However, a possible limitation is the applicability in very severely affected patients and patients with major cognitive impairment who may need supervision. For the first time, this study provided data on fluctuation of ataxia severity. Fluctuations of the SARAhomescore of at least 1 point were observed in all patients. However, we detected neither systematic differences of ataxia severity between morning and evening nor a training effect. To fully determine the causes of fluctuations, larger trials are required. Based on the analysis of confidence intervals for cumulative days, we suggest that a recording period of 4 days is representative for the entire 14-day period and provides a more meaningful measure of ataxia severity than a single conventional SARA assessment in the hospital.

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References
1. Schmitz-Hubsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 2006;66(11):1717–1720.
2. Bloem BR, Henderson EJ, Dorsey ER, et al. Integrated and patient-centred management of Parkinson’s disease: a network model for reshaping chronic neurological care. Lancet Neurol 2020;19(7):623–634.
3. Warmbergen E, Hausdorff JM, Atsai A, et al. Long-term unsupervised mobility assessment in movement disorders. Lancet Neurol 2020;19(3):462–470.
4. Jacobs H, du Montcel ST, Bauer P, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. Lancet Neurol 2015;14(11):1101–1108.
5. Schmitz-Hubsch T, Coudert M, Bauer P, et al. Spinocerebellar ataxia types 1, 2, 3, and 6: disease severity and nonataxia symptoms. Neurology 2008;71(13):982–989.
6. Arcuria G, Marcotulli C, Amuso R, et al. Developing a smartphone application, triaxial accelerometer-based, to quantify static and dynamic balance deficits in patients with cerebellar ataxias. J Neurol 2019;267:625–639.
7. Jaroensri R, Zhao A, Balakrishnan G, et al. A video-based method for objectively rating ataxia. PMLR 2017;68:204–216.
8. Matsushima A, Yoshida K, Genn H, et al. Clinical assessment of standing and gait in ataxic patients using a triaxial accelerometer. Cerebellum Ataxias 2015;2:9.
9. Gajos KZ, Reinecke K, Donovan M, et al. Computer mouse use captures ataxia and parkinsonism, enabling accurate measurement and detection. Mov Disord 2020;35(2):354–358.
10. Summa S, Schirinzzi T, Bernava GM, et al. Development of SarAHome: a novel, well-accepted, technology-based assessment tool for patients with ataxia. Comput Methods Programs Biomed 2019;188:105257.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.
Cervical dystonia (CD) is characterized by involuntary activity of cervical muscles leading to involuntary movements and postures of the head, neck, and shoulders.\(^1,2\) It is often associated with dystonic head tremor and neck pain.\(^3\) Although CD has traditionally been described as a disorder of basal ganglia motor control; nonmotor symptoms such as depression, obsessive–compulsive disorders, and anxiety are common in this condition.\(^4,5\) Conflicting results have been published related to the cognitive function of patients with CD, with some studies failing to detect cognitive deficits,\(^6,7\) others attributing deficits on cognitive testing to pain and abnormal head movements,\(^8\) and more recent studies reporting impairment in set shifting and working memory.\(^9\) The latter domains require intact dorsolateral prefrontal cortex (DLPFC) function and a variety of structural and functional abnormalities of the DLPFC in CD patients have been published.\(^10,11\) The DLPFC and its projections via the striatum are important for response inhibition and for regulating the superior colliculus (SC), a multilayered structure in the midbrain involved in saccadic eye movement generation.\(^12\) Furthermore, the SC receives projections from other cortical structures such as the frontal eye fields for volitional and the parietal eye fields for reflexive saccades.\(^13\) Until now, only a few studies have assessed saccadic eye movements in patients with CD, and results have again been inconsistent. Although some studies reported slower saccadic reaction times,\(^14\) others did not find any difference compared with controls.\(^15\)

Based on findings of DLPFC dysfunction in CD, we hypothesized that CD patients may have difficulties in inhibitory saccadic control compared with healthy volunteers and that abnormalities described in saccadic behavior may help to understand the neural networks involved in this disease.

## Methods

### Participants

Forty-eight subjects were included: 31 patients with isolated or segmental idiopathic CD and 17 age- and sex-matched healthy controls (HCs).

A Mini–Mental State Examination score below 26, psychiatric disorders, or uncorrected visual impairments were exclusion criteria. Drugs affecting the central nervous system were not allowed with the exception of antidepressants, if on a stable dose for 4 weeks prior to testing. CD patients were on regular treatment with botulinum toxin and had received their last botulinum injection at least 90 days prior to testing.\(^16\)

### Experimental Protocol

Participants filled out the Barratt Impulsiveness Scale (BIS-11) and the Hospital Anxiety and Depression Scale. We adopted the Toronto Western Torticollis Rating Scale\(^17\) and a modified version of the Tsui scale\(^18,19\) to assess disease and tremor severity in CD patients.

