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Cognitive Flexibility in Primary Dystonia

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Abstract

Objectives: Although primary dystonia is typically characterized as a movement disorder, it is also associated with cognitive alterations in the domain of executive functioning which may arise from changes in cortico-basal ganglia circuits. Specifically, in comparison to healthy controls, patients with dystonia show deficits in neuropsychological tests of cognitive flexibility. However, it is unclear whether cognitive inflexibility is caused by the pathomechanisms underlying primary dystonia or by confounding factors such as depression or symptom-related distraction. **Methods:** The present study aimed to eliminate these confounds by examining cognitive flexibility in dystonia patients and in patients with similar motor symptoms but without a comparable central pathophysiology. Eighteen patients with primary blepharospasm, a common form of dystonia affecting the muscles around the eyes, and 19 patients with hemifacial spasm, a facial nerve disorder causing similar eyelid spasms, completed a computerized version of the Wisconsin Card Sorting Test (cWCST). The two groups were further compared on tests of global cognitive functioning, psychiatric symptoms, health status, and impulsiveness. **Results:** Blepharospasm patients committed significantly more errors on the cWCST than patients with hemifacial spasm. Group differences were most pronounced with regard to integration errors, a measure of rule-inference processes on the cWCST. Integration errors were also associated with impulsiveness in patients with blepharospasm. **Conclusions:** Primary blepharospasm is related to deficits in cognitive flexibility, even when blepharospasm patients are compared with patients who suffer from motor symptoms of non-dystonic origin. Our results support the possibility that cognitive inflexibility results from the specific pathophysiological processes underlying primary dystonia. (*JINS*, 2016, *22*, 662–670)

Keywords: Primary dystonia, Blepharospasm, Hemifacial spasm, Executive functioning, Cognitive flexibility, Wisconsin Card Sorting Test, Set shifting, Rule inference

INTRODUCTION

Primary dystonia is a neurological disorder characterized by twisting or repetitive movements or abnormal postures that develop in the absence of any apparent cause (Fahn, 1988; Tarsy & Simon, 2006). In addition to these motor symptoms, there is some evidence for distinct cognitive alterations in primary dystonia, particularly in the domain of executive functioning (Jahanshahi et al., 2014). Executive functions allow for the pursuit of complex goals by exerting top–down control on cognitive representations (Diamond, 2013; Elliott, 2003). Cognitive flexibility (i.e., the ability to adapt cognitive sets to changing environmental demands) has been identified as one of the most basic executive functions (Miyake et al., 2000).

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Cognitive flexibility in primary dystonia has most frequently been investigated using the Wisconsin Card Sorting Test (WCST) (Berg, 1948; Grant & Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). The WCST is the best-established neuropsychological procedure to assess cognitive flexibility (Rabin, Barr, & Burton, 2005) with documented sensitivity to frontal lobe lesions (Demakis, 2003; Milner, 1963), to neurodegenerative diseases (Dirnberger & Jahanshahi, 2013; Lange, Vogts, et al., 2016), and to healthy aging (Kopp, Lange, Howe, & Wessel, 2014; Rhodes, 2004). On the WCST, participants have to sort cards in accordance with one of three viable task rules. After several trials, the valid task rule changes. Participants are then required to identify the new task rule by evaluating the experimenter's feedback. When having found the correct new rule, participants have to maintain it until they are informed that the rule has changed again.

When compared to healthy controls, patients with primary dystonia have been described to perform worse on the WCST

(Alemán, de Erausquin, & Micheli, 2009; Bugalho, Corrêa, Guimarães, & Xavier, 2008; but see Jahanshahi, Rowe, & Fuller, 2003). Similarly, dystonia patients appeared to be impaired on the intra-/extradimensional set-shifting task (Scott et al., 2003; but see Balas, Peretz, Badarny, Scott, & Giladi, 2006), an executive functioning test similar to the WCST.

