Social cognition in cervical dystonia: A case-control study

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A B S T R A C T

Background: Although considered a motor disorder, adult onset isolated focal dystonia has many non-motor symptoms. There is a paucity of neuropsychological research on cognitive processing in adult onset focal dystonia.

Methods: We employed a battery of clinical and cognitive assessments, including basic and complex social cognition, and assessed 46 patients with adult-onset cervical dystonia, compared to 46 age-, sex-, education-, and premorbid IQ-matched healthy controls.

Results: Significant between-group differences were observed in relation to measures of memory encoding, recall and recognition, as well as multimodal measures of basic Social Cognition (emotion recognition: face and prosody), but not complex Social Cognition (mentalising). There were no deficits observed in multimodal measures of executive function.

Controlling for mood did not affect performance.

Conclusion: In this multi-dimensional assessment of cognition in cervical dystonia, we report deficits in memory encoding, and in social cognition. Further investigation of social cognitive processes, memory, and sustained attention are required.

Longitudinal studies are also needed to further delineate the role of psychological distress on cognitive outcomes and document the cognitive profile over time.

1. Introduction

Cervical Dystonia (CD) is the most common adult onset idiopathic isolated focal dystonia (AOIFD) [1]. Cervical dystonia is a hyperkinetic movement disorder characterized by irregular, involuntary, spasmodic neck movements and postures, with or without head tremor [2]. There is growing evidence that the basal ganglia, specifically cortico-striatal-thalamo-cortical networks, play a role in the clinical presentation of dystonia, with non-motor brain regions negatively implicated in CD [3], which may result in non-motor symptoms. In AOIFD, GABAergic mechanisms are affected at all levels of the central nervous system [4], specifically in basolateral regions of the amygdala [5]. While traditionally considered a ‘pure motor’ disorder, patients with CD have non-motor features such as anxiety and depression (40–60%) [6], abnormal sensory processing [7], sleep difficulties, and cognitive deficits [8]. Recently, it has been shown that people with CD experience increased levels of perceived stigmatisation [9], neuropsychiatric comorbidities [10], and a range of non-motor symptoms recently summarised [11]. Temporal discrimination deficits in CD would suggest dysfunctional subcortical mechanisms for covert orienting of attention, specifically that involving salient environmental sensory stimuli, through the superior colliculus [12]. The superior colliculus is also involved in visual processing of emotional facial recognition [13] with anterior signalling through the pulvinar to the amygdala [14]. As a result, some individuals with CD are postulated to have impaired salient emotional face processing due to collicular-pulvinar-amygda pathway dysfunction.

1.1. Cognitive dysfunction in AOIFD

There is a paucity of cognitive assessment research in AOIFD, especially in relation to CD; nine patients with cranial dystonia were reported to have sustained attention deficits compared to matched controls, despite intact global intelligence [15]. Similarly, a study of people with primary dystonia (n = 10; torticollis [50%]; arm dystonia [20%]; and generalised [30%]) and matched controls (n = 12) compared outcomes on a battery of measures, with only categorical fluency being impaired in patients [16]. In

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contrast, Balas and colleagues [17] found better performance on semantic fluency when comparing 20 symptomatic DYT1 dystonia patients to a healthy cohort (n = 20). In terms of impairment, however, they did find poorer performance on a verbal memory task (list). In a study by Scott and colleagues, attention and executive deficits were reported, though their findings might be confounded by concomitant dopaminergic and anti-cholinergic medication use by the participants [18]. Alemán and colleagues reported, in 20 patients with blepharospasm, deficits on measures of attention and a decreased capacity of performing complex motor tasks compared to matched controls, independent from depression, anxiety, and premorbid intelligence [19]. When compared to healthy controls, a heterogeneous group of 45 patients with various phenotypes of AOIFD performed worse on measures of executive function i.e., set maintenance and set shifting, such as the Wisconsin Card Sorting Task [20], similar to the findings of Lange and colleagues [21]. In a cohort of 36 patients with cervical and generalised dystonia, 7 of 12 impaired patients had CD, and were impaired on measures of speed and attentional shifting [22], with the authors controlling for medication, disease severity, and onset as co-variates, suggesting that cognition was independent of medication effects. A larger study of 45 people with primary adult-onset dystonia (16 B.P. 15CD; 14 segmental dystonia) found working memory deficits, impaired mental control, visual memory (visual reproduction task), processing speed, and set-shifting [23].

