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Abnormal interhemispheric inhibition in musician's dystonia – Trait or state?

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ABSTRACT

Introduction: A clustering of relatives with dystonia has been reported in families with musician's dystonia suggesting a genetic contribution to this disease. The aim of the present study was to determine whether interhemispheric inhibition (IHI) measured with transcranial magnetic stimulation is impaired in healthy family members rendering it a suitable endophenotypic marker for musician's dystonia.
Methods: Patients with musician's hand dystonia (n = 21), patients with sporadic writer's cramp (n = 15), their healthy family members (n = 27), healthy musicians (n = 12) and healthy non-musicians (n = 12) were included. An extended interview about the family history and musical activity was performed. IHI in both hemispheres was measured using transcranial magnetic stimulation.
Results: A stepwise regression analysis revealed musical activity ($p = 0.001$) and a family history of dystonia ($p = 0.008$) but not dystonia per se, age, handedness or gender as relevant factors modulating IHI.
Conclusion: These data support the notion of a genetic background of musician's hand dystonia and suggests that reduced IHI is a possible endophenotypic marker of this disorder.

1. Introduction

Focal hand dystonia is a movement disorder that impairs hand control during certain tasks such as writing or playing a musical instrument [1,2].

A clustering of focal hand dystonia has been reported in families of index patients with musician's dystonia suggesting autosomal dominant inheritance with very low penetrance [3,4].

This is inline with reports on other types of dystonia including cervical dystonia. In these patients and their first-degree relatives impaired temporal discrimination of sensory stimuli appears to be an endophenotype inherited in an autosomal dominant fashion with low penetrance [5–7]. Similarly, abnormal vibration induced illusions might be an endophenotypic trait in patients with focal dystonia [8]. Interhemispheric inhibition (IHI) determined with paired-pulse transcranial magnetic stimulation (TMS) was reported to be reduced in the affected hemisphere in patients with focal hand dystonia in the study of Nelson et al. [9,10] In the studies of Beck et al. and Sattler et al. [11,12] it was reduced in those dystonia patients who also had mirror dystonia. IHI that is mediated by transcallosal fibres [13,14] may represent a marker of bimanual control and could therefore also be a valuable endophenotypic feature in dystonia patients.

Highly skilled hand functions require independence of hand

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movements. Reduced IHI associated with mirror movements could be a contributing factor to the development of disturbed hand function, particularly in highly demanding tasks like playing an instrument at a professional level [15].

In the present study, IHI was tested in musician's hand dystonia and writer's cramp patients, their healthy first-degree family members and two control groups (healthy musicians and healthy non-musicians).

Our aim was to further elucidate the impact of a familial background of dystonia as a marker of a genetic susceptibility, the presence of dystonia as a sign and musical activity as an index of hand skill function on IHI to determine whether IHI could serve as an endophenotypic marker for focal hand dystonia.

Our main hypotheses were i) that musical activity is associated with stronger IHI and ii) that a positive family history of dystonia reflecting genetic susceptibility and dystonia as a sign are associated with weaker IHI.

2. Methods

2.1. Subjects

Twenty-one professional musicians with musician's hand dystonia (14 men, mean age 50 years (9 ± SD), range 35–80 years), 15 patients with sporadic writer's cramp (7 men, mean age 52 years (15 ± SD), range 26–73 years), 27 healthy first-degree family members of the patients with musician's hand dystonia or writer's cramp (12 men, mean age 41 years (20 ± SD), range 19–77 years), 12 professional healthy musicians (7 men, mean age 48 years (8 ± SD), range 36–59 years) and 12 healthy non-musicians (7 men, mean age 50 years (5 ± SD), range 40–57 years) participated in the study. Patients and their relatives were recruited by experienced movement disorders specialists at the Hanover Institute of Music Physiology and Musician's Medicine and the Movement Disorders Clinics in the Neurology Departments of the University hospitals of Lübeck and Hamburg, Germany between 2010 and 2012. A diagnosis of musician's hand dystonia and writer's cramp was made according to published standard criteria [16,17]. Healthy musicians and healthy non-musicians were recruited by the same examiners in Lübeck or Hamburg, Germany. Clinical details of participants are given in Table 1.