This dystonia-related deficit in cognitive flexibility might be due to functional or microstructural alterations in the basal ganglia and their cortical projection sites (Romano et al., 2014). Primary dystonia has been found to be associated with metabolic, physiological, and microstructural changes in cortico-basal ganglia loops (Breakefield et al., 2008; Lehéricy, Tijssen, Vidailhet, Kaji, & Meunier, 2013; Neychev, Gross, Lehéricy, Hess, & Jinnah, 2011; Zoons, Booij, Nederveen, Dijk, & Tijssen, 2011). In addition to their role in motor control, cortico-basal ganglia loops have been hypothesized to underlie executive functioning (Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, & O'Reilly, 2007; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006; Robbins & Cools, 2014; Saint-Cyr, 2003). Although it appears plausible to attribute cognitive inflexibility in primary dystonia to pathophysiological changes in cortico-basal ganglia loops, this conclusion is hampered by several confounding factors.

The available evidence for cognitive inflexibility in primary dystonia comes from studies comparing dystonia patients with healthy controls. While these groups might differ with regard to the integrity of cortico-basal ganglia loops, other variables might account for differences in cognitive flexibility as well. For instance, depression is more prevalent in patients with primary dystonia than in general population (Lencer et al., 2009) and its presence is associated with cognitive inflexibility (Snyder, 2013). Moreover, patients might generally perform worse than healthy controls because the label of "being a patient" induces an expectation to perform worse (Schwarz, 2015). Finally, in contrast to healthy controls, dystonia patients might be distracted by their motor symptoms during cognitive testing (Jahanshahi et al., 2014, 2003; Stamelou, Edwards, Hallett, & Bhatia, 2012). These confounds can be eliminated by examining cognitive flexibility in dystonia patients and in control patients who show similar motor symptoms, but who do not suffer from a comparable central pathophysiology.

The present study aimed to contrast cognitive flexibility between primary blepharospasm patients and patients with hemifacial spasm. Blepharospasm is characterized by abnormal bilateral contractions of the eyelid, leading to excessive blinking or difficulty opening the eyes (Tarsy & Simon, 2006). Patients with hemifacial spasm also suffer from abnormal eyelid contractions, but these are typically restricted to one side of the face (Wang & Jankovic, 1998). In most cases, hemifacial spasm can be attributed to peripheral facial nerve damage, whereas primary blepharospasm has been related to microstructural (Etgen, Mühlau, Gaser, & Sander, 2006; Obermann et al., 2007) and functional (Obermann et al., 2008; Schmidt et al., 2003) alterations in the basal ganglia.

The comparison of primary blepharospasm and hemifacial spasm thus offers the possibility to investigate basal ganglia contributions to cognitive inflexibility in primary dystonia while controlling for typical confounds of patients-*versus*-healthy-controls studies (Dias et al., 2009). Both groups are affected by motor symptoms and might be distracted by their occurrence during cognitive testing. Similarly, facial spasms are associated with mental distress giving rise to an increased risk for depression both in blepharospasm patients (Müller et al., 2002) and in patients with hemifacial spasm (Tan et al., 2005). However, only primary blepharospasm is associated with basal ganglia changes. Here, we compared patients with primary blepharospasm and patients with hemifacial spasm with regard to their performance on a computerized version of the WCST.

PATIENTS AND METHODS

Participants

Nineteen patients with primary blepharospasm (BSP) and 21 patients with hemifacial spasm (HSF) were recruited from the outpatient clinic of the Department of Neurology of Hannover Medical School. The diagnosis was made by an experienced neurologist in the field of movement disorders (D.D.). In two of the patients, BSP was combined with oromandibular dystonia. All patients were free of psychiatric disease and neurological disorders other than the cranial muscle contractions. All patients were treated with local subcutaneous injections of botulinum toxin on a regular basis and had normal or corrected-to-normal vision. In one blepharospasm patient and two patients with hemifacial spasm poor performance on the computerized WCST (cWCST, see below) resulted in an insufficient number of trials for analysis (i.e., less than 30 of 40 possible runs were completed). These patients were excluded from all analyses.

Within the final sample, the two patient groups were matched with regard to gender (blepharospasm: 10 female, 8 male; hemifacial spasm: 11 female, 8 male), age, and education (see Table 1). All patients were compensated for their participation by payment (25 €). The study was reviewed and approved by the local ethics committee. All patients gave informed consent in accordance with the Declaration of Helsinki. The patients with blepharospasm were also included in an event-related potential study that will be reported in a separate publication (Lange et al., under review).

