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Clinical Study

Motor sequence learning and motor adaptation in primary cervical dystonia

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ABSTRACT

Motor sequence learning and motor adaptation rely on overlapping circuits predominantly involving the basal ganglia and cerebellum. Given the importance of these brain regions to the pathophysiology of primary dystonia, and the previous finding of abnormal motor sequence learning in DYT1 gene carriers, we explored motor sequence learning and motor adaptation in patients with primary cervical dystonia. We recruited 12 patients with cervical dystonia and 11 healthy controls matched for age. Subjects used a joystick to move a cursor from a central starting point to radial targets as fast and accurately as possible. Using this device, we recorded baseline motor performance, motor sequence learning and a visuomotor adaptation task. Patients with cervical dystonia had a significantly higher peak velocity than controls. Baseline performance with random target presentation was otherwise normal. Patients and controls had similar levels of motor sequence learning and motor adaptation. Our patients had significantly higher peak velocity compared to controls, with similar movement times, implying a different performance strategy. The preservation of motor sequence learning in cervical dystonia patients contrasts with the previously observed deficit seen in patients with DYT1 gene mutations, supporting the hypothesis of differing pathophysiology in different forms of primary dystonia. Normal motor adaptation is an interesting finding. With our paradigm we did not find evidence that the previously documented cerebellar abnormalities in cervical dystonia have a behavioral correlate, and thus could be compensatory or reflect "contamination" rather than being directly pathological.

1. Introduction

Historically considered a disorder of the basal ganglia, there is now evidence for a wider network of neuroanatomical structures involved in the pathophysiology of dystonia. Recent research has particularly focused on the cerebellum against the background of clinical reports of patients with cerebellar lesions presenting with dystonia and animal models of dystonia in which the cerebellum appears to play a critical pathophysiological role [1]. Radiological studies have demonstrated an increase in metabolic activity in the basal ganglia, supplementary motor areas and the cerebellum in a variety of forms of primary dystonia [2–4]. Additionally, diffusion tensor imaging data have demonstrated reduced integrity of cerebellothalamic tracts in DYT1 and DYT6 dystonia, which correlates with the clinical penetrance of the mutation [5]. Abnormal patterns of cerebellar activation are also seen using functional MRI blood oxygen level dependent techniques in motor tasks such as tapping and eye blinking in patients with dystonia of the corresponding regions [6,7]. Preliminary neurophysiological data lends support to the notion that the cerebellum is affected in patients with primary focal dystonia of the neck or hand, with disturbed eye blink conditioning occurring in these patients [8]. The absence of overt cerebellar signs on clinical examination in dystonia, however, suggests that the experimentally observed cerebellar dysfunction may either be too mild to be expressed clinically, might simply reflect unimportant "contamination" of a structure directly connected to the basal ganglia, or might represent a compensatory response to the primary pathophysiology within the basal ganglia.

Behavioural paradigms can be used to study function of neuroanatomical structures likely to be involved in dystonia. Two of these are motor sequence learning (MSL; the incremental acquisition of sequential movement patterns) and motor adaptation (MA; paradigms that test capacity to compensate for environmental changes). Serial reaction time tasks can be used to study MSL; following training blocks with randomly presented targets, sequence learning is demonstrated by faster reaction times to sequence presentation compared with random trials [9]. MA paradigms require

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participants to implicitly adapt to changes in the environment caused by experimental manipulations such as altered visual feedback produced by prisms, perturbations to visual feedback on a computer monitor or force fields applied to movements of a robotic limb. The anatomical substrate of implicit sequence learning is extensive but is thought to be critically dependent on the basal ganglia while MA requires an intact cerebellar circuitry [10–13].

Impaired MSL has been described in both manifesting and non-manifesting patients with the DYT1 mutation, but is normal in patients with DYT6 mutations [3,14]. To our knowledge MA has not previously been assessed in any patients with dystonia. Here we hypothesized that MSL would be impaired in cervical dystonia patients due to the presumed basal ganglia dysfunction that underlies the pathophysiology of this condition, but that MA would be normal, reflecting a compensatory rather than a primary pathological role for the cerebellum in this form of primary dystonia.

2. Methods

2.1. Participants

We recruited 12 patients (nine women, three men; mean age 58.8 ± standard deviation 9.6 years, range 40–77 years) with idiopathic cervical dystonia from the Movement Disorder Outpatient Clinic at the National Hospital for Neurology and Neurosurgery, Queen Square London, UK, and 11 healthy control subjects (seven women, four men) who were matched for age (mean age 55.4 ± standard deviation 9.6 years, range 43–70 years) and years in education. Disease duration ranged from 6 to 36 years. All participants were right-handed and without cognitive impairment or psychiatric disease. Patients did not suffer from head tremor and there was no segmental spread of dystonia to the hands. Mobility at the elbow and shoulder joints was unrestricted and painless in all subjects. Dystonia severity was evaluated with the Toronto Western Spasmodic Torticollis Rating Scale [15] ranging from 5 to 49 out of 85 points. All patients receiving botulinum toxin treatment had their last injections at least 3 months before the study. Informed consent was obtained and the study was approved by the local Ethics Committee.

