Title: Social cognition and idiopathic isolated cervical dystonia

Running head: Social cognition in cervical dystonia

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Abstract

Background

For a long time cervical dystonia (CD) has been characterized only by disturbances in motor functioning. Despite accumulating evidence for symptomatology in various non-motor domains, to date no study has investigated social cognition in CD. The aim of this study was to compare performance of CD patients and healthy controls in neurocognitive and socio-cognitive domain.

Methods

Twenty-five non-depressed patients with CD and 26 healthy controls underwent neuropsychological testing. This involved assessment of cognitive status (general intellect, verbal memory, and executive function), and socio-cognitive functions using a theory of mind task and self-report on empathy and emotion regulation.

Results

In comparison to controls, CD patients displayed significantly decreased cognitive abilities, particularly in executive function and verbal memory tasks. Difficulties in inferring mental states on both cognitive and affective levels were also observed. The largest discrepancies were detected in understanding intentionality in others. Poorer performance in cognitive and socio-cognitive tasks was unrelated to severity of the disease.

Conclusions

This is the first evidence of compromised socio-cognitive functions in CD patients, highlighting this domain as another facet of non-motor symptoms of this disease. Future studies should advance our understanding of the extent, nature, and time course of these deficits in other aspects of social cognition in this patient population.

Introduction

Adult-onset idiopathic isolated cervical dystonia (CD) is a condition that is defined traditionally only by observable motor symptoms – that is, recurrent or continuous involuntary muscle contractions and subsequent abnormal postures of head and neck (Albanese et al., 2013). This relatively narrow description has been challenged over recent years, however, as evidence accumulates for a range of non-motor symptoms accompanying this disease. The most frequent findings include psychiatric comorbidities (Smit et al., 2016; Stamelou et al., 2012), alterations in sensory processing (including disease-related pain) and sensorimotor integration (Avanzino et al., 2015), sleep disturbances, and fatigue (Conte et al., 2016; Klingelhoefer et al., 2014). Importantly, some of these disturbances (e.g. depression) do not appear to be related to severity of motor difficulties (Stamelou et al., 2012) and can manifest even before onset of the disease suggesting they are an integral part of it (Conte et al., 2016). The topic is highly relevant since non-motor symptomatology (not motor difficulties as such) has a major negative impact on quality of life of dystonia patients (Smit et al., 2016; Zettenberg et al., 2012).

In light of the non-motor symptomatology of CD, there has been an increased effort to investigate neural abnormalities in brain areas beyond basal ganglia circuits. Existing data suggest that CD is a network disorder with several regions affected, including cerebellum, thalamus, frontal cortices, and brainstem (Battistella et al., 2015; Lehèricy et al., 2013; Zoons et al., 2011). Studies report structural abnormalities in these regions, together with alterations within various networks including abnormal hemispheric asymmetry and aberrant plasticity (Battistella et al., 2015; Quartarone and Hallett, 2013). Such extensive brain changes raise the possibility of additional higher-order (or complex) cognitive capacities that could be affected in focal dystonia, and in CD specifically. Evidence for impairments in cognitive functioning is not yet conclusive (Lange et al., 2016; Stamelou et al., 2012), but subtle deficits in specific

domains such as attention, processing speed, and verbal memory have been reported (Kuyper et al., 2011; Romano et al., 2014; Scott et al., 2003; but see Pillon et al., 2006). This is due partly to relatively modest number of conducted studies, and also because existing data have been collected predominantly from samples that comprise different dystonia subgroups. Different forms of dystonia appear to have different phenotypes (Battistella et al., 2015; Romano et al., 2014; Scott et al., 2003), and this should be reflected in the design of studies.

