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Non-motor features of cervical dystonia: Cognition, social cognition, psychological distress and quality of life

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ABSTRACT

Introduction: Non-motor features of cervical dystonia (CD) have been identified, including depression, anxiety, and neuropsychological deficits. The aims were: to provide a clinical neuropsychological profile of CD patients with specific focus on social cognition; assess levels of psychological distress; and investigate the relationship between non-motor features of CD, including cognitive functioning, psychological distress, CD severity, pain, and health-related quality of life (HR-QoL).

Methods: A multi-domain neuropsychological assessment battery was administered to 46 participants with CD, examining cognitive and social cognitive domains. Clinical data on dystonia severity, pain, psychological distress and HR-QoL were collected.

Results: The majority of participants with CD performed within the average range across most tests of cognition. Scores were significantly lower than standardized norms in social cognition, processing speed, and aspects of memory. High levels of anxiety (Hospital Anxiety and Depression Scale [HADS-A] ≥ 11, 30%) and depression (HADS-D ≥ 11; 29%) were observed. Psychological distress, CD severity, pain and HR-QoL were not significantly associated with neuropsychological functioning after controlling for multiple comparisons. Low HR-QoL was associated with higher levels of pain and psychological distress, but not severity of motor symptoms.

Conclusion: Results indicate that psychological distress and deficits in cognitive and social cognitive functioning are likely distinct features of CD. While motor symptoms do not appear to impact HR-QoL, pain and psychological distress were associated with low HR-QoL. Findings highlight the importance of addressing non-motor symptoms in the treatment of CD.

1. Introduction

Dystonia is a hyperkinetic movement disorder marked by involuntary muscle contractions causing abnormal, often repetitive, movements and postures [1]. Adult-onset isolated cervical dystonia (CD) is the most common form of focal dystonia, and presents with abnormal dynamic, often painful, postures of the neck, head and shoulders, which are ameliorated by botulinum toxin injections. Non-motor symptoms including depression and anxiety (in 25–50%) have also been reported [2–5].

The evidence for cognitive deficits in dystonia remains uncertain. While a number of studies report no cognitive impairments in individuals with CD [6–8], others have reported subtle impairments in the domains of executive functioning [9–13], verbal and visual memory [14,15] and attention and speed of information processing [16,17]. Reported social cognition impairments include understanding the intentionality of others and inferring mental states, which have been associated with discrepancies in working memory and verbal semantic fluency, but not disease severity [18,19].

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Structural abnormalities in networks involving the brainstem, cerebellum, frontal cortices, and thalamus in CD may be associated with deficits in higher-order cognitive functions including attention and executive function [20–22]. It has also been suggested that disordered social cognition, an aspect of which includes emotional sensory processing, is related to a disrupted collicular–pulvinar–amygdala subcortical pathway [23]. For some, the observed cognitive deficits may simply reflect the distracting effect of motor symptoms, as cognitive performance improved in nine patients with cranial dystonia following botulinum toxin treatment [24]. However, others have noted that cognitive functioning was independent of pain or symptom severity [9,11,19]. Accordingly, the extent to which observed deficits in cognitive functioning are due to the distracting effects of motor symptoms and pain is still uncertain.

The relationship between psychological distress and cognitive performance in isolated dystonia also remains unclear. Depression has been negatively associated with executive functioning [25], working [8]. However, others have found no association between cognitive performance and anxiety or depression [8]. Dystonia severity, pain and psychological distress are commonly considered the primary causes of reduced quality of life for individuals with CD [26]. Cognitive deficits have been shown to be associated with reduced health-related quality of life (HR-QOL) in patients with blepharospasm [27] but as yet the relationship between cognitive and social cognitive functioning and quality of life in people with CD has not been examined.

The aims of the current study were:

(1) to comprehensively assess cognition and social cognition in cervical dystonia patients, both in relation to: a) age matched norms; and b) measures of disease severity, pain, disability, psychological distress and health-related quality of life.
(2) to assess levels of psychological distress in this CD cohort;
(3) to investigate the interrelationship between non-motor features of CD, including CD severity, psychological distress, pain, HR-QoL and aspects of neuropsychological functioning including social cognition.

2. Materials and methods

2.1. Study participants

46 participants (31 women) with adult-onset CD, satisfying standard diagnostic criteria [1] were recruited from the Department of Neurology Dystonia Botulinum Toxin clinic at the host institution. Participants were invited by the Clinical Neurologists to participate in the study, and following informed consent were recruited and assessed over a nine-month period. Participants were initially seen at their regular 3-monthly clinic visit by the treating neurologists and given their botulinum toxin (onabotulinumtoxinA) injections prior to neuropsychological assessment. The median onabotulinumtoxinA dosage was 210 Units (range 140–350 Units). The median visit interval between injections was 13 weeks. Following administration of the botulinum toxin injections, the neurologists assessed TWSTRS-2 scores at that clinic. Non-native English speakers, and patients with other forms of dystonia, other neurological disorders, or comorbidities were excluded from the study. Demographic information of the participants is displayed in Table 1.

2.2. Assessment measures

2.2.1. Clinical

Basic demographic information including age, sex, years of education, marital status, medication, age at onset and duration of CD were gathered. Disease severity, disability and pain were measured using the Toronto Western Spasmodic Torticollis Scale-2 (TWSTRS-2) [28].