1.2. Social cognition in cervical dystonia

Social cognition incorporates the ability to represent and attribute affective and cognitive mental states to others, non-humans, and/or non-living things [24]. It integrates cognitive processes such as the ability to follow eye-gaze, share attention, recognize emotion, to distinguish between self and others' intentions [25], and to construct and judge a social narrative. Some elements of social cognition have been examined in patients with AOIFD. In 26 non-depressed people with cervical dystonia, significant impairments were reported on a measure of cognitive theory of mind, the Social Faux Pas Recognition Test, when compared to controls [26]. Two studies have examined emotion recognition in AOIFD; using visual stimuli, 32 patients (20 with cervical dystonia and 12 with blepharospasm) had difficulty identifying disgust, compared to age-matched controls [27]. Using auditory stimuli, significant deficits were also found in the recognition of angrily intoned words in 30 patients with cervical dystonia when compared to controls [28].

The literature on cognitive function in CD specifically, is scarce. Limited research suggests that patients with CD, specifically, may have deficits in attention and executive function, as well as social cognition. While aspects of cognitive deficits may relate to illness-specific features or mood, cognitive dysfunction may also represent a core feature of CD.

1.3. Study objective

The objective of this study was to assess the cognitive profile of CD patients in comparison to matched healthy controls. Based on the literature, we hypothesised that people with CD would perform less well than healthy controls on measures of social cognition, attentional-based tasks, and measures of executive function.

2. Methods

2.1. Study Population

Patients with adult-onset CD, satisfying standard diagnostic criteria [1], were approached consecutively and invited to take part at the botulinum toxin injection clinic at the host institution, with an uptake of approximately 90%. Following informed consent, participants were recruited and assessed from September 2018 to April 2019. Exclusion criteria included other neurological disorders; comorbidities precluding completion of questionnaires or cognitive assessments i.e., physical, psychiatric disorders, or substance misuse disorders. All participants were native English speakers.
3. Results

3.1. Demographics

A total of 46 people with cervical dystonia (CD) and 46 healthy controls (HCs) were enrolled. The groups were matched in age (CD: 58.79 ± 10.37 years; HC: 59.86 ± 5.82, p = 0.543), years of education (16.25 ± 3.70 years and 15.56 ± 3.90, respectively; p = 0.395), and estimated premorbid IQ (z = −0.01 ± 0.98, p = 0.944). There was a similar sex distribution between groups (CD: 67% women; HC: 69% women; n = 32).

3.2. Cervical dystonia patients

Average age of CD onset was 41.3 ± 11.2, with an average illness duration of 17 years. The mean TWSTRS-2 Severity scale score was 10.52 (± 4.40), TWSTRS-2 Disability was 5.43 (± 3.77) and TWSTRS-2 Pain was 11.20 (± 8.07).

In relation to the Anxiety, 41% were in the normal range; 15% borderline; and 26% were above cut-off for clinical caseness. Considering Depression, 65% were within the normal range; 10% considered borderline; with 6% above clinical cut-off. Each participant with borderline depression had borderline anxiety; the cohort with clinically elevated depression had comorbid clinically abnormal anxiety. Of the total cohort, 26% (n = 12) were actively engaged in treatment for psychological distress at the time of cognitive assessment.

3.3. Between-group comparisons

3.3.1. Anxiety and depression

CD patients reported significantly higher HADS-Anxiety (CD: 7.89 ± 4.48 v HC: 4.22 ± 2.81; p < 0.001), HADS-Depression (CD: 4.60 ± 3.66 v HC: 2.81 ± 2.57; p = 0.033) and HADS-Total (CD: 12.5 ± 7.56 v HC: 7.03 ± 5.12, p = 0.002).

3.3.2. Cognitive composite and task comparisons

CD patients were compared to controls on the a priori cognitive composites, reported in Table 1.

In the Executive Composite, there was no significant between-group difference (p = 0.647). There were no significant differences on individual measures: Fluency: p = 0.757; Forward Digit Span: p = 0.750; Reverse Digit Span: p = 0.065; Stroop Trial 3: p = 0.501. There was no significant difference on the Speed composite (p = 0.539), which considered Trial 1 (Colour Naming: p = 0.614) and Trial 2 (Word Reading: p = 0.549) of the Stroop test.