A critical determinant for optimal functioning in our social world is having intact socio-cognitive abilities. This is true especially for a construct that is central to social cognition – Theory of Mind (ToM). ToM is defined as an ability to understand and interpret the intentions, emotions, and beliefs of others in order to predict their behaviour accurately and act accordingly (Frith and Frith, 2003). Currently, there seems to be general agreement that ToM is a multifaceted construct, encompassing cognitive (understanding intentions and beliefs) and affective components (understanding feelings and emotions; e.g. Abu-Akel & Shamay-Tsoory, 2011). The neural network subserving ToM involves posterior cortices primarily, including temporo-parietal junction, superior temporal sulcus, posterior cingulate, and precuneus. The two components of ToM can be dissociated reliably with respect to anterior and subcortical structures, however; whilst the brain circuit engaged during cognitive ToM includes dorsal parts of the anterior cingulate, medial and lateral prefrontal cortex, and the striatum, affective ToM is associated with activity in ventral aspects of these brain regions together with orbitofrontal and inferolateral frontal cortices (Abu-Akel & Shamay-Tsoory, 2011; Poletti et al., 2012). Recently, there has also been an increased interest in the role of the cerebellum in ToM processing, and evidence is accumulating for its involvement in abstract mentalizing tasks (Van Overwalle & Mariën, 2016).

Any disturbance within this diffuse network impacts negatively on ToM abilities. Indeed, deficits in ToM have been reported in other movement disorders, including

Parkinson's (PD; Santangelo et al., 2012) and Huntington's disease (HD; Brüne et al., 2011; Eddy, Sira Mahalingappa, and Rickards, 2012), and essential tremor (ET; Santangello et al., 2013). This has not been investigated in patients with idiopathic CD, however. Abnormalities found within networks involving basal ganglia-thalamo-cortical as well as cerebello-thalamo-cortical pathways in idiopathic dystonia (e.g., Lehèricy et al., 2013) should impact negatively on ToM abilities of these individuals.

The aim of this study was to compare performance of patients with CD and their healthy counterparts on socio-cognitive tasks, including examination of relationships with cognitive functioning and severity of the disease. Given the aforementioned neuroanatomical correlates of ToM and previous research in related populations we hypothesised that disturbances would be observed in CD patients on complex tasks and those assessing social cognition, especially its cognitive component.

Methods

Participants

The sample consisted of 25 patients with idiopathic CD (8males; M_{age}=56.5; SD=12.4; $M_{education}$=13.3; SD=2.8) and 26 age- sex- and education-matched healthy controls (HC; 7males; M_{age}=56.7; SD=11.9; $M_{education}$=13.3; SD=2.6). The patients were recruited from Movement Disorders Outpatient Clinic at St. Anne's University Hospital, Brno, Czech Republic. To eliminate any confounding effects of depressive symptomatology on cognitive and socio-cognitive performance, we used the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) to recruit only participants who did not suffer from clinical depression (MADRS $\leq$ 16; see Ketharanathan et al., 2016; M_{MADRS}=4.55, SD=4.10). Further exclusion criteria included other forms of dystonia and additional neurological/psychiatric condition. All patients were receiving regular treatment with Botulinum toxin A for at least one year. None of the patients received further medication (anticholinergics, neuroleptics, or benzodiazepines) or deep brain stimulation treatment. Severity of the disease was assessed by experienced neurologist using Toronto Western Spasmodic Torticollis rating scale (TWSTRS; Consky et al., 1990). Average duration of CD was 12.6 years (SD=6.8; range 1-25 years). HCs were recruited via flyers at local community centres. Exclusion criteria constituted neurological and/or psychiatric diagnosis. The study was approved by the Institutional Review Board of the St. Anne's University Hospital, and all participants provided informed consent before taking part in the study.

Materials

The entire neuropsychological battery was completed during the morning, in a single session that lasted approximately 3 hours.