2.2.2. Psychological distress and HR-QoL

HR-QoL was assessed by the Cervical Dystonia Impact Profile (CDIP-58) [29] and EuroQol Utility Values from the EQ-5D-5L [30]. The Beck Anxiety Inventory (BAI), Beck Depression Inventory, second edition (BDI-II) and the HADS were employed to assess current levels of anxiety and depression symptoms. The BAI and BDI-II are both 21-item self-report assessment tools for anxiety and depression, respectively [31,32]. The HADS is a 14 item self-report measure which generates subscales of anxiety (HADS-A) and depression (HADS-D) [35]. Presence of anxiety and depression were determined using a cut-off score of 13 on the BAI/BDI-II [33,34], and 11 on the HADS-A/HADS-D [36].

2.2.3. Neuropsychological measures

The range of domains assessed included general intellectual functioning, processing speed, memory, executive function and social cognition. Supplementary Table II provides a description of the tests of social cognition employed. The battery of standardized clinical neuropsychological assessments, selected to provide a comprehensive profile of cognitive and social cognitive functioning, was administered over approximately 75–90 min (battery described in detail in Supplementary Table I and Supplementary Table II). Higher scores indicate better performance in all neuropsychological measures.

2.3. Statistical analysis

Neuropsychological outcomes were transformed into standardized scores using manualized normative data, where available. Accordingly, for the purpose of this study, participants' performance was categorized into the 'impaired' range if the range of their performance on a given test was $z \leq -1.5$ [37]. A z-score ≥ -1.49 was considered within the Average range without upper categorical stratification.

Mann-Whitney U tests and Spearman's rank correlation coefficient were used to examine relationships between clinical, cognitive and social cognitive measures. Standard scores were obtained by comparing sample means and standard deviations against means of published age-matched normative values for each assessment, where available in neuropsychological test manuals (e.g. WAIS-IV; D-KEFS). z-scores were calculated using $z = (x-\mu)/\sigma$, where x s the raw score, μ is the population mean, and σ is the population standard deviation. One-sample t-tests were used to assess whether the assessment scores of the sample differed from manualized norms. Similar analyses have been previously shown to allow for an inferential estimation of whether cognitive functioning of a sample differs from manualized norms [38,39].

Reported effect sizes are Cohen's d (small ≥ 0.2; medium ≥ 0.5; large ≥ 0.8). To control for multiple comparisons the Holm's method of correction was used on a family-wise basis [40,41]. Data were analyzed using IBM SPSS Statistics Version 21.

2.4. Ethics

The study was reviewed and approved by the Research Ethics Committee at SVUH. All participants gave written informed consent prior to their participation.

3. Results

Demographic and clinical characteristics of this CD cohort are summarized in Table 3. Thirty percent presented with clinically significant

Table 1
Demographic and clinical characteristics of the sample.

Variable	Level	N	M ± SD	%	Range
Age (y)		46	68 ± 10.7		33–80
Gender	Male	15			
	Female	31			
Education (y)		43	16.2 ± 3.7		10–24
Marital Status	Single	5			
	Married	4			
	In a relationship	19			
	Divorced/separated	5			
	Widowed	1			
Age at onset (y)		45	41.3 ± 11.16		20–64
HADS Anxiety		38	7.9 ± 4.83	30%*	1–17
HADS Depression		38	4.61 ± 3.67	29%*	0–15
BAI		44	9.48 ± 9.5	30%*	0–47
BDI		44	10.32 ± 10.91	30%*	0–39
Utility Values		44	0.75 ± 0.21		0.182–1.0
CDIP-58Total Score †		44	30.41 ± 20.83		3–83
CDIP-58 Head & Neck		44	49.73 ± 26.75		0–100
CDIP-58 Pain		44	43.39 ± 30.09		0–100
CDIP-58 Sleep		44	23.23 ± 30.00		0–100
CDIP-58 Upper Limb		44	27.59 ± 25.48		0–83
CDIP-58 Walking		44	23.5 ± 23.77		0–94
CDIP-58 Annoyance		44	27.39 ± 24.87		0–8
CDIP-58 Mood		44	23.57 ± 27.46		0–100
CDIP-58 Psychosocial		44	30.61 ± 27.68		0–100

Abbreviations: HADS, Hospital Anxiety and Depression Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CDIP-58, Cervical Dystonia Impact Profile.
*Percentage of participants presenting with clinical levels of psychological distress.
†0 = least impact; 100 = greatest impact.

levels of anxiety as measured by the BAI (≥13) and HADS-A (≥11). Clinically significant levels of depression were evident in 29% of the sample as measured by the BDI (≥13); 33% as measured by the HADS-D (≥11). According to CDIP-58 scores, participants rated head and neck symptoms and pain symptoms as having the greatest impact (moderate impact) on HR-QoL.

3.1. Performance on individual neuropsychological tests

As outlined in Table 2, overall this CD cohort performed in the average range across most neuropsychological tests, but significantly lower than manualized norms on a time restricted task (Wechsler Adult Intelligence Scale-Fourth Edition [WAIS-IV] coding, $d = -0.615$); and on measures of memory encoding, including immediate story memory (Weschler Memory Scale-IV [WMS-IV] Logical Memory I, $d = -0.513$) and reproduction of a complex geometric line drawing after a short delay (Rey Complex Figure, [RCF] immediate recall, $d = -0.504$). As evidenced in Fig. 1, the CD cohort also performed significantly lower than manualized norms on tests of social cognition, with large effect sizes evident for the naming facial affect ($d = -1.022$), naming emotional prosody ($d = -0.928$) and matching ($d = -1.08$) subtests of the Florida Affect Battery (FAB).