Eye tracking was carried out using a Tobii TX300 system (www.tobii.com). All subjects were tested by the same investigator under identical light conditions in the early afternoon. The assessment consisted of a prosaccade task, an antisaccade task, and a countermanding task, always performed in this order.

1. In the prosaccade task subjects were required to fixate a target in the middle of the screen; the target disappears, and a peripheral cue appears. Subject had to perform a saccade toward the cue. We employed an overlapping variant, with target and cue on the screen simultaneously for a short time, delaying the visually guided saccade. This task was repeated 80 times. (2) The antisaccade task was cognitively more demanding than a prosaccade: subjects were required to perform a mirror saccade in the opposite direction of the cue. Saccades to cue were considered errors.\(^20\) This task was divided in 2 blocks of 20 repetitions each.\(^21\) (3) In the countermanding task the central target was followed by a green arrow anticipating the appearance of the peripheral cue. The arrow was randomly followed by a red stop signal in a fourth of trials. In this case, the subject had to refrain from looking at the peripheral cue. This task was performed 60 times. Anticipatory errors in the prosaccade task, directional errors in the antisaccade task, and inhibition errors in the countermanding task were the main outcome measures.

For each task, reaction times were measured from the appearance of the peripheral cue until the first saccade; any saccade with latency under 50 milliseconds was discarded. In the pros- and antisaccade task, reaction times shorter than 140 milliseconds were classified as “express saccades.”\(^22\) Variance of the reaction times in the prosaccade task were expressed using the coefficient of variation, defined as the interquartile range of the reaction time divided by the median.\(^23\)

Prior to each of the 3 tasks, participants performed a practice run consisting of 4 task repetitions for which verbal feedback was given. A break of a maximum of 2 minutes was allowed between the 3 tasks.
Statistical Analysis

The statistical analysis was carried out using SPSS (v24). Normality of the data was assessed with Shapiro–Wilk test. Based on the distribution of the data, parametric and nonparametric tests were employed. The level of significance for all analyses was set at a 2-sided \( P < 0.05 \).

Results

Demographics and Disease Characteristics

No differences in sex, age, or education were found. CD patients had higher scores for anxiety and depression symptoms compared with HCs (\( P = 0.010 \) and \( P = 0.002 \), respectively). However, none of the cutoff values for depression and anxiety were reached by subjects in either of the 2 groups. There was no difference in the BIS-11 total score between the CD and control groups; a subscore comparison revealed a higher score in dystonia patients in the attentional impulsiveness domain (\( P = 0.031 \)).

Saccadic Tasks

CD patients had higher anticipation errors (\( P = 0.041 \)), made more express saccades (\( P = 0.042 \)) in the pro-saccade task, had longer reaction times (\( P = 0.036 \)), and made more directional errors at normal and express latencies in the antisaccade task (\( P = 0.011 \)) compared with HCs. Furthermore, patients made more saccades toward the target in the No-Go trial of the countermanding task (\( P = 0.001 \)). There was no significant difference in reaction time variance between CD and HC (Table 1, Fig. 1).

Next, we performed a subanalysis on error rates and reaction times in the antisaccade task comparing the first 20 trials (block 1) with the second 20 trials (block 2). Patients made fewer errors (23.0 ± 20.0 vs 27.9 ± 21.1, \( P = 0.02 \)) and had shorter reaction times for correctly performed antisaccades (298.2 ± 70.9 vs 329.3 ± 84.0, \( P < 0.01 \)) in block 2. HCs showed no difference between blocks (\( P > 0.05 \)). Similarly, we analyzed the error rate in the countermmanding task dividing it in half. Again patients performed significantly better in the second half (CD, 46.9 ± 31.9 vs 25.9 ± 27.5; \( P < 0.01 \); HC, 16.4 ± 20.8 vs 8.9 ± 13.6; \( P = 0.09 \)).

To account for possible effects of the laterality of dystonic head rotation, we compared reaction times and error rates separately for either direction (right or left).