Cognitive abilities

Current cognitive status was assessed by selected subtests from Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981): Picture Completion (visual perception and attention to detail), Similarities (abstract verbal reasoning and concept formation), Digit-Symbol Coding (cognitive processing speed), and Arithmetic (working memory and numerical reasoning). The word list from Wechsler Memory Scale-III (WMS-III; Wechsler, 1997) was used as a measure of verbal memory, and the interference score from Stroop test calculated according to Chafetz and Matthews (2004) was our index of cognitive control. Visual attention, task switching and planning abilities, executive control, and verbal abilities were tested by both versions of Trail Making Test (TMT; Lezak, 2004), Tower of London (Shallice, 1982), and lexical (phonemic) and semantic verbal fluency tasks (Spreen and Strauss, 2006), respectively.

Social cognition

The Faux Pas Recognition Test (FPRT) was selected as a measure of cognitive and affective ToM due to its potential to differentiate among populations with neurodegenerative diseases (Bora, Walterfang, and Velakoulis, 2015a). The full version of the test was administered together with self-report methods on related constructs: empathy (Questionnaire of Cognitive and Affective Empathy; QCAE; Reniers et al., 2011) and emotion dysregulation (Difficulties in Emotion Regulation Scale; DERS; Gratz and Roemer, 2004). Both instruments were translated into Czech using a standard procedure of independent forward and backward translation to ensure conceptual equivalency of the items. Final versions of the translated questionnaires were then pre-tested on a large sample of healthy participants (n=255; 88 males; M_{age}=22.5; SD=3.1), which revealed excellent levels of internal consistency (QCAE

cognitive: α=.87; QCAE affective: α=.77; DERS: α=.91). No difficulties with clarity or understanding were encountered with the patients themselves.

Cognitive and affective empathy

The QCAE includes 31 items divided into factors of cognitive and affective empathy: (1) Cognitive empathy is captured by Perspective Taking (seeing things from perspective of the others intuitively) and Online Simulation (effortful understanding of others' perspective by imagining oneself in the situation); (2) Affective empathy consists of Emotion contagion (mirroring of feelings of the others) and Proximal and Peripheral responsivity (affective responsivity in emotionally charged situations within close and detached contexts, respectively). All items are rated on a four-point Likert scale ranging from Strongly Agree to Strongly Disagree.

Emotion dysregulation

Over 36 items, DERS measures six aspects of emotion dysregulation: Non-acceptance of emotional responses, difficulties engaging in goal directed behaviour, impulse control difficulties, lack of emotional awareness, limited access to emotion regulation strategies, and lack of emotional clarity. Participants indicate frequency of their difficulties to regulate emotions on a scale ranging from 1 (almost never – 0-10% of time) to 5 (almost always – 91-100% of time).

Theory of Mind

The FPRT consists of 20 short stories describing everyday interpersonal situations. Participants listen to each story and are asked subsequently to determine whether anyone said something inappropriate of hurtful (i.e. social faux pas; FP). Ten stories include social FP

(FP+) and 10 control stories describe minor misunderstanding (FP-). ToM abilities are assessed using four scores: (1) FP detection (detection), (2) understanding inappropriateness of described behaviour (inappropriateness), (3) understanding intentions of story characters (intentions), (4) belief about unintentionality of FP (belief), and (5) empathy for story character affected by remark (empathy). The first and last aspect tap into affective ToM, while the rest of the scores represent cognitive ToM (Poletti, Enrici, and Adenzato, 2012). To control for the possible influence of cognitive functions of participants (e.g., attention, working memory), printed stories are available to consult for the entire testing time (without time limit). General comprehension is tested by two questions. Since four FPRT protocols did not contain data for all items, they were excluded from further analyses. FPRT responses were coded by two raters independently, with an excellent level of inter-rater reliability achieved (κ=.86).

Data analyses

For subsequent analyses, raw scores from WAIS-R and WMS III subtests were transformed into standard (scaled) scores. The rest of the variables are expressed as raw scores. The FPRT scores were calculated according to the test manual (Stone, Baron-Cohen, and Knight, 1998) and interpreted in terms of separate cognitive and affective ToM (see above; Poletti, Enrici, and Adenzato, 2012). Since a majority of the variables violated assumptions of normality, performance of the two groups was compared by means of the Mann-Whitney test, and relationships between the studied variables were calculated using Spearman correlation. Effect size calculation is indicated by *r* (Cohen, 1998). Statistical analyses were performed in SPSS 23.