3.2. Frequency of impairments in the sample

As outlined in Fig. 1, in overall general intellectual functioning 21.7% of the CD cohort performed in the impaired range. There were low frequencies of impairment on tasks of executive function (range = 0–8.7%) and language (range = 2.2–10.9%). Frequencies of impairment ranged from 10.9 to 32.6% on memory encoding; 10.2 to 39.2% on memory recall; and 0 to 39.2% on memory recognition. The frequency of impairments on speed of information processing tasks ranged from 8.7 to 10.8%. Proportions of those in the impaired range varied across measures of social cognition, ranging from 8.8 to 32.6%.

3.3. Correlates of cognitive, psychological distress, HR-QoL and CD severity measures

There were a number of correlations nearing statistical significance. For example, HR-QoL as measured by the Utility Index was positively correlated with the RAVLT total ($r_s = 0.37, p = .004$) and Letter Fluency ($r_s = 0.4, p = .009$) scores. In addition, semantic fluency as measured by Category Fluency was negatively correlated with depression as measured by the HADS-D ($r_s = -0.405, p = .006$) and BDI-II ($r_s = -0.377, p = .006$), and positively correlated with quality of life as measured by the Utility Index ($r_s = 0.376, p = .007$). After controlling for multiple comparisons using the Holm's method, none of the cognitive measures correlated significantly with psychological distress or HR-QoL measures. Similarly, no cognitive measures were significantly correlated with pain, severity of motor symptoms, or disability, as measured by TWSTRS-2.

3.4. Psychological distress, HR-QoL and CD severity

As outlined in Table 3, no psychological distress or HR-QoL measures were significantly correlated with TWSTRS-2 Severity. HR-QoL as measured by the Utility Values scale was negatively correlated TWSTRS-2 Pain ($r_s = -0.543, p < .003$), but not TWSTRS-2 Severity ($r_s = -0.165, p = .29$), or TWSTRS-2 Disability after controlling for multiple comparisons ($r_s = -0.359, p = .017$). Impact of CD as measured by the CDIP-58 was significantly positively correlated with the HADS-A ($r_s = 0.498, p = .001$), BAI ($r_s = 0.771, p < .001$), and the BDI ($r_s = 0.579, p < .001$), and had a positive correlation nearing significance with the HADS-D ($r_s = 0.422, p = .005$). The health impact of CD as measured by the CDIP-58 had a significant negative correlation with the HR-QoL as measured by the Utility Index ($r_s = -0.455$, $p = .001$).

While the BAI was significantly correlated with TWSTRS-2 Pain ($r_s = 0.55, p < .001$) and TWSTRS-2 Disability ($r_s = 0.437$, $p = .003$), the HADS-A was not correlated with either measure

Table 2
Neuropsychological assessments scores.

Domain	Assessment	Score type (Normative M ± SD)	n	M (SD)	Min to Max	T (df)	Effect Size
Estimated Premorbid Intellectual Ability	TOPF	SCL (100 ± 15)	46	98.77 (9.92)	68.2 to 120.9	− 0.84 (45)	NS
General Intellectual Ability	WASI-II FSIQ-2	SCL (100 ± 15)	44	92.23 (19.1)	62 to 135	− 2.68 (43)	NS
Processing Speed	WAIS Coding	SCL (10 ± 3)	46	8.48 (2.47)	3 to 14	− 4.17 (45)	Med (-)
	Stroop Trial 1: Color Naming	SCL (10 ± 3)	46	9.39 (2.9)	2 to 14	− 1.42 (45)	NS
	Stroop Trial 2: Word reading	SCL (10 ± 3)	46	9.52 (2.61)	2 to 13	−1.24 (45)	NS
Motor Speed	Pegboard	Raw (n/a)	42	9.23 (1.84)	5.6 to 13.33	n/a	n/a
Visuospatial Processing	RCF Copy	Raw (n/a)	45	29.6 (7.5)	7.5 to 36	n/a	n/a
Language	BNT-15	Z (0 ± 1)	42	- 0.58 (1.42)	− 4.5 to 1.13	− 2.7 (43)	NS
	DKEFS Semantic Fluency	SCL (10 ± 3)	45	11.18 (3.09)	6 to 19	2.55 (44)	NS
Memory: Encoding	WMS LM1	SCL (10 ± 3)	46	8.48 (2.97)	3 to 14	− 3.48 (45)	Med (-)
	RAVLT A1-A5	Z (0 ± 1)	45	0.06 (1.36)	− 2.45 to 2.6	0.27 (45)	NS
	RCF Immediate	T (50 ± 10)	45	42.13 (15.6)	20 to 80	− 3.38 (44)	Med (-)
Memory: Recall	WMS LM2	SCL (10 ± 3)	44	7.45 (2.97)	2 to 13	− 5.68 (43)	Lrg (-)
	RAVLT Recall	Z (0 ± 1)	45	- 0.24 (1.1)	−3.28 to 1.92	− 1.48 (44)	NS
	RCF Recall	T (50 ± 10)	44	41.16 (15.6)	20 to 80	− 3.74 (43)	Med (-)
Memory: Recognition	WMS LM Rec	Raw (n/a)	44	22.66 (3.25)	15 to 30	n/a	n/a
	RAVLT Rec	Z (0 ±)1	43	0.671 (0.65)	− 1.18 to 1.5	6.73 (42)	Lrg (+)
	RCF Rec	T (50 ± 10)	43	41.39 (16.3)	20 to 73	− 3.51 (43)	Med (-)
Executive Function	WAIS DS: Forward	SCL (10 ± 3)	45	10.42 (3.15)	2 to 19	2.6 (43)	NS
	WAIS DS: Reverse	SCL (10 ± 3)	45	10 (2.37)	5 to 18	0.00 (43)	NS
	WAIS DS: Sequencing	SCL (10 ± 3)	45	9.93 (2.41)	5 to 15	-0.187 (43)	NS
	Stroop Trial 3: Inhibition	SCL (10 ± 3)	46	10.17 (2.82)	1 to 14	0.63 (44)	NS
	Letter fluency	SCL (10 ± 3)	45	10.24 (3.56)	4 to18	0.46 (44)	NS
Social Cognition:	FAB: Naming Facial Affect	Z (0 ± 1)	34	- 0.79 (0.82)	− 2 to 0	−5.58 (33)	Lrg (-)
	FAB: Name Emotional Prosody	Z (0 ± 1)	34	−1.11 (1.2)	−4.36 to 0.62	− 5.41 (33)	Lrg (-)
	RMET	Z (0 ± 1)	40	- 0.36 (1.39)	− 2.96 to 2.2	− 1.98 (39)	NS
	FAB: Matching	Z (0 ± 1)	31	− 1.5 (1.4)	− 5.24 to 0.42	− 6 (30)	Lrg (-)
	FAB: Incongruent	Z (0 ± 1)	34	0.64 (1.35)	−3.04 to 2.92	2.76 (33)	NS
	FAB: Congruent	Z (0 ± 1)	34	1.08 (0.93)	-0.88 to 2.06	6.81 (33)	Lrg (+)
	QCAE: Cognitive	Raw (n/a)	36	58.75 (10.0)	20 to 73	n/a	n/a
	QCAE: Affective	Raw (n/a)	36	36.64 (10.3)	23 to 76	n/a	n/a

