shifting abilities was significantly associated with a poor performance on time-based, event-based PM and recognition tasks in focal dystonia.

Our results of a dysfunction of time-based PM ability rather than event-based one in BSP and in CD groups suggested that patients with focal dystonia may be characterized by difficulties in intention recall at a specific time and therefore in performing some activities of daily living, such as remembering an appointment at 3 p.m. Time-based PM paradigms generally place greater demands on self-initiated monitoring such as clock checking and intention retrieval processes, but even require preserved shifting abilities that allow the flexible allocation of attention from ongoing activity without the facilitation of an external cue (event). In more detail, to perform successfully the time-based PM tasks, after forming an intention to execute in the future, an individual has to maintain the intention during a delay filled by another activity, then to reinstate the intention and to engage the top-down, self-initiated processes such as switching from the ongoing activity to execute the intention at a specific time [14,15]. Taking into account that shifting abilities are a significant predictor of PM performance in young and older adults [16], deficits of these cognitive functions may predict impaired time-based PM abilities in our patients with focal dystonia. Indeed, this idea is supported by our findings from regression analysis revealing a relationship between poor performance on time-based PM task and on MCST which assesses cognitive flexibility and set-shifting ability.

In the present study, we observed that both patient groups scored lower than HCs on event-based PM task but the difference did not reach the statistical significance; this finding might strengthen the selective deficit of time-based PM abilities in dystonic patients. Unexpectedly, the regression analysis revealed that a lower performance on event-based PM task in patient with focal dystonia was associated with cognitive rigidity. This finding may be interpreted as a further support to the idea that a poor performance on PM tasks independently from their type (i.e., event-based or time-based PM tasks) is due to set shifting difficulties from the ongoing to the PM task. This result can be interpreted also in the conceptual framework of the preparatory attentional and memory processes model theory [17,18] and the two components theory of PM [19], which propose that executive system or controlled attention play a critical role in carrying out adequate PM responses.

In the present study, the results that dystonic patients and HCs significantly differed on recognition task of the MIST indicated that impaired PM in dystonia might be likely to reflect deficits in retrospective rather than prospective memory and deficit of encoding. However, on the other hand, the findings of similar performances between patients and HCs on 24-hr item evaluating ecologically memory functions did not support the aforementioned idea of an impairment of encoding and/or retrieval aspect of retrospective memory as cognitive neural of impaired PM. The poorer performance of the patients compared to HCS on recognition task of the MIST and its relationship between performance PM tasks and more severe cognitive rigidity (mediated by prefrontal cortex) in dystonia indicated that impaired PM in dystonia might reflects executive dyscontrol of encoding rather than retrieval failures as also reported in other movement disorders [20]. Our findings of impaired time-based PM in dystonia are in line with results from a meta-analysis by Ramanan and Kumar [21], revealing that deficit of time-based PM occurred in patients affected by Parkinson's Disease and is related to failure in self-initiated retrieval of intention to be executed rather than forgetting the content of the