Results

Cognition

Compared with HCs, CD patients performed significantly poorer in majority of WAIS-R subtests: Picture Completion (U=186.50; p=.008; r=.37), Arithmetic (U=203.00; p=.021; r=.32), and Digit-Symbol Coding (U=178.00; p=.006; r=.39).

In addition, the CD group was significantly slower at both forms of TMT, displaying difficulties in visuomotor speed and attention (TMT A: U=179.50; p=.006; r=.38) and attention distribution and cognitive flexibility (TMT B: U=193.00; p=.013; r=.35). Patients' performance was also significantly worse in lexical and semantic verbal fluency (U=129.50; p<.001; r=.52; and U=168.00; p=.003; r=.42) and Tower of London tasks (U=170.50; p=.003; r=.41). Immediate (U=191.00; p=.011; r=.36) and delayed verbal memory (U=174.00; p=.004; r=.40) were also significantly poorer in the patients; ability to recognize verbal material was, however, comparable in both groups (p=.772). Similarly, no differences were found in cognitive control measured by interference score of Stroop test (p=.917; for descriptive statistics see Table 1).

Table 1

Social cognition

There were no differences between the groups in self-reported cognitive and affective empathy (QCAE: p=.678; p=.713) and emotion regulation (DERS: p=.955).

Actual performance in the FPRT revealed a different pattern of results, however: overall FPRT scores showed that patients performed significantly worse in FP+ (U=72.50; p<.001; r=.63) as well as FP- stories (U=119.50; p<.001; r=.53). In other words, the patients had difficulties not only in identifying and understanding FP accurately when it was present,

but also perceived inappropriate behaviour more frequently than HCs in stories, where no FP actually occurred.

For FP+ stories, the distinctions between CD patients and controls were significant in both cognitive (inappropriateness: U=114.50; p<.001; r=.51; intentions: U=97.00; p<.001; r=.56; belief: U=112.50; p<.001; r=.51) and affective domains (detection: U=120.00; p=.001 r=.50; empathy: U=142.50; p=.004; r=.43; see Figure 1).

Next, we analysed relationships between socio-cognitive measures and other relevant variables in our patient group. Neither cognitive nor affective empathy (as measured by QCAE) were related to FPRT performance. Emotion dysregulation indexed by DERS was, however, associated negatively with FP intentions (ρ=-.42; p=.038). In other words, better emotion regulation was related to a higher belief that FP was unintentional.

With respect to cognitive status, patients who achieved higher scores in cognitive aspects of ToM – namely, FP intentions and belief – performed significantly better in Arithmetic subtest (ρ=.61, p=.001; ρ=.55; p=.005). The former FP score was also related positively to semantic verbal fluency (ρ=.51, p=.009).

Finally, there was no relationship between severity of CD as defined by TWSTRS and any aspect of cognitive or socio-cognitive functioning (p>.09). We observed, however, association of CD duration and FP inappropriateness (ρ=-.49; p=.014).

Figure1

Discussion

The aim of this study was to add to an existing literature on the non-motor symptomatology of idiopathic isolated CD by examining cognitive status and social cognition in this population.

The most important finding is a considerable decrease of performance in both aspects of ToM identified in non-depressed CD patients compared with HCs. These impairments were significant for all scores, but the largest differences were detected in cognitive component of FPRT – namely, understanding intentions of story characters. When asked about character‘s intentions *(“Why do you think they said it?"*), correct answer should express understanding that the main character did not know or realise something. The CD patients quite frequently provided answers that indicated deliberate behaviour (*e.g. “He was rude and tactless.”, “She was jealous and wanted to make her friend upset.”, “He was showing off.”),* failing to realize that the character said something awkward only because they were not aware of an important detail in that particular situation. Such answers have been reported in patients with frontal lobe impairment (e.g. Gregory et al., 2002).