No between group difference was found on the Complex Social Cognition composite (p = 0.407) which included the Reading the Mind in the Eyes test (p = 0.403), Conflicting Emotional Prosody (p = 0.171), and cross-modal matching of emotional faces to emotional prosody (p = 0.892). However, there was a significant difference in the Basic Social Cognition composite (p = 0.007); performance on both the Name Facial Affect (Picture), and Name Emotional Prosody (Audio) tasks were significantly lower for CD participants than HC (p = 0.033; p = 0.045, respectively). A detailed breakdown of between-group comparisons per test can be seen in Table 2.

Each individual memory composite i.e., Encoding (p = 0.028), Recall (p < 0.001), and Recognition (p = 0.006), was significantly different between CD patients and controls. The Encoding composite contained the RAVLT Total Score (p = 0.926), Logical Memory I (p = 0.038), and the Immediate production of the Complex Figure Test (p < 0.001). Of note, performance on the Complex Figure Copy trial, a measure of visual-spatial constructional abilities was also significantly lower in CD patients than controls. A MANCOVA using the HADS total as a covariate did not affect performance on the encoding composite. The Recall Composite contained the RAVLT Delayed Recall (p = 0.509), Logical Memory II (p < 0.001), and the Complex Figure Recall (p < 0.001). The Recognition composite contained the recognition paradigms from the RAVLT (p = 0.007), Logical Memory (p = 0.01), and Complex Figure (p = 0.001). Considering Retention percentages of recalled information compared to encoded material, no significant difference was observed on the RAVLT (p = 0.151) or on the Complex Figure (p = 0.878). The Logical Memory percentage retention was significantly lower than the control cohort (p < 0.001).

3.4. Correlates: cognitive composites and clinical measures

3.4.1. Clinical measures

In CD patients, there were no significant correlations between performance on the Copy Trial of the Complex Figure Test and the TWSTRS-2 Pain (r = 0.141; p = 0.367), Severity (r = −0.188; p = 0.226), or Disability (r = 0.141; p = 0.367) sub-scales. None of the cognitive composite scores correlated with the TWSTRS-2 subscales, however, the TWSTRS-Disability correlated with the HADS-D (r = 0.397; p < 0.05).

3.4.2. Cognitive composites

As reported in Table 3, the Encoding composite significantly correlated with the Recall Composite (r = 0.858; p < 0.001), the Executive composite (r = 0.622; p < 0.001), Speed Composite (r = 0.365; p < 0.05), and Complex Social Cognition (r = 0.417; p < 0.05). The Recall composite correlated with the Recognition Composite (r = 0.433; p < 0.001), the Executive composite (r = 0.573; p < 0.001), and Basic Social Cognition (r = 0.367; p < 0.05). The Executive composite correlated with the Speed Composite (r = 0.539; p < 0.001), Basic Social Cognition (r = 0.411; p < 0.05), and Complex Social Cognition (r = 0.429; p < 0.05). The Speed Composite correlated with Basic Social Cognition (r = 0.351; p < 0.05), and Complex Social Cognition (r = 0.372; p < 0.05). Basic Social Cognition and Complex Social Cognition correlated (r = 0.558; p < 0.001).

4. Discussion

In this study we investigated the cognitive profile of 46 people with cervical dystonia (CD), compared to 46 healthy controls matched by age,
Values in bold highlight significant results between CD and healthy controls. RAVLT: Rey Auditory Verbal Learning Task; A1: First time hearing the list of words; A5: final trial of encoding; A6: Proactive interference task; Stroop CWI: Colour Word Interference Test; ROCFT: Rey-Osterrieth Complex Figure Test; RMET: Reading the Mind in the Eyes Test.

* p < 0.05.
** p < 0.01.
*** p ≤ 0.001.

sex, years of education, and estimated premorbid IQ on a detailed battery of neuropsychological measures. CD patients performed significantly worse on encoding, recall, and recognition aspects of memory, as well as in basic social cognition (namely facial affect, and naming emotional prosody). CD patients did not perform lower than controls on measures of speed, executive function, or complex social cognition. CD patients reported significantly lower performance on the encoding composite is likely to have reduced the potential volume of information which could be recalled or retained the potential volume of information which could be recalled or recognised after the standardised delay. We computed retention percent-age, found that, relative to what was encoded, patients did not differ to the cognitive load and temporal gradient of the story. This may also suggest that patients had an inability to attend to the stimuli for a sufficient time to allow for semantic organisation or deeper encoding, which may be due to the cognitive load and temporal gradient of the story. This may also reflect the incidental learning required for the Complex Figure. This pattern of shallow encoding, for both auditory information as well as incidental visual learning, is likely to be why there were no significant deficits in