TOPF: Test of Premorbid Functioning; WAIS: Wechsler Adult Intelligence Scale-Fourth Edition; DS: Digit Span; WASI: Wechsler Abbreviated Scale of Intelligence - Second Edition; DKEFS: Delis-Kaplan Executive Function System; FAB: Florida Affect Battery; RAVLT: Rey Auditory Verbal Learning Task; RCF: Rey Complex Figure; RMET: Reading the Mind in the Eyes Test; SCL: Scale score; ST, standard score; NS: Not significant; QCAE: Questionnaire of Cognitive and Affective Empathy; Lrg: Large; Med: Medium.
*Significant ($p \leq 0.002$) after the Holm method of correction for multiple comparisons was employed.

Table 3
Correlations of quality of life, psychological distress, and severity measures.

Variable	1
1 HADS-A	1
2 HADS-D	**0.704***
3 BAI	**0.701***
4 BDI-II	**0.711***
5 Utility Index	-0.381
6 TWSTRS Pain	0.321
7 TWSTRS Disability	0.231
8 TWSTRS Severity	-0.115
9 CDIP-58	**0.498***

*Significant (p ≤ 0.003) after the Holm method of correction for multiple comparisons was employed (two-tailed).
HADS-A: Hospital Anxiety and Depression Scale - Anxiety; HADS-D: Hospital Anxiety and Depression Scale – Depression; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory; CDIP-58: Cervical Dystonia Impact Profile.

($r_s = 0.321, p = .06$; $r_s = 0.231, p = .17$). The HADS-D was also not significantly correlated with any of the TWSTRS-2 measures, although the BDI had correlations approaching significance with TWSTRS-2 Pain ($r_s = 0.419, p = .005$) and TWSTRS-2 Disability ($r_s = 0.418$, $p = .005$).

4. Discussion

Results indicate that for some individuals, cognitive and social cognitive impairments are a distinct feature of CD. Subtle deficits in the domains of social cognition, processing speed and memory were observed in this cohort, although most participants performed within the average range on most neuropsychological assessments. Severity of motor symptoms and pain, as assessed by TWSTRS-2 Severity and Pain subscales, were not associated with performance on cognitive or social cognitive measures, indicating that poor cognitive performance is not a reflection of distracting symptoms. After controlling for multiple comparisons, cognitive performance was not associated with psychological distress or HR-QoL. While HR-QoL was not associated with severity of motor symptoms, low HR-QoL was associated with higher levels of pain and psychological distress. Furthermore, high levels of psychological distress were observed in the CD cohort. Results draw attention to the importance of addressing non-motor symptoms in the treatment of CD.