Neuropsychological and Clinical Testing

In addition to the cWCST, patients were examined using several cognitive tests, clinical ratings, and psychometric questionnaires. General cognitive status was examined using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). Premorbid intelligence was estimated using a German vocabulary test (Wortschatztest, WST; Schmidt & Metzler, 1992). The Jankovic Rating Scale

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Table 1. Demographic, Clinical, and Psychological Characteristics of the Patients with Blepharospasm ($N = 18$) and Hemifacial Spasm ($N = 19$) Examined in our study

	Blepharospasm	Hemifacial spasm		
	Mean (*SD*)	Mean (*SD*)	*t*	*p*-Value
Age [years]	65.89 (8.55)	62.46 (11.12)	1.05	.303
Education [years]	12.83 (1.86)	13.42 (2.75)	−0.76	.453
Disease duration [years]	7.88 (4.28)	9.47 (5.89)	−0.88	.387
JRS (symptom severity)	3.94 (2.39)	3.00 (2.03)	1.30	.202
WST (premorbid intelligence)	29.83 (3.40)	30.11 (3.77)	−0.23	.818
MoCA (cognitive status)	26.94 (1.55)	27.82 (1.32)	−1.86	.071
BIS-Brief (impulsiveness)	15.39 (3.31)	13.16 (2.83)	2.21	.034
AES (apathy)	14.50 (8.16)	11.67 (5.27)	1.24	.224
BDI-II (depression)	12.72 (13.18)	6.53 (5.56)	1.85	.078
BSI-18 (psychiatric status)	9.61 (11.32)	3.59 (2.62)	2.20	.041
SF-36 (health status)				
Average score	66.50 (20.66)	75.84 (17.83)	−1.45	.156
Physical functioning	71.39 (24.90)	75.28 (29.43)	−0.43	.671
Physical role functioning	59.72 (42.99)	68.06 (43.56)	−0.58	.567
Bodily pain	67.50 (30.83)	76.56 (26.95)	−0.94	.355
General health perceptions	57.17 (18.94)	63.37 (25.49)	−0.84	.408
Vitality	53.06 (20.45)	63.06 (16.64)	−1.61	.117
Social role functioning	79.86 (14.94)	92.36 (13.65)	−2.62	.013
Emotional role functioning	77.78 (36.16)	87.04 (32.62)	−0.81	.425
Mental health	65.56 (22.59)	76.67 (12.06)	−1.84	.077

Note. JRS = Jankovic Rating Scale, WST = Wortschatztest (German vocabulary test of premorbid intelligence), MoCA = Montreal Cognitive Assessment, BIS-Brief = Barratt Impulsiveness Scale-Brief, AES = Apathy Evaluation Scale, BDI-II = Beck's Depression Inventory, BSI-18 = Brief Symptom Inventory – short version, SF-36 = Short Form Health Survey.

(JRS; Jankovic & Orman, 1987) served as a measure of the severity and frequency of eyelid contractions. Throughout the manuscript, we report the sums of the scores on the severity and on the frequency item with a range from 0 (indicating the absence of any symptoms) to 8 (indicating the frequent occurrence of severe symptoms). Patients further completed self-report measures of psychiatric symptoms (Beck's Depression Inventory, BDI-II; Beck, Steer, Ball, & Rainieri, 1996; Brief Symptom Inventory – short form, BSI-18; Derogatis, 2001), health status (short form 36 health survey, SF-36; Ware & Sherbourne, 1992), impulsiveness (Barratt Impulsiveness Scale-Brief, BIS-Brief; Steinberg, Sharp, Stanford, & Tharp, 2013), and apathy (Apathy Evaluation Scale, AES; Marin, Biedrzycki, & Firinciogullari, 1991).

The Computerized WCST

Patients completed an established computerized version of the WCST (cWCST, Barceló, 2003; Kopp & Lange, 2013; Lange, Vogts, et al., 2016; Lange, Seer, Finke, Dengler, & Kopp, 2015; Lange, Seer, Müller, & Kopp, 2015). The task required participants to match cards according to one of three possible sorting rules. Target displays consisted of four key cards which appeared invariantly above one stimulus card, all configured around the center of the computer screen (Figure 1). Stimulus cards varied on three dimensions (color, shape, number), and these dimensions equaled the three viable task rules. None of the 24 different stimulus cards shared more than one attribute with any of the keycards, so the sorting rule applied by the participant could unambiguously be identified (Barceló, 2003; Nelson, 1976).