Interestingly, misinterpretation of social signals was observed in both FP+ and FP- stories. Apart from poorer understanding of individual aspects of social FP, our patients also demonstrated difficulties in interpreting minor social conflicts in otherwise neutral contexts. This cannot be interpreted as a direct consequence of poorer cognitive abilities, however, since the stories were available in front of all participants for the entire testing time. Corresponding errors have been observed in patients with other neurological and neuropsychiatric diagnoses such as HD (Eddy and Rickards, 2015), frontotemporal dementia (Gregory et al., 2002), and Asperger Syndrome (Zalla et al., 2009).

Poorer performance of the patient group in FPRT was in contrast to the data on self-reported cognitive and affective empathy and emotion dysregulation, where patients and controls scored similarly. This particular pattern of results – that is, a decline in both aspects

of ToM in patients but comparable levels in self-report – might be associated with reduced emotional awareness, interoception, or alexithymia (see Moriguchi et al., 2006). Since current knowledge on the structure of social cognition remains limited (Happé, Cook, & Bird, 2017), the relationship between higher and lower levels of socio-cognitive abilities need to be investigated further in future research. Alexithymia is often measured only via self-report (e.g., TAS-20), which might not yield reliable data owing to the possibility of poor emotional introspection in these patients. Furthermore, most recent research shows that there might be two dissociable aspects in alexithymia – affective anomia and affective agnosia (Lane et al., 2015). Any association between ToM and alexithymia should be therefore addressed using other measures such as the Levels of Emotional Awareness Scale (Lane et al., 1990) or the Modified Beth Israel Questionnaire (Taylor, Bagby, and Parker, 1997).

A decline in socio-cognitive abilities and ToM especially is well-documented in other movement disorders involving the basal ganglia (Poletti, Enrici, and Adenzato, 2012; Bora, Walterfang, and Velakoulis, 2015b), but the majority of published studies do not distinguish between affective and cognitive component of FPRT. Moreover, the manner of scoring of this test varies, so it is relatively problematic to determine which aspect – when considering FPRT in particular – is impaired more severely. Using different socio-cognitive tasks, existing evidence seems to point largely in the direction of cognitive ToM being affected in ET and PD (Santangelo et al., 2013; Poletti, Enrici, and Adenzato, 2012), although most recent studies show deficits also in affective ToM for PD patients (Adenzato and Poletti, 2013; Bora, Walterfang, and Velakoulis, 2015b). Additionally, both components seem to be impaired in HD (Brüne et al., 2011; Eddy, Sira Mahalingappa, and Rickards, 2012). Abnormal performance in ToM tasks manifests in neurological populations very early in the course of disease (Adenzato and Poletti, 2013; Eddy and Rickards, 2015) and tends to get more pronounced over time (Poletti, Enrici, and Adenzato 2012).

Regarding cognitive status, significantly worse performance of CD patients was shown in attention, set-shifting capacity, working memory, processing speed, planning, verbal memory and verbal fluency in particular. Similar patterns of cognitive impairments have been reported already in patients with focal dystonia and specifically CD (Lange et al., 2016; Romano et al., 2014). Furthermore, cognitive decline was not associated with severity of the disease, as corroborated previously by studies with similar study samples (Alemán, de Erausquin, and Micheli, 2009; Romano et al., 2013).

Although the relationship between social cognition and executive function in populations with neurodegenerative diseases is still a subject of ongoing discussion (Poletti Enrici, and Adenzato 2012; Adenzato and Poletti 2013; Eddy et al., 2013), some studies do report poorer social cognition in individuals with compromised executive function; for instance, verbal fluency appears to be associated with social cognition reliably in patients with PD, ET, and HD (Bora, Walterfang, and Velakoulis 2015b; Santangelo et al., 2013; Eddy, Sira Mahslingappa, and Rickards, 2012), and working memory demands seem to reduce errors made by PD patients on false-belief task (Eddy et al., 2013). This association was confirmed also in our sample, with patients' cognitive ToM related positively to working memory and verbal semantic fluency.