By employing a broad range of specific multi-modal measures to assess multiple facets of cognition and social cognition in cervical dystonia patients, this work expands on prior research published by Foley et al. [9] and Czekóová et al. [18]. On **neuropsychological measures**, the majority of participants with CD performed within the average range across all cognitive domains. This is largely consistent with existing literature, which has noted that most global aspects of cognitive functioning such as IQ and language are not typically impaired in CD [25]. However, there were a number of subtle impairments. This CD cohort performed significantly lower than manualized norms on tests of processing speed (8.7% impaired), encoding verbal memory (21.7% impaired), immediate visual memory (32.6% impaired), verbal recall memory (26% impaired) and visual recall memory (39.2% impaired). This is in line with previous reports of impairments in processing speed and memory in CD [13,14]. **Executive function** scores of the cohort did not statistically differ from manualized norms, and frequency of impairment was similar to that of manualized normative data (range of 0–8% impaired). Findings suggest that individuals with

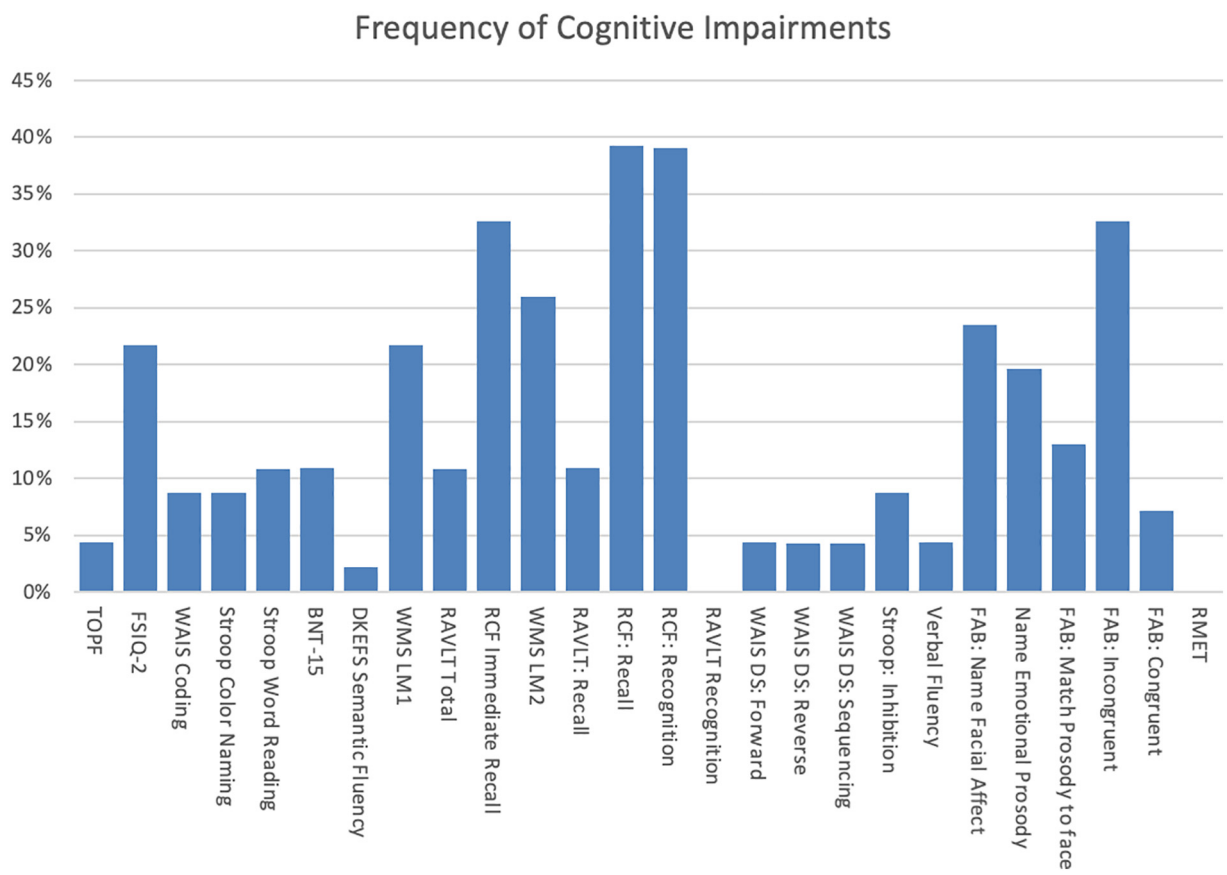

Fig. 1. Mean z-scores of CD cohort on tests of social cognition (z-scores normalized using manualized norms). Error bars show standard error of the mean.

CD do not have deficits in response inhibition, idea generation, executive control, rule inference and set shifting. Results are consistent with those from a previous study comparing the same sample to aged-matched controls [19].

Social Cognition: This CD cohort also performed significantly lower than standardized norms on a number of social cognition measures, including the Naming Facial Affect (8.8% impaired), Recognizing Emotional Prosody Affect (19.6% impaired) and Matching Emotional Prosody to Facial Affect (21.7% impaired) subtests of the Florida Affect Battery (FAB). This supports previous findings that individuals with CD have emotional recognition impairments for both auditory (prosody) [54] and visual (face) stimuli [55]. It is possible that disordered social cognition, which includes emotional sensory processing, may be related to a disrupted collicular–pulvinar–amygdala subcortical pathway in individuals with CD [23]. Indeed, the role of cerebellar dysfunction in driving dystonic movements has been highlighted in a number of recent studies [56,57] and has been shown to be implicated in the social processes of "mirroring" (e.g., understanding intentions of others from observing movements) and mentalizing (e.g., inferring intentions, beliefs or personality traits of others) [58]. However, as poor performance in social cognitive tasks has been associated with working memory and verbal semantic fluency in CD patients [18], further research is needed to delineate social cognitive deficits in CD patients from other cognitive impairments within the context of disease severity and duration. As severity of motor symptoms and pain were not associated with performance on neuropsychological tests, findings indicate that subtle cognitive and social cognitive impairments may be part of the primary pathophysiological process in CD [9,11,18], rather than a result of the distracting effect of motor symptoms, as suggested by Allam et al. [24].