Participants were required to match the stimulus card with one of the four key cards in accordance with the appropriate rule. They indicated their sorting choice by pressing one of four keys on a response pad. Target displays remained on screen until a response was recognized.

After an interval of 800 ms following participants' response, a feedback cue was presented for 400 ms indicating whether the applied sorting rule should be maintained or changed on the upcoming trial. The German words for "REPEAT" ("BLEIBEN") and "SHIFT" ("WECHSELN"), displayed in 28-point Arial, were used as feedback cues. Subsequent target stimuli appeared 1200 ms after feedback-cue onset.

Rules changed in an unpredictable manner (Altmann, 2004) after runs of two or more rule repetitions (average run length: 3.5 trials). Participants completed 40 runs involving 39 rule shifts. Before the experimental sequence, five practice runs were administered. Participants were informed about the three possible sorting rules and about the fact that the valid rule would change from time to time.

Data Analysis

The cWCST allows distinguishing between three different situations that place demands on dissociable facets of cognitive flexibility (Barceló, 1999; Barceló & Knight, 2002;

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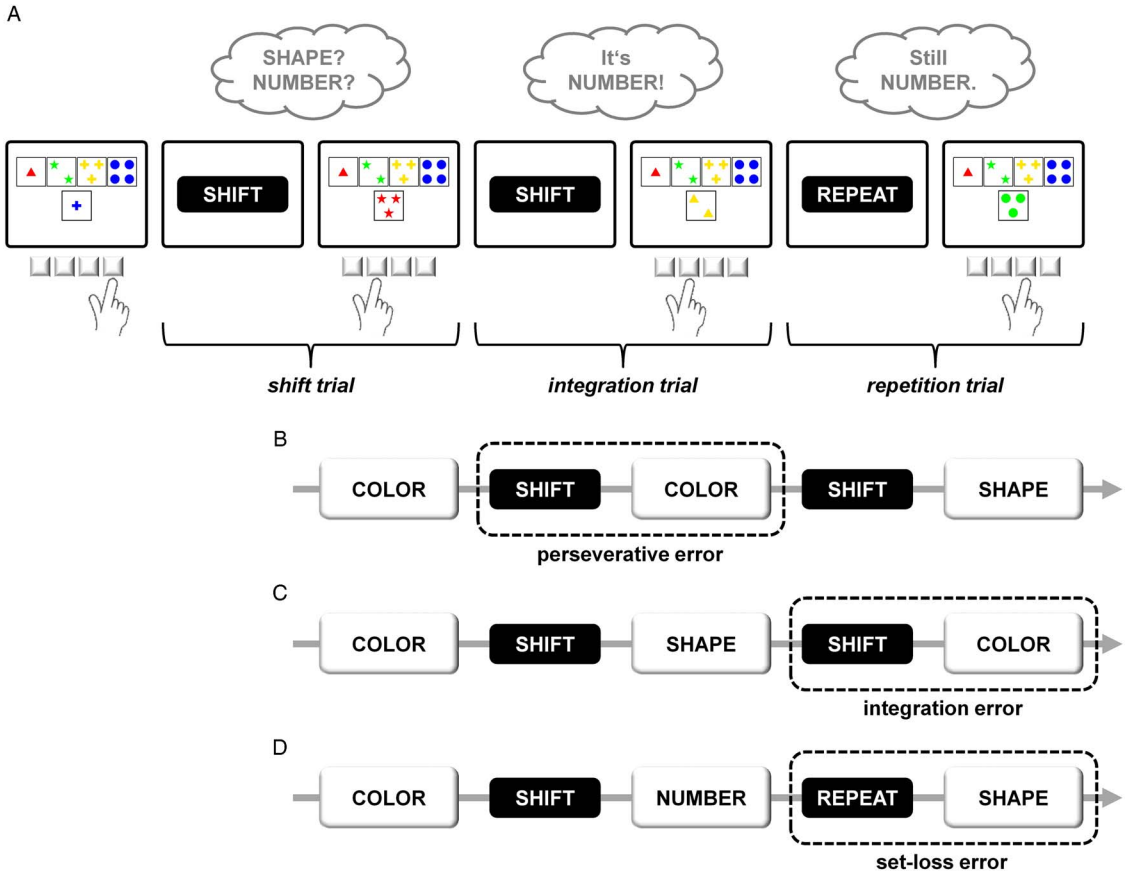