Table 2

| Cognitive domain | Cognitive measure | Subdomain/score | z-Score | p-Value |
|------------------|------------------|----------------|--------|---------|
| **Memory**       |                  |                |        |         |
| RAVLT            |                  |                | −0.03 ± 0.98 | 0.834   |
| A5               |                  |                | 0.05 ± 0.94 | 0.793   |
| Total Encoding   |                  |                | 0.05 ± 1.14 | 0.926   |
| A6               |                  |                | 0.03 ± 0.81 | 0.855   |
| Delayed Recall   |                  |                | 0.17 ± 0.70 | 0.589   |
| Recognition      |                  |                | 0.48 ± 0.74 | 0.007** |
| **Logical Memory** |                  |                |        |         |
| Encoding         |                  |                | −0.43 ± 1.16 | 0.038***|
| Delayed Recall   |                  |                | −0.87 ± 0.99 | <0.001***|
| Recognition      |                  |                | −0.50 ± 1.02 | 0.01**  |
| **ROCFT**        |                  |                |        |         |
| Immediate Recall |                  |                | −0.85 ± 1.34 | <0.001***|
| Delayed Recall   |                  |                | −0.99 ± 1.36 | <0.001***|
| Recognition      |                  |                | −1.47 ± 2.39 | ≤0.001***|
| **Visuo-spatial** |                  |                |        |         |
| ROCFT            |                  |                | −0.14 ± 0.96 | 0.757 |
| Copy Figure      |                  |                | −0.10 ± 1.40 | 0.403   |
| **Social cognition** |               |                |        |         |
| RMET             |                  |                | −0.53 ± 1.01 | 0.033*  |
| Florida Affect   |                  |                | −0.61 ± 1.07 | 0.045*  |
| Name Face Affect |                  |                | −0.32 ± 1.13 | 0.171   |
| Conflicting Prosody (Total: i = 36) | | | −0.18 ± 0.83 | 0.394   |
| Subscale: Conflicting (i = 12) | | | −0.20 ± 0.99 | 0.364   |
| Subscale: Congruent (i = 12) | | | −0.21 ± 0.91 | 0.335   |
| Matching Face to Prosody | | | −0.01 ± 0.95 | 0.892   |
| **Executive function** | | |        |         |
| Lexical Fluency  |                  |                | −0.14 ± 0.96 | 0.757 |
| Total Score (F, A, S) | | | −0.10 ± 1.40 | 0.403   |
| Digit Span       |                  |                | −0.38 ± 1.06 | 0.065   |
| Reverse          |                  |                | −0.14 ± 1.57 | 0.614   |
| **Speed**        |                  |                | −0.15 ± 1.37 | 0.549   |

Table 3

| Variable            | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|
| 1 TWSTRS Pain       | 1 | - | - | - | - | - | - | - | - | -  | -  | -  | -  |
| 2 TWSTRS Disability | 0.447** | 1 | - | - | - | - | - | - | - | - | - | - | - |
| 3 TWSTRS Severity   | 0.164 | 0.151 | 1 | - | - | - | - | - | - | - | - | - | - |
| 4 Anxiety           | 0.265 | 0.213 | 0.006 | 1 | - | - | - | - | - | - | - | - | - |
| 5 Depression        | 0.320 | 0.397* | −0.015 | 0.723** | 1 | - | - | - | - | - | - | - | - |
| 6 HADS Total        | 0.310 | 0.317 | −0.004 | 0.942** | 0.912** | 1 | - | - | - | - | - | - | - |
| 7 Encoding          | 0.041 | 0.094 | −0.088 | −0.215 | −0.096 | −0.174 | 1 | - | - | - | - | - | - |
| 8 Recall            | 0.199 | 0.286 | −0.135 | −0.040 | 0.034 | −0.007 | 0.858** | 1 | - | - | - | - | - |
| 9 Recognition       | 0.032 | 0.009 | −0.004 | −0.068 | −0.071 | −0.075 | 0.266 | 0.433** | 1 | - | - | - | - |
| 10 Executive        | −0.116 | 0.044 | −0.211 | −0.240 | −0.070 | −0.175 | 0.622** | 0.573** | 0.149 | 1 | - | - | - |
| 11 Speed            | 0.065 | 0.064 | −0.024 | −0.185 | −0.217 | −0.215 | 0.365* | 0.297 | −0.090 | 0.539* | 1 | - | - |
| 12 Basic Social Cognition | −0.060 | 0.081 | −0.088 | 0.105 | 0.158 | 0.136 | 0.328 | 0.367* | 0.067 | 0.411* | 0.351 | 1 | - |
| 13 Complex Social Cognition | −0.241 | −0.037 | 0.083 | 0.004 | 0.097 | 0.045 | 0.417* | 0.190 | −0.155 | 0.429* | 0.372* | 0.588** | 1 |