Psychological distress: Higher proportions of participants with CD had clinically significant levels of anxiety and depression than have been reported in other chronic conditions, such as diabetes [59] or spinal cord injury [60]. Levels of depression and anxiety were comparable when using the Beck scales relative to the HADS. However, the two anxiety measures had different correlates, whereby the BAI was significantly correlated with measures of pain and disability, whereas the HADS-A was not. As the BAI contains a number of somatic symptoms of anxiety (e.g., "hands trembling" or "shaky/unsteady") commonly experienced in CD, this likely confounded the BAI results. Further research is warranted to determine the most suitable measure of psychological distress for CD patients.

Psychological distress and HR-QoL were not associated with severity of CD motor symptoms, although higher reported levels of pain were associated with poorer HR-QoL. This supports previous findings that pain has a greater impact on HR-QoL than the severity of motor symptoms alone [9]. As one might anticipate, low HR-QoL was associated with higher levels of psychological distress. Psychological distress was not significantly associated with cognitive or social cognitive functioning after controlling for multiple comparisons, which suggests that subtle observed cognitive impairments are not a reflection of underlying anxiety or depression but may be part of the primary pathophysiological process in CD. However, it should be noted that a number of correlations approached significance. For example, poor performance on a semantic fluency task was associated with higher levels of depression. Similarly, while HR-QoL did not correlate with measures of cognitive functioning after controlling for multiple comparisons, associations which approached significance were found between low HR-QoL and poor performance on certain measures of verbal memory and fluency measure of executive function. As current research on the

relationship between psychological distress and cognitive functioning in CD is mixed [8,9,13], and cognitive deficits have been associated with reduced HR-QoL in individuals with Primary Blepharospasm [27], research with a larger sample size is needed to determine whether impairments in these specific cognitive domains are associated with psychological distress and quality of life for individuals with CD.

The main strength of this study is the multi-faceted, multidisciplinary assessment of a well-characterized, representative sample of patients with CD, including a number of multi-modal social cognitive measures. This paper adds to a case-control study using the same sample of patients with CD [19] by comprehensively assessing their cognition and social cognition in relation to age matched norms, and by investigating the relationships between the non-motor features of cervical dystonia, including cognition, social cognition, psychological distress, pain and HR-QoL. The lack of randomization in the order the tests were administered must be considered, as fatigue or procedural effects may have influenced performance on certain tests, as well as self-reported measures of psychological distress.

5. Conclusions

Results indicate that psychological distress and deficits in cognitive and social cognitive functioning are likely distinct features of CD. While this cohort of patients with CD generally performed within the average range across a wide range of neuropsychological measures, participants performed significantly lower than normative standardized means on measures of social cognition, processing speed and memory. Findings suggest that these cognitive and social cognitive impairments are a distinct feature for some with CD, rather than a reflection of distracting motor symptoms and pain. While HR-QoL was not associated with severity of motor symptoms, higher levels of pain and psychological distress were associated with low HR-QoL. Furthermore, this cohort presented with high levels of anxiety (30%) and depression (29%). Findings highlight the importance of addressing non-motor symptoms in the treatment of CD. This may be achieved by clarifying subtle neurocognitive patterns, improving accessibility to neuropsychological assessments, and providing interventions to alleviate physical pain and psychological distress.

Disclosures

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Ethical compliance statement

Ethical approval

The study was approved by the Research Ethics Committee (REC) at St Vincent's University Hospital Dublin. All procedures followed were in accordance with the ethical standards of the REC.

Informed consent

Written informed consent was obtained from all participants in the study.

Compliance with the Journal's position on issues involved in ethical publication

We confirm that all authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

10. Data statement

The research data is confidential and thus not available.

CRediT authorship contribution statement

Ruth Monaghan: Data curation, Formal analysis, Investigation, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review editing. **Clodagh Cogley:** Formal analysis, Validation, Visualization, Writing - original draft, Writing - review editing. **Tom Burke:** Conceptualization, Project administration, Validation, Visualization, Writing - review editing. **Derval McCormack:** Data curation, Investigation, Project administration, Writing - review editing. **Sean O'Riordan:** Writing - review editing. **Ihedinachi Ndukwe:** Writing - review editing. **Michael Hutchinson:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing - review editing. **Niall Pender:** Conceptualization, Investigation, Methodolog, Resources; 9. Software, Validation, Visualization, Writing - original draft, Writing - review editing. **Fiadhnait O'Keeffe:** Conceptualization, Data curation, Investigation; 6. Methodology, Supervision, Validation, Visualization, Writing - original draft, Writing - review editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2020.100084.

References

[1] A. Albanese, K. Bhatia, S.B. Bressman, et al, Phenomenology and classification of dystonia: a consensus update, Mov. Disord. 28 (7) (2013 Jun 15) 863–873.

[2] M. Stamelou, M.J. Edwards, M. Hallett, K.P. Bhatia, The non-motor syndrome of primary dystonia: clinical and pathophysiological implications, Brain 135 (6) (2012 Jun 1) 1668–1681.