Fig. 1. Four exemplary trial sequences in the computerized Wisconsin Card Sorting Test. Each sequence begins with a negative feedback cue ("SHIFT"), signaling that the previously correct rule is no longer valid. In (**A**), the examinee shifts away from the previously correct rule on the shift trial. However, the selected rule is not the correct one as signaled by a second negative feedback cue. The examinee then needs to integrate the information about the previously applied rules to infer the correct task rule on the integration trial. Here, this integration is successful. Following the identification of the correct rule (signaled by a positive feedback cue, "REPEAT"), the individual repeats sorting by this rule. **B:** This examinee does not shift to another sorting rule on the shift trial, but repeats sorting by the rule that has been signaled to be incorrect. S/he commits a perseverative error. **C:** As in (A), the examinee shifts rules on the shift trial, but then fails to integrate the information about the previously applied rules which results in an integration error, that is, a sort by rule that could have already been eliminated. **D:** This examinee directly shifts to the correct new rule on the shift trial. However, after positive feedback has signaled that this rule needs to be repeated, the examinee fails to maintain set. S/he commits a set-loss error.

Lange, Kröger, et al., 2016; Lange, Vogts, et al., 2016). The first trial after patients have been informed that the rule has changed constitutes a shift trial. On shift trials, patients have to disengage from the old and adopt a new mental set (*set shifting*). Failures to perform a set shift result in *perseverative errors* (Figure 1B). Even when patients do not perseverate they can be expected to shift to a wrong rule in 50% of the trials. In these trials, they are informed (by means of a feedback cue) that they have chosen the wrong of the two remaining task rules. On the following trial, patients have to integrate information about previous card sorts and feedback cues to infer the correct rule (*rule inference*). We refer to these trials as *integration trials*, and to errors on these trials as *integration errors* (Figure 1C). Once patients have inferred the correct rule, a feedback cue signals that this rule needs to be repeated (*set maintenance*). The following trial constitutes a *repetition trial*. Failures to maintain cognitive set manifest in *set-loss errors* (Figure 1D).

Error rates (i.e., the percentages of erroneous responses) and response times on shift trials, integration trials, and repetition trials were compared between blepharospasm patients and patients with hemifacial spasm by means of 2×3 mixed analyses of variance (ANOVAs) involving the factors group (blepharospasm *vs*. hemifacial spasm) and trial type (shift *vs*. integration *vs*. repeat).

Responses were only considered for response time analysis when participants met the task demands (i.e., they had to shift rules on shift trials, to infer the correct rule on integration trials, and to repeat the rule on repeat trials). Response times smaller than 100 ms or greater than three standard deviations above the individual mean for each patient were excluded before mean response times were calculated.

We further explored whether measures of cognitive flexibility on the cWCST were associated with indicators of health status or psychiatric symptoms in blepharospasm and

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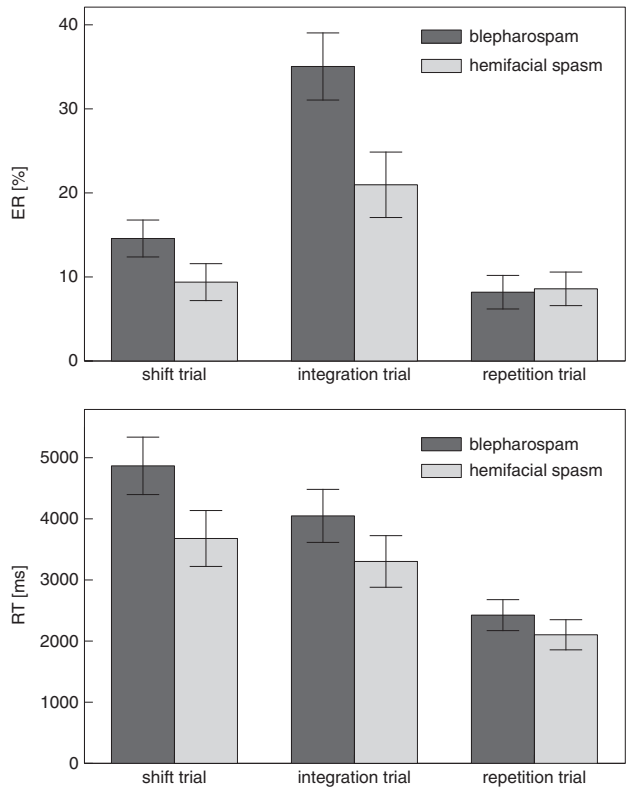