Values in bold highlight significant correlations within CD cohort.
* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
executive function found, as goal-orientated task-specific shorter tasks can be completed due to a relatively intact executive system. As CD patients performed significantly worse than controls when required to copy the complex figure, one could interpret this as either being due to executive dysfunction (planning, or organisation), or a deficit in visual attention (i.e., sustained attention to visual stimuli). To distinguish between attentional processes which may underlie the observed discrepancy, as Posner and colleagues describe [42–44], a deficit in alerting and orientating attention, rather than executive attention, may be present, hence the intact performance on executive tests. We propose that the pattern of deficits in the complex figure represents a visual analogue to the attentional deficits observed on the story encoding trial. Of note, controlling for elevated anxiety and depression did not account for this finding, suggesting that this performance pattern is independent of mood.

This study further provides evidence for impaired basic social cognition in people cervical dystonia i.e., emotion recognition. Our patient cohort performed significantly lower than controls when requested to correctly label affect (happy, sad, angry, fearful, or neutral) for both visual (face) and auditory (prosody) stimuli.

Studies show the bidirectional modulation of ventromedial prefrontal cortico-amygdala circuitry (whereby ventral amygdalo-fugal pathways projects anteriorly to the prefrontal cortex and anterior cingulate, [45]), though our results may be better contextualised by a postulated focal dysfunction in the collicular-pulvinar-amygdala pathway. Many of the tasks linked to the former were intact i.e., mentalising, working memory, and executive functions etc. More focal dysfunction in the collicular-pulvinar-amygdala pathway may explain why neither measures of executive function nor complex social cognition tasks were significantly impaired in CD patients compared to controls. Notwithstanding, aspects of visual orientation, visual attention, automatic/unconscious visual and auditory orientation, and visual and auditory attention are evident on measures with a high temporal gradient i.e., large volumes of information in the story encoding, and high visual orientation and attention required for the incidental learning trial on the Complex Figure.

In essence, we hypothesise that disruption in this network (collicular-pulvinar-amygdala) may contextualise the cognitive findings in relation to differences in social cognitive performance on basic processing, and also encoding aspects of memory performance requiring sustained attention due to reduced cerebral GABA levels both in the superior colliculus and in the amygdala. We also suggest that this postulated collicular-pulvinar-amygdala dysfunction causes the other observable features of cervical dystonia i.e., abnormal temporal discrimination and a predisposition to anxiety and depression.

Our findings are congruent with previous reports of lower performance on measures of naming affect [27] and identification of emotional prosody [28], as well as elevated anxiety and low mood [6]. Considering tasks that specifically assess executive function, unlike other studies in the AOIFD literature [15,18–20], our CD patient cohort did not differ significantly from our healthy controls on measures of executive function.

A limitation of our study is that our test battery did not specifically include measures of sustained attention such as the Sustained Attention to Response Task (SART), N-Back test, or Attention Network Test (ANT), unlike Allam and colleagues [23], who found a deficit comparing patients to controls; nor did our test battery include a serial test of executive function, such as the Paced Auditory Serial Attention Task (PASAT). Our battery was also not comprehensive from a language perspective. Despite that, a strength of the battery is the large social cognitive component from both a basic (emotional recognition) and complex (mentalling and cross-modal integration) perspective, as well as many measures of executive function.

There are many avenues for future research following this study. A large-scale case-matched longitudinal study of people with CD could allow for greater interpretation of the interaction effects of disease duration on cognitive outcomes, as well as the natural history of the cognitive profile in CD. The subcortical pathway for emotional face recognition and attentional networks should be assessed in patients with cervical dystonia, using complementary ancillary methodologies i.e., functional and/or structural neuroimaging.

In conclusion, this study adds to the known literature in relation to basic emotional processing in patients with cervical dystonia, and finds that patients may also have impaired encoding, recall, and recognition capacity as well as impaired basic social cognition (namely facial affect and emotional prosody); further research and therapeutic intervention trials are warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2020.100072.

Declaration of competing interest

There are no other potential conflicts of interest for research relating to this article, for all authors.

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