[3] I. Berardelli, G. Ferrazzano, M. Pasquini, M. Biondi, A. Berardelli, G. Fabbrini, Clinical course of psychiatric disorders in patients with cervical dystonia, Psychiatry Res. 229 (1–2) (2015 Sep 30) 583–585.

[4] A. Conte, I. Berardelli, G. Ferrazzano, M. Pasquini, A. Berardelli, G. Fabbrini, Non-motor symptoms in patients with adult-onset focal dystonia: sensory and psychiatric disturbances, Parkinsonism Related Disord. 1 (22) (2016 Jan) S111–S114.

[5] I. Ndukwe, C.B. Walsh, M. Hutchinson, Mood & age at onset of cervical dystonia, Clin. Parkinsonism Related Disord. 100049 (2020).

[6] J.L. Ostrem, C.A. Racine, G.A. Glass, et al, Subthalamic nucleus deep brain stimulation in primary cervical dystonia, Neurology 76 (10) (2011 Mar 8) 870–878.

[7] A.E. Taylor, A.E. Lang, J.A. Saint-Cyr, D.E. Riley, R. Ranawaya, Cognitive processes in idiopathic dystonia treated with high-dose anticholinergic therapy: implications for treatment strategies, Clin. Neuropharmacol. 14 (1) (1991 Feb) 62–77.

[8] M.J. van Tricht, Y.E. Dreissen, D. Cath, et al, Cognition and psychopathology in myoclonus-dystonia, J. Neurol. Neurosurg. Psychiatry 83 (8) (2012 Aug 1) 814–820.

[9] J.A. Foley, R.S. Vinke, P. Limousin, L. Cipolotti, Relationship of cognitive function to motor symptoms and mood disorders in patients with isolated dystonia, Cogn. Behav. Neurol. 30 (1) (2017 Mar 1) 16–22.

[10] F. Lange, C. Seer, C. Salchow, R. Dengler, D. Dressler, B. Kopp, Meta-analytical and electrophysiological evidence for executive dysfunction in primary dystonia, Cortex 82 (2016) 133–146.

[11] G.G. Alemán, G.A. de Erausquin, F. Micheli, Cognitive disturbances in primary blepharospasm, Movement Disord. Official J. Movement Disord. Soc. 24 (14) (2009 Oct 30) 2112–2120.

[12] P. Bugalho, B. Corrêa, J. Guimarães, M. Xavier, Set-shifting and behavioral dysfunction in primary focal dystonia, Mov. Disord. 23 (2) (2008 Jan 30) 200–206.

[13] M. Jahanshahi, J. Rowe, R. Fuller, Cognitive executive function in dystonia, Movement Disord. Official J. Movement Disord. Soc. 18 (12) (2003 Dec) 1470–1481.

[14] R. Romano, A. Bertolino, A. Gigante, D. Martino, P. Livrea, G. Defazio, Impaired cognitive functions in adult-onset primary cranial cervical dystonia, Park. Relat. Disord. 20 (2014) 162–165.

[15] M. Balas, C. Peretz, S. Badarny, R.B. Scott, N. Giladi, Neuropsychological profile of DYT1 dystonia, Movement Disord. Official J. Movement Disord. Soc. 21 (12) (2006 Dec) 2073–2077.

[16] D.J. Kuyper, V. Parra, S. Aerts, M.S. Okun, B.M. Kluger, Nonmotor manifestations of dystonia: a systematic review, Mov. Disord. 26 (7) (2011 Jun) 1206–1217.

[17] R.B. Scott, R. Gregory, J. Wilson, et al, Executive cognitive deficits in primary dystonia, Mov. Disord. 18 (5) (2003 May) 539–550.

[18] K. Czekóová, P. Zemánková, D.J. Shaw, M. Bareš, Social cognition and idiopathic isolated cervical dystonia, J. Neural Transm. (Vienna) 124 (9) (2017 Sep) 1097–1104, https://doi.org/10.1007/s00702-017-1725-8.

[19] T. Burke, R. Monaghan, D. McCormack, C. Cogley, M. Pinto-Grau, S. O'Connor, B. Donohoe, L. Murphy, S. O'Riordan, I. Ndukwe, M. Hutchinson, Social cognition in cervical dystonia: A case-control study, Clinical Parkinsonism & Related Disorders 3 (2020) 100072.

[20] G. Battistella, P. Termsarasab, R.A. Ramdhani, S. Fuertinger, K. Simonyan, Isolated focal dystonia as a disorder of large-scale functional networks, Cereb. Cortex 27 (2) (2015 Dec 1) bhv313.

[21] S. Lehéricy, M.A. Tijssen, M. Vidailhet, R. Kaji, S. Meunier, The anatomical basis of dystonia: current view using neuroimaging, Mov. Disord. 28 (7) (2013 Jun 15) 944–957.

[22] E. Zoons, J. Booij, A.J. Nederveen, J.M. Dijk, M.A. Tijssen, Structural, functional and molecular imaging of the brain in primary focal dystonia—a review, Neuroimage 56 (3) (2011 Jun 1) 1011–1021.

[23] M. Hutchinson, E.M. McGovern, S. Narasimham, et al, The premotor syndrome of cervical dystonia: disordered processing of salient environmental stimuli, Movement Disord. Official J. Movement Disord. Soc. 33 (2) (2018 Feb) 232.

[24] N. Allam, J.E. Frank, C. Pereira, C. Tomaz, Sustained attention in cranial dystonia patients treated with botulinum toxin, Acta Neurol. Scand. 116 (3) (2007 Sep) 196–200.