Fig. 2. Error rates and response times from the computerized Wisconsin Card Sorting Test. Error bars indicate standard error of the mean.

hemifacial spasm patients. Specifically, Pearson correlations were calculated between the percentages of perseverative errors (as a measure of set shifting), integration errors (as a measure of rule inference), and set-loss errors (as a measure of set maintenance) on the one hand, and measures of impulsiveness, apathy, depression, psychiatric symptoms, health status, symptom severity, and disease duration on the other hand. As we did not have any specific *a priori* hypotheses with regard to these relationships, correlation analyses were conducted in an exploratory way.

RESULTS

BSP and HFS patients did not differ significantly with regard to premorbid intelligence, general cognitive status, disease duration, symptom severity, apathy, or depression (see Table 1). Significant group differences were observed with regard to impulsiveness (as measured by the BIS-Brief; $t(35) = 2.21$; $p = .034$; $d = 0.73$), global psychiatric status (as measured by the BSI-18; $t(35) = 2.20$; $p = .041$; $d = 0.72$), and social role functioning (as measured by the SF-36; $t(34) = -2.62$; $p = .013$; $d = -0.87$).

Overall, BSP patients committed more errors ($M = 19\%$) on the cWCST than HFS patients ($M = 13\%$), as indicated by a significant main effect of group in the 2 × 3 mixed ANOVA, $F(1,35) = 4.20$, $p = .048$, $\eta_p^2 = .11$. This effect was moderated by a significant group × trial type interaction, $F(2,70) = 5.33$, $p = .015$, $\eta_p^2 = .13$. In contrast to HFS patients, BSP patients made significantly more errors on integration trials, $t(35) = 2.54$, $p = .018$, $d = 0.84$, but not on shift trials, $t(35) = 1.67$, $p = .104$, $d = 0.55$, or repetition trials, $t(35) = -0.17$, $p = .868$, $d = -0.06$.

The 2 × 3 mixed ANOVA on RT data revealed no significant main effect of group, $F(1,35) = 2.15$, $p = .151$, $\eta_p^2 = .06$. The group × trial type interaction did not reach statistical significance, $F(1,35) = 2.15$, $p = .079$, $\eta_p^2 = .07$. The percentages of errors committed on shift trials, repetition trials and integration trials as well as response latencies on these trials are depicted in Figure 2.

The percentage of integration errors as a measure of rule inference on the cWCST was correlated with patients' impulsiveness (as indicated by the BIS-Brief, see Table 2). In the whole sample, impulsiveness was significantly associated with integration errors ($r = .39$; $p = .017$), but not with perseverative errors ($r = .00$; $p = .989$) or set-loss errors ($r = .08$; $p = .631$). The correlation between impulsiveness and integration errors could only be observed in blepharospasm patients ($r = .50$; $p = .034$), but not in patients with hemifacial spasm ($r = -.07$; $p = .788$).

Table 2. Associations (Pearson Correlation Coefficients) between Error Measures from the Computerized Wisconsin Card Sorting Test and Measures of Clinical Status

	Total sample ($N = 37$)			Blepharospasm ($n = 18$)			Hemifacial spasm ($n = 19$)		
	PE	IE	SE	PE	IE	SE	PE	IE	SE
Impulsiveness (BIS-Brief)	.00	.39*	.08	.04	.50*	.03	−.33	−.07	.20
Apathy (AES)	.11	.10	.30	.07	.04	.30	.02	−.04	.37
Depression (BDI-II)	−.01	.01	.24	−.12	−.21	.22	−.02	.17	.41
Psychiatric status (BSI-18)	.06	.13	.07	.07	−.02	.08	.09	−.02	.28
Health status (SF-36)	−.08	−.25	−.19	.02	−.12	−.07	−.07	−.29	−.39
Symptom severity (JRS)	.26	.08	.10	.34	−.24	.14	.01	.39	.07
Disease duration [years]	.26	.20	.17	.41	.29	.24	.44	.37	.15

Note. BSP = Blepharospasm, PE = perseverative error, IE = integration error, SE = set-loss error, BIS-Brief = Barratt Impulsiveness Scale-Brief, AES = Apathy Evaluation Scale, BDI-II = Beck's Depression Inventory, BSI-18 = Brief Symptom Inventory – short form, SF-36 = Short Form Health Survey, JRS = Jankovic Rating Scale.
*$p < .05$.