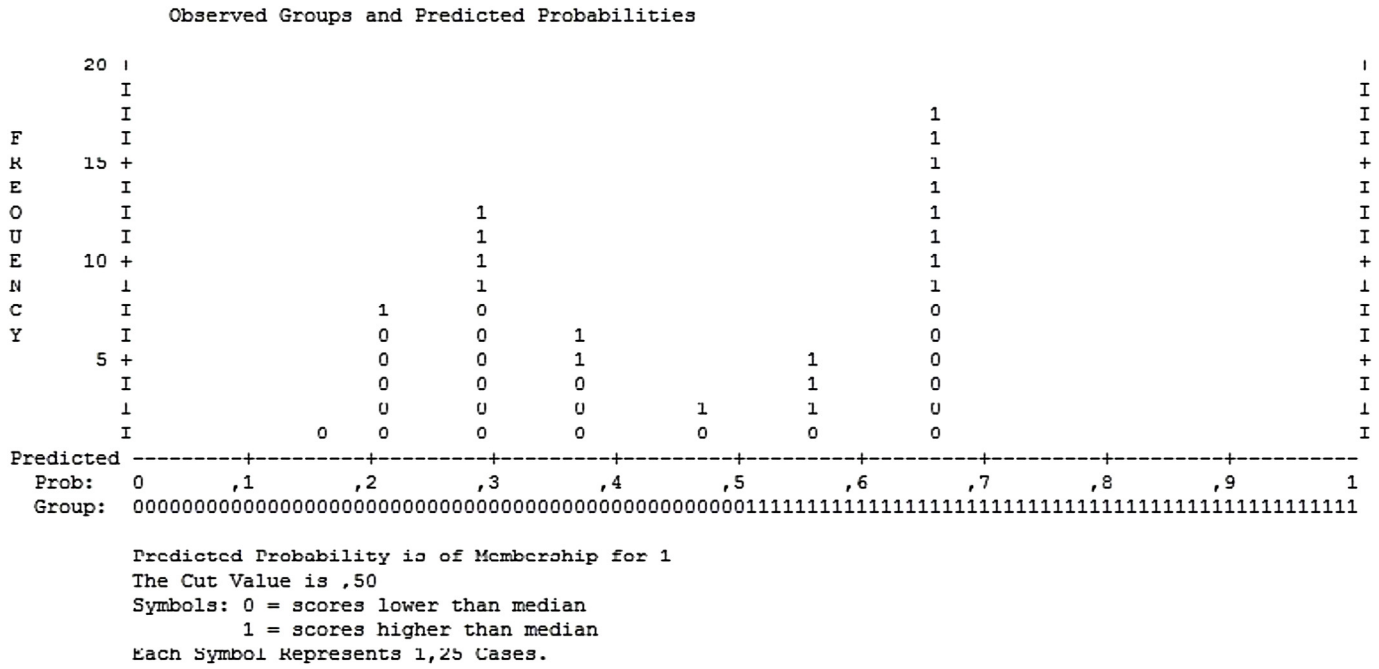

Fig. 1. Graph of the relationship between time-based PM scores and MCST-Categories score within focal dystonia group.

intention itself.

Neuroimaging studies have consistently revealed the involvement of the rostral prefrontal cortex (RPFC; BA 10) in PM tasks in healthy subjects [9,22,23]. A recent fMRI study confirmed that time-based and event-based PM tasks share a similar cerebral network, but time-based tasks mainly recruited frontal regions [24]. Since abnormalities of prefrontal cortex are related to cognitive rigidity [25] and occur in dystonia [26,27], taken together our results might suggest that reduced performance on PM tasks may be a consequence of a dysfunction of the prefrontal cortex (i.e. frontopolar cortex) in dystonia. However, this issue deserves to be investigated in future functional neuroimaging studies in dystonic patients.

In the present study, an interesting result is that dystonic patients and HCs showed different performances on objective PM tasks, but no difference on a self-report questionnaire assessing perceived prospective memory failures. This finding indicated that the PM functioning should be assessed in clinical practice by standardized cognitive tests rather than by subjective measures in dystonic patients. The identification of impairment of PM has a clinical implication since it is related to more reduced functional autonomy and quality of life [11].

The present study is characterized by some limitations. When performing regression analysis, we considered the whole group of patients with focal dystonia and we did not evaluate the cognitive correlates of the PM abilities within CD or BSP groups, separately. However, we followed the methodological procedure employed in previous studies where BSP patients and CD ones were analyzed as one group [5,6]. Moreover, we also took into account the results of no cognitive difference between the two groups as reported in Yang et al. [7].

In the present study, the absence of an evaluation of time estimation abilities in our dystonic patients which reported deficits of time-based PM task might represent another limitation. In fact, in particular, time-based PM tasks involve time-related processes as the time estimation [28]. However, since that our participants were provided with an external clock, their performances on time-based PM task were not based only on time estimation abilities but rather than on the ability to shift from an ongoing activity and prospective intention. Finally, although patients with depressive symptoms were excluded from the study, we did not evaluate non-motor symptoms (i.e., pain) which could potentially affect cognitive attentional processes [29] involved in prospective memory.

In conclusion, the present study revealed a selective deficit of time-based PM functioning in patients with BSP and with CD. Moreover, in dystonic patients an alteration of cognitive flexibility seems to be the cognitive correlate underlying the PM performance. The above-mentioned findings provide clinically relevant evidences which could represent the starting point for the implementation of compensatory strategies, such as the use of external cues in everyday life, and for the improvement of cognitive abilities underpinning PM functioning in dystonic patients.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.06.027.

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