### Table 1. Results and comparison between groups of the saccadic tasks’ error rates and reaction times

| Parameters of saccadic tasks | CD          | HC          | Independent t test/Mann–Whitney test |
|------------------------------|-------------|-------------|-------------------------------------|
| Prosaccade reaction time (ms) | 31 269.9 75.6 | 15 292.9 65.1 | 0.313 |
| Prosaccade anticipation errors (%) | 31 33.7 30.5 | 15 14.2 8.0 | 0.041 |
| Prosaccadic express saccades (%) | 31 21.5 19.3 | 15 12.5 8.9 | 0.036 |
| Prosaccadic coefficient of variance | 31 0.7 0.3 | 15 0.5 0.1 | 0.281 |
| Incorrect antisaccade reaction time (ms) | 31 210.3 53.1 | 17 200.9 65.8 | 0.614 |
| Correct antisaccade reaction time (ms) | 31 310.7 72.7 | 17 259.0 39.2 | 0.002 |
| Antisaccade directional errors (%) | 31 25.5 19.7 | 17 13.1 13.7 | 0.011 |
| Antisaccade express errors (%) | 31 20.1 23.7 | 17 8.6 15.2 | 0.039 |
| Countermmanding inhibition errors (%) | 31 37.9 28.6 | 17 13.1 16.7 | 0.001 |
| Countermmanding task (Go) | 31 290.7 37.3 | 17 207.8 62.2 | 0.911 |
| Reaction time (ms) | 31 279.5 88.3 | 17 298.5 179.8 | 0.663 |
| Countermmanding task (No-Go) | 31 290.7 37.3 | 17 207.8 62.2 | 0.911 |

*Significant \( P \) values are represented in bold text.

Abbreviations: CD, cervical dystonia; HC, healthy controls.
Discussion

In this study we describe poorer saccadic response inhibition in CD patients compared to HCs. More specifically, CD patients made more anticipatory prosaccades, more directional errors in the antisaccade task, and more errors in the countermanding task.

A loss of inhibition can occur at different levels in patients with focal dystonia. At least 2 mechanisms of inhibition are required in the antisaccade task: at the beginning of the task a preemptive top-down inhibition, which relies on intact frontal areas (mainly the DLPFC and frontal eye fields but also the superior colliculus), is necessary to avoid express latency errors. In contrast, once the stimulus appears automated saccades toward the target are suppressed by the supplementary eye field. A failure of this system leads to longer latency errors. Crucially, both these mechanisms are mediated by the basal ganglia. Furthermore, a large network of other brain areas including the thalamus, the cerebellum, the brain stem reticular formation, the parietal eye field, and other cortical areas are necessary for visual fixation and saccadic control.

In this study, CD patients made more directional errors than controls, at both longer and express latencies, implying a dysfunction of both mechanisms. The countermanding task differs from the antisaccade task. Here, the inhibition of an already started action is necessary. In addition to the DLPFC and frontal eye fields, the supplementary eye field and other frontal areas such as the right ventrolateral prefrontal cortex as well as intact basal ganglia function are required.

Our results highlight a dysfunction of the frontal cortical top-down inhibitory control in CD and are also consistent with previous results in other focal dystonias. In line with this, functional imaging studies have shown that successful top-down inhibition to prevent the automatic prosaccade relies on an intact network comprising the DLPFC together with the frontal eye field, basal ganglia, and SC. Importantly, imaging studies suggest that this network is altered in CD. In accordance with our findings, neuropsychological tests have revealed impairment in working memory, cognitive flexibility, and frontal lobe function in patients with CD. Finally, disruption of sensory-motor integration in patients with focal dystonia may also affect oculomotor performance.

The results of the antisaccade task presented here are in contrast with a previous small study in CD (n = 8). However, because of the small sample size, a direct comparison of the 2 studies is not possible.

It is important to note that the impairment described here is not specific to CD. Poorer saccadic performance has been previously described in patients with dementia as well as patients with other basal ganglia disorders such as Huntington’s disease, atypical parkinsonism, idiopathic Parkinson’s disease, and patients with schizophrenia, strengthening the hypothesis that dysfunction of the corticobasal network, either because of basal ganglia lesions, frontal cortex dysfunction, or both may lead to poorer saccadic control.

We want to highlight a limitation of this study: we used a fixed order for the eye-tracking paradigms. Future studies should consider using a pseudorandomized order to avoid possible learning effects. Importantly, however, poorer performance of the CD group was not because of fatigue, as patients performed significantly better in the second half of the antisaccade and countermanding task.

In conclusion, we demonstrate impaired saccadic response inhibition in CD patients, which may be because of dysfunction of the corticostral network. Saccadic assessment in CD is noninvasive, time, and cost effective and could represent a viable biomarker of disease to be implemented both in research and clinical practice. Further studies are needed to assess whether this impairment is shared by other focal or segmental dystonias.