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DISCUSSION

We examined executive functioning on a computerized version of the WCST in patients with blepharospasm and patients with hemifacial spasm. Blepharospasm patients committed significantly more errors than patients with hemifacial spasm. A detailed analysis of patients' error rates revealed that this group difference was mainly driven by the percentage of integration errors. The increase in integration errors in patients with blepharospasm is indicative of dystonia-related rule-inference deficits on the cWCST. In addition, we found integration errors on the cWCST to specifically relate to self-reported impulsiveness in patients with blepharospasm.

In line with previous studies (Alemán et al., 2009; Bugalho et al., 2008), our analysis revealed impaired performance on a variant of the WCST in patients suffering from a form of primary dystonia. However, previous studies comparing dystonia patients with healthy controls did not allow attributing this cognitive flexibility deficit to the pathomechanisms underlying primary dystonia. In contrast, by comparing dystonia patients to a clinical control group, we were able to eliminate confounding factors such as symptom-related distraction (Jahanshahi et al., 2003, 2014; Stamelou et al., 2012).

Both the group of blepharospasm patients and the control group of patients with hemifacial spasm suffered from eyelid spasms, and symptom severity did not differ significantly between these groups. Hence, the executive deficits observed in blepharospasm patients are unlikely to result from distracting motor symptoms or attempts to control them. Instead, our results provide new support for the possibility that the blepharospasm-related deficit in cognitive flexibility results from microstructural and functional alterations in cortico-basal ganglia loops that occur in blepharospasm but not in hemifacial spasm. The basal ganglia do not only play a role in the selection of motor programs, but they have also been proposed to be critical for the selection of more abstract cognitive programs (Hazy et al., 2007). Specifically, the need to dynamically update the selection of abstract sorting rules on the WCST has been shown to rely on basal-ganglia activity (Monchi et al., 2001, 2006). When being disrupted by dystonia-related basal-ganglia alterations, this selection process might become less reliable, resulting in WCST performance deficits in patients with primary dystonia. Along the lines of Parkinson's disease research (Monchi et al., 2004; Monchi, Petrides, Mejia-Constain, & Strafella, 2007), it is now important to characterize *how* basal-ganglia alterations give rise to these executive deficits in primary dystonia using neuroimaging methods.

Our results further point to a potential role for impulsiveness in dystonia-related cognitive inflexibility. Blepharospasm patients reported significantly higher levels of impulsiveness than patients with hemifacial spasm. Moreover, individual differences in impulsiveness were related to the percentage of integration errors in patients suffering from blepharospasm. This association was markedly specific as it could not be observed in patients with hemifacial spasm or with regard to any other type of cWCST error. Elevated levels of impulsiveness may thus partially account for the observed pattern of cWCST deficits in patients with blepharospasm. Impulsiveness as measured by the BIS-Brief is characterized by, for example, a lack of self-control, deficits to concentrate and a tendency to act on the spur of the moment (Patton, Stanford, & Barratt, 1995; Steinberg et al., 2013). These traits may specifically relate to integration errors on the cWCST because integration trials require acting on more than just the most recent piece of information (Lange, Kröger, et al., 2016). On shift trials and repetition trials, participants can directly follow cue instructions: they just have to focus on the most recent feedback cue to know whether they have to shift or to maintain the rule. On integration trials, however, participants have to combine information about tested rules across the last two trials to infer the correct rule. A tendency to act only "on the spur of the moment" likely leads to a large number of errors on these trials.

Importantly, the relationship between integration errors committed on the cWCST and impulsiveness also illustrates that cognitive inflexibility might have profound impact on the everyday life of patients with primary dystonia. Impulsiveness is associated with an increased risk of engaging in deviant or addictive behavior as well as with impaired decision-making and difficulties inhibiting inappropriate responses (Dalley, Everitt, & Robbins, 2011; de Ridder, Lensvelt-Mulders, Finkenauer, Stok, & Baumeister, 2012; Lange & Eggert, 2015). Cognitive inflexibility and impulsiveness thus appear to be relevant points to consider in the study of the non-motor syndrome of primary dystonia (Stamelou et al., 2012).