[25] M. Jahanshahi, M. Torkamani, The cognitive features of idiopathic and DYT1 dystonia, Mov. Disord. 32 (10) (2017 Oct) 1348–1355.

[26] J. Van den Dool, M.A. Tijssen, J.H. Koelman, R.H. Engelbert, B. Visser, Determinants of disability in cervical dystonia, Parkinsonism Related Disord. 1 (32) (2016 Nov) 48–53.

[27] J. Yang, W. Song, Q. Wei, et al, Screening for cognitive impairments in primary blepharospasm, PLoS ONE 11 (8) (2016).

[28] C.L. Comella, S.H. Fox, K.P. Bhatia, et al, Development of the comprehensive cervical dystonia rating scale: methodology, Mov. Disord Clin. Pract. 2 (2) (2015 Jun) 135–141.

[29] S.J. Cano, T.T. Warner, J.M. Linacre, et al, Capturing the true burden of dystonia on patients: the Cervical Dystonia Impact Profile (CDIP-58), Neurology 63 (9) (2004 Nov 9) 1629–1633.

[30] A. Hobbins, L. Barry, D. Kelleher, et al, Utility values for health states in Ireland: a value set for the EQ-5D-5L, Pharmacoeconomics 36 (11) (2018 Nov) 1345–1353.

[31] A.T. Beck, N. Epstein, G. Brown, R.A. Steer, An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (1988) 893–897.

[32] A.T. Beck, C.H. Ward, M. Mendelson, J. Mock, J. Erbaugh, An inventory for measuring depression, Arch. Gen. Psychiatry 4 (1961) 561–571.

[33] L.J. Julian, Measures of anxiety: state-trait anxiety inventory (STAI), Beck anxiety inventory (BAI), and Hospital anxiety and Depression scale-anxiety (HADS-A), Arthritis Care Res. 63 (S11) (2011 Nov) S467–S472.

[34] M. Hautzinger, F. Keller, C. Kühner, Beck depressions-inventar (BDI-II), Harcourt Test Services (2006).

[35] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr. Scand. 67 (6) (1983 Jun) 361–370.

[36] K.Z. Bambauer, S.E. Locke, O. Aupont, M.G. Mullan, T.J. McLaughlin, Using the hospital anxiety and depression scale to screen for depression in cardiac patients, Gen. Hosp. Psychiatry 27 (4) (2005 Jul 1) 275–284.

[37] M.D. Lezak, D.B. Howieson, D.W. Loring, J.S. Fischer, Neuropsychological Assessment, Oxford University Press, USA, 2004.

[38] S.J. Morgan, V.E. Kelly, D. Amtmann, R. Salem, B.J. Hafner, Self-reported cognitive concerns in people with lower limb loss, Arch. Phys. Med. Rehabil. 97 (6) (2016 Jun 1) 912–918.

[39] R. Lombard-Vance, F. O'Keeffe, D. Desmond, R. Coen, N. Ryall, P. Gallagher, Comprehensive neuropsychological assessment of cognitive functioning of adults with lower limb amputation in rehabilitation, Arch. Phys. Med. Rehabil. 100 (2) (2019 Feb 1) 278–288.

[40] K.E. Eichstaedt, K. Kovatch, D.A. Maroof, A less conservative method to adjust for familywise error rate in neuropsychological research: the Holm's sequential Bonferroni procedure, NeuroRehabilitation 32 (3) (2013 Jan 1) 693–696.

[41] J. Gaetano, Holm-Bonferroni sequential correction: an EXCEL calculator Available at: www.researchgate.net/publication/236969037_Holm, 2018.

[54] Z.T. Nikolova, A. Fellbrich, J. Born, R. Dengler, C. Schröder, Deficient recognition of emotional prosody in primary focal dystonia, Eur. J. Neurol. 18 (2011) 329–336.

[55] M. Rinnerthaler, C. Benecke, L. Bartha, T. Entner, W. Poewe, J. Mueller, Facial recognition in primary focal dystonia, Mov. Disord. 21 (2006) 78–82.

[56] V.G. Shakkottai, A. Batla, K. Bhatia, W.T. Dauer, C. Dresel, M. Niethammer, D. Eidelberg, R.S. Raike, Y. Smith, H.A. Jinnah, E.J. Hess, Current opinions and areas of consensus on the role of the cerebellum in dystonia, Cerebellum 16 (2) (2017 Apr 1) 577–594.

[57] L. Avanzino, D. Martino, I. Martino, E. Pelosin, C.M. Vicario, M. Bove, G. Defazio, G. Abbruzzese, Temporal expectation in focal hand dystonia, Brain 136 (2) (2013 Feb 1) 444–454.

[58] F. Van Overwalle, K. Baetens, P. Mariën, M. Vandekerckhove, Social cognition and the cerebellum: a meta-analysis of over 350 fMRI studies, Neuroimage 1 (86) (2014 Feb) 554–572.

[59] C.E. Lloyd, P.H. Dyer, A.H. Barnett, Prevalence of symptoms of depression and anxiety in a diabetes clinic population, Diabet. Med. 17 (3) (2000 Mar) 198–202.

[60] R. Williams, A. Murray, Prevalence of depression after spinal cord injury: a meta-analysis, Arch. Phys. Med. Rehabil. 96 (1) (2015 Jan 1) 133–140.