References

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28:863–873.
2. Defazio G, Jankovic J, Giel JL, Papapetropoulos S. Descriptive epidemiology of cervical dystonia. Tremor Other Hyperkinet Mov (N Y) 2013;3. https://doi.org/10.7916/D80C4TGJ
3. Dauer WT, Burke RE, Greene P, Fahn S. Current concepts on the clinical features, aetiology and management of idiopathic cervical dystonia. Brain 1998;121:547–560.
4. Stamelou M, Edwards MJ, Hallett M, Bhatia KP. The non-motor syndrome of primary dystonia: clinical and pathophysiological implications. Brain 2012;135:1668–1681.
5. Jinnah HA, Neychev V, Hess EJ. The anatomical basis for dystonia: the motor network model. Tremor Other Hyperkinet Mov (N Y) 2017;7:506.
6. Taylor AE, Lang AE, Saint-Cyr JA, Riley DE, Ranawaya R. Cognitive processes in idiopathic dystonia treated with high-dose anticholinergic therapy. Clin Neuropharmacol 1991;14:62–77.
7. Jahanshahi M, Rowe J, Fuller R. Cognitive executive function in dystonia. Mov Disord 2003;18:1470–1481.
8. Allam N, Frank JE, Pereira C, Tomaz C. Sustained attention in cranial dystonia patients treated with botulinum toxin. Acta Neurol Scand 2007;116:196–200.
19. Jost WH, Hefer H, Stenner A, Reichel G. Rating scales for cervical dystonia: a critical evaluation of tools for outcome assessment of botulinum toxin therapy. J Neural Transm 2013;120:487–496.

20. Hallett PE. Primary and secondary saccades to goals defined by instructions. Vision Res 1978;18:1279–1296.

21. Antoniades C, Ettinger U, Gaymard B, et al. An internationally standardised antisaccade protocol. Vision Res 2013;84:1–5.

22. Fischer B, Ramsperger E. Human express saccades: extremely short reaction times of goal directed eye movements. Exp Brain Res 1984;57:191–195.

23. Smyrnios N, Karantinos T, Malogianis I, et al. Larger variability of saccadic reaction times in schizophranina patients. Psychiatry Res 2009;168:129–136.

24. IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp.

25. Zigmond AS, Snauth RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–370.

26. Hallett M. Neurophysiology of dystonia: the role of inhibition. Neurol Res 2011;42:177–184.

27. Coe BC, Munoz DP. Mechanisms of saccade suppression revealed in the antisaccade task. Philos Trans R Soc B Biol Sci 2017;372(1718):20161019. https://doi.org/10.1098/rstb.2016.0192

28. Xu KZ, Anderson BA, Emeric EE, et al. Neural basis of cognitive control over movement inhibition: human fMRI and primate electrophysiology evidence. Neuron 2017;96:1447–1458.

29. Stinear CM, Byblow WD. Impaired inhibition of a pre-planned response in focal hand dystonia. Exp Brain Res 2004;158:207–212.

30. Everling S, Dorris MC, Klein RM, Munoz DP. Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. J Neurosci 1999;19:2740–2754.

31. Everling S, Munoz DP. Neuronal correlates for preparatory set associated with pre-saccades and anti-saccades in the primate frontal eye field. J Neurosci 2000;20:387–400.

32. Mahajan A, Zillgitt A, Alishammar A, et al. Cervical dystonia and executive function: a pilot Vigitime fMRI study. Brain Sci 2018;8(9):159. https://doi.org/10.3390/brainsci8090159

33. Ospina-Garcia N, Escobar-Barrios M, Rodriguez-Violante M, Benitez-Valenzuela J, Covantes-Arriaga A. Neuropsychiatric profile of patients with cranio-cervical dystonia: a case-control study. Clin Neurol Neurosurg 2020;193:105794. https://doi.org/10.1016/j.clineuro.2020.105794

34. Avanzino L, Tinazzi M, Ionta S, Fiorio M. Sensory-motor integration in focal dystonia. Neuropsychologia 2015;79:288–300.

35. Destrochers P, Brunfeldt A, Sidiropoulos C, Kagerer F. Sensorimotor control in dystonia. Brain Sci 2019;9:1–18.

36. Zee DS, Lasker AG. Antisaccades: probing cognitive flexibility with eye movements. Neurology 2004;63:1534.

37. Barbosa P, Kaksi D, Castro P, Lees AJ, Warner TT, Djamshidian A. Saccadic direction errors are associated with impulsive compulsive behaviours in Parkinson’s disease patients. J Parkinsons Dis 2019;9:625–630.

38. Reuter B, Rakusan I, Kathmann N. Poor antisaccade performance in schizophrenia: an inhibition deficit? Psychiatry Res 2005;135:1–10.

39. Kahana Levy N, Lavidor M, Prosack VE. Antisaccade paradigms in persons with Alzheimer’s disease: a meta-analytic review. Neuropsychol Rev 2018;28:16–31.

Supporting Data

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The Parkinson’s Disease DNA Variant Browser

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