Note that we have excluded one patient with blepharospasm and two patients with hemifacial spasm because poor cWCST performance resulted in an insufficient number of trials for analysis. As the mean JRS score (indicating the severity and frequency of eyelid contractions) of these patients (3.33) was lower than the mean JRS score of the included patients (3.46), it is unlikely that performance deficits in the excluded patients were primarily caused by motor symptoms. Instead, we have observed (in the present sample and in previous studies using a similar paradigm; Lange, Vogts, et al., 2016; Lange, Kröger, et al., 2016) that the cWCST can be very challenging for some participants, even in the absence of a neurological condition. While the loss of data due to task difficulty was tolerable in the present study, it might be advisable to use simplified paradigms when studying cognitive flexibility in more severely impaired patients.

Limitations

It is widely accepted that the construct of executive functioning is multidimensional rather than unitary (Delis, Kramer, Kaplan, & Holdnack, 2004; Miyake et al., 2000). According to an influential taxonomy, cognitive flexibility (as assessed by, e.g., the WCST) constitutes one of the basic factors of executive functioning (next to inhibition and updating) (Miyake et al., 2000). In our study, we focused on the processes that give rise to cognitive flexibility on the

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WCST. To this end, we used a computerized variant of the WCST that involved considerably more trials and rule shifts than the established manual versions of the WCST. Only by using such an extensive test version, we were able to obtain reasonable estimates of response latency and accuracy on the separate trial types and hence to contrast processes of set shifting, rule inference, and set maintenance. This focus on cognitive flexibility necessarily implies that our results do not paint a complete picture of executive functioning in blepharospasm and hemifacial spasm. As a consequence, our finding of impaired cognitive flexibility in patients with blepharospasm cannot be generalized to other domains of executive functioning such as inhibition or updating. To examine which facets of executive functioning are affected by dystonia-related changes in which way, further studies involving more comprehensive test batteries are required.

Although our approach of comparing blepharospasm patients to patients with hemifacial spasm eliminates some of the confounding factors involved in patients-*versus*-healthy-controls studies, our design does not allow inferring a causal relationship between pathophysiological changes and cognitive flexibility in primary dystonia. Similarly, it is not possible to map deficits in cognitive flexibility to dysfunction in a specific neural area or circuit. One possible way to further elucidate the relationship between pathophysiological and cognitive alterations in primary dystonia is to examine the effects of deep-brain stimulation on cognitive processes (Hälbig et al., 2005; Jahanshahi et al., 2014; Pillon et al., 2006). Of interest, both in the study by Jahanshahi et al. (2014) and in the study by Pillon et al. (2006), the number of non-perseverative errors but not the number of perseverative errors on the WCST decreased following deep-brain stimulation of the internal segment of the globus pallidus (GPi). By pointing to a differential sensitivity of WCST measures to GPi modulation, these results highlight the potential of combining deep-brain stimulation with the in-depth analysis of distinct executive processes involved in WCST performance.

Given the lack of prior research on the correlates of cognitive inflexibility in primary dystonia and the rather small size of our sample, correlation analyses were necessarily exploratory. This implies that especially our results with regard to the selective association between integration errors and impulsiveness should be regarded as preliminary. Larger confirmatory studies are needed to arrive at a reliable estimate of the strength of this relationship.

CONCLUSION

We found evidence for cognitive inflexibility in patients with blepharospasm when compared to patients with hemifacial spasm who show similar motor symptoms, but who do not share a central pathophysiology. Thus, our study design allowed for a test of the widely held distraction hypothesis (Jahanshahi et al., 2003, 2014; Stamelou et al., 2012). Our results suggest that the observed pattern of cWCST performance deficits is related to the pathophysiological processes underlying blepharospasm. Studies using different imaging techniques or deep-brain stimulation may help to further characterize the exact relationship between neural alterations (e.g., in cortico-basal ganglia circuits) and cognitive inflexibility in primary dystonia. Additional research is also needed to examine the effects of cognitive inflexibility on daily functioning and quality of life in dystonia patients. To this end, the study of impulsiveness and related constructs might prove useful to improve our understanding of dystonia-related cognitive changes and to mitigate the consequences of cognitive inflexibility in primary dystonia.

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