Observed results fit with the neuroanatomical correlates of CD, which points towards network-level disturbance encompassing multiple systems – not only cortico-basal-ganglia-thalamo-cortical- but also cortico-ponto-cerebello-thalamo-cortical loops with a recent focus on the role of cerebellum (Filip, Lungu, and Bareš, 2013; Lehèricy et al., 2013). Altered functioning of these large-scale circuits explains not only motor symptomatology, but also impairments in cognition and social cognition; it is becoming increasingly obvious that structures traditionally associated with motor processing such as basal ganglia and cerebellum are involved in numerous aspects of social cognition (Kemp et al., 2013; Van Overwalle &

Mariën, 2016). More specifically, decline in ToM as well as executive function in CD patients might be related to disturbances in fronto-striatal circuits implicated in CD (Kemp et al., 2013). We observed the largest differences in the cognitive component of ToM, which is thought to be processed by dorsolateral prefrontal cortex and dorsal striatum among other regions (Poletti, Enrici and Adenzato, 2012). This corresponds with neuroimaging data of idiopathic dystonia that points toward dysfunction in the putamen and caudate nucleus (e.g., Lehèricy et al., 2013). Further, grey matter changes in CD were reported in the cingulate cortex and precuneus (Piccinin et al., 2015) – additional brain regions implicated in ToM processing.

This is the first study to report disturbances in social cognition in patients with CD. Although we have investigated a relatively small sample, we observed medium to large effect sizes for differences in cognitive and socio-cognitive abilities. Since our clinical sample was defined specifically to comprise patients with CD without clinically significant depressive symptomatology, however, the extent to which our results can be generalised to the population of CD patients in whom depression is of high incidence (e.g. Stamelou et al., 2012) or other dystonia subtypes is unknown. Secondly, because our sample included patients with a range of disease durations our data offer no insights into socio-cognitive difficulties in various stages of CD. However, our correlations suggest that socio-cognitive decline might be worsening with longer disease duration. Poor performance on the social-cognitive task we have revealed was associated with working memory and semantic verbal fluency, but not with severity of the disease. Another question worth investigating in the future is whether the decline in ToM we have observed impacts upon the quality of life in CD patients. Although depressive symptoms, disease-related pain and disability are among the most important predictors of quality of life in the CD population (Kuyper et al., 2011; Stamelou et al., 2011; Smit et al., 2016), difficulties in social interaction are also likely to contribute to worsened

quality of life. Since we did not administer any measure on health-related quality of life, no inferences can be made with regard to this relationship on the basis of our data. Current research in similar neurodegenerative diseases is inconclusive; while some studies report difficulties in cognitive ToM being associated with poorer quality of life (Santangelo et al.,2012), others report no such relationship (e.g., Santangelo et al., 2013). As mentioned above, our data do seem to suggest that the patients with CD might not be aware of their difficulties in social interaction. As such, it is worth investigating reports of social interactions and quality of life not only from the patients themselves, but also from their relatives or close friends.

Future studies are required to replicate our findings on larger samples consisting of patients with and without depressive symptomatology, and to investigate additional socio-cognitive aspects, their relationship with cognition, and the neural basis of these disturbances. Incorporating socio-cognitive tasks into routine neuropsychological assessment might help to understand challenges in every-day functioning of affected individuals and their families (Adenzato and Poletti 2013).

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Figure 1. Differences in cognitive and affective components of FPRT

Note: FPRT responses in patients (dark) and controls. Cognitive variables are highlighted;*p<.01;**p<.001

Table 1. Descriptive statistic for cognitive measures

Note: Parametric indices are reported here to allow comparisons with other studies. SD=standard deviation