2.2. General characteristics of the motor task

Subjects were seated in front of a computer screen with a joystick secured to the table directly in front of them. Subjects were instructed to move the cursor representing the joystick position from a central starting point on the computer screen to one of eight radial targets, which were evenly spaced 45° apart and displayed as red squares (1 cm^2). Subjects were asked to move the cursor into the target as fast and accurately as possible upon target appearance. They were required to retain the cursor in the target until it switched to green (1 second following entrance to the square). At this point subjects were instructed to release their grip on the joystick handle, allowing the spring-loaded device to re-center for the next trial. There were three task conditions. In the motor reference task (R), targets were presented in a pseudo-randomized order in blocks of 40 trials. We used four random blocks (R1–R4) at the beginning of the experiment to familiarize subjects with the task. Further random blocks were inserted after the sequence learning (R5, R6) and adaptation tasks (R7, R8). In the MSL task, a sequence of six targets was repeated seven times per block (42 movement trials). The presence of a sequence was not revealed to the subjects. Four identical sequence blocks (S1–S4) were presented. In the motor adaptation block (MAB) the order of target presentation was pseudo-randomized and consisted of 40 movement trials. The direction of the cursor movement on the screen was rotated clockwise by 30° relative to hand movement.

Patients and controls performed 13 blocks in the following order: R1-R2-R3-R4-S1-S2-S3-S4-R5-R6-MAB-R7-R8. The total time of the experiment was 1 hour with opportunities for patients to rest between random blocks. No patient reported problems with fatigue or concentration.

2.3. Data acquisition and analysis

Targets were presented and data acquired using MATLAB (version 7; The MathWorks, Natick, MA, USA) with Cogent Toolbox, interfaced with a CED 1401 analogue digital converter device (Cambridge Electronic Design, Cambridge, UK). Data were stored in a computer for offline analysis.

The following parameters were measured for each movement trial in the MSL task: onset time (OT), the time from target presentation to movement onset; movement time (MT), the time from movement onset to target hit; response time (RT), the time from target presentation to target hit (sum of OT and MT); peak velocity (pV); directional error (DE), the angle between the ideal path (straight line) and trajectory taken at pV, which was also the parameter used for MA. A directional error of <22° was set to identify movements to the correct target [2]. In addition, a ratio between the length of the cursor path recorded in the trial and the length of a straight line connecting the start point and the target was calculated (displacement ratio) but data are not shown due to non-significant differences between the groups.

Means of parameters across each block (R, MSL) and means across every ten movement trials (MAB) were entered in separate repeated measures analysis of variance with *post hoc* comparisons to assess the effects of GROUP, BLOCK and their interaction. The Greenhouse-Geisser method was used to correct for non-sphericity. Effects were considered significant if $p < 0.05$. All values are given as mean ± standard deviation.

3. Results

3.1. Motor reference task

pV was significantly higher in patients with cervical dystonia (542.5 ± 71.3 mm/s) compared to controls (463.2 ± 83.8 mm/s) indicated by a significant effect of GROUP ($F_{(1,21)} = 6.0$, $p = 0.023$). All subjects showed similar levels of improved motor performance over the course of the four blocks, revealed by a significant effect of BLOCK for OT ($F_{(1.1,23.5)} = 9.7$, $p = 0.004$), MT ($F_{(1.4,30.1)} = 25.1$, $p < 0.001$), RT ($F_{(1.3,27.7)} = 23.7$, $p < 0.001$), and DE ($F_{(3,63)} = 9.7$, $p < 0.001$) in the absence of any GROUP × BLOCK interaction. Both groups achieved stability in movement and temporal parameters by block R4, indicated by a lack of significant difference in any parameters between block R3 and R4 ($p > 0.90$ for all comparisons).

3.2. Motor sequence learning

To investigate MSL we compared the performance in block S4 with R5. Both groups successfully learned the sequence, indicated by a significant effect of BLOCK for OT ($F_{(1,21)} = 20.9$, $p < 0.001$), MT ($F_{(1,21)} = 6.8$, $p = 0.016$), RT ($F_{(1,21)} = 13.6$, $p = 0.001$) and DE ($F_{(1,21)} = 4.4$, $p = 0.048$). Figure 1 shows the mean ± standard error of each parameter for both groups plotted against block. As in the motor reference task, we found a significant GROUP effect for pV and additionally for DE. *Post hoc* analyses revealed this to be due to a significantly higher pV in patients (563.6 ± 75.9 mm/s) compared to controls (491.5 ± 71.9 mm/s, $p = 0.030$), but controls had overall lower DE compared with patients (7.1 ± 1.3° *versus*