The vast majority of participants were right-handed (68 right handed, 6 left handed and 5 ambidextrous) according to the Edinburgh handedness inventory [18](Table 1). Gender distribution, age and handedness did not differ significantly between groups. Healthy musicians were matched for instrument groups to the musician's hand dystonia patients. All musician's hand dystonia and writer's cramp patients had isolated dystonia with simple task-specific cramps and the majority (43 of 46) only had unilateral symptoms on their right hand. None of the patients had mirror dystonia. They had not received botulinum toxin injections for at least three months prior to the study. Twelve musician's hand dystonia patients had a positive family history of dystonia according to the examination procedure published previously [4]. Thus, 12 cases with familial musician's hand dystonia, 9 with sporadic musician's hand dystonia and 15 with sporadic writer's cramp were included. The musical activity of all participants was classified into the categories professionals, amateur and no musician. All participants provided written informed consent. The study was approved by the Hamburg Ethics Board.

2.2. EMG recording

Subjects were seated in a comfortable armchair. A TMS coil and subject head holder (Brainsight TMS frame; Roque Research Inc. Montreal; Canada) were adjusted to a frame surrounding the subjects' chair. The head holder fixed to the frame allowed for a comfortable sitting position with the subjects' heads resting on the holder and neck muscles relaxing. The coil holder ensured an accurate positioning of the TMS coils onto the subjects' heads. The arms of the subjects were supported by a pillow so that arm muscles were completely relaxed. Subjects were instructed to relax but to keep their eyes open throughout the experiment.

EMG was recorded with disc surface electrodes placed over first dorsal interosseous muscles bilaterally, using a belly-tendon montage. In addition to the target first dorsal interosseous muscle where motor evoked potential (MEP) were measured, contralateral first dorsal interosseous muscle was also recorded to capture baseline EMG activity during measurements. EMG signals were continuously monitored acoustically with loudspeakers and visually by means of an oscilloscope. The ground electrode was placed at the wrist. EMG signals were amplified and filtered (20 Hz–1 kHz) with a D360 amplifier (Digitimer Limited, Welwyn Garden City, UK). The signals were sampled at 5000 Hz, digitised using a laboratory interface (Micro1401, Cambridge Electronics Design (CED), Cambridge, UK) and stored on a personal computer for display and later off-line data analysis.

2.3. TMS technique

Measurements were performed with two *Magstim* 200 magnetic stimulators, each connected with a figure-of-eight shaped coil with an outer winding diameter of approximately 70 mm ("baby coil"; Magstim Company, Whitland, Dyfed, UK) with handles perpendicular to the coil windings ("Branding-Iron-Style") both for conditioning pulse and test pulse to measure IHI.

The coil was placed tangentially to the scalp at a 45° angle away from the midline, approximately perpendicular to the line of the central sulcus inducing a posterior to anterior directed current in the brain. We determined the optimal position for activation of the first dorsal interosseous muscles by moving the coil in 0.5 cm steps around the presumed primary motor hand area of both hemispheres. The sites where stimuli of slightly suprathreshold intensity consistently produced the largest MEPs with the steepest negative slope in the corresponding first dorsal interosseous muscle (referred to as "motor hot spot") were marked with a wax pen. TMS coils were fixed to the frame using coil holders and placed at the marked stimulation sites.

Resting motor threshold was defined as the minimum stimulus intensity that produced an MEP of more than 50 μV in 5 out of 10 consecutive trials. It was expressed as a percentage of maximum stimulator output and was determined bilaterally over the primary motor hand areas. The intensity of the test pulse was set at an intensity that, when it was given alone, would evoke an EMG response of approximately 1 mV peak-to-peak size in the left first dorsal interosseous muscle.

IHI was probed using a conditioning-test paradigm. Conditioning pulses were applied to left and test pulse given to right primary motor hand area and vice versa. The intensity was always set at 120% of the resting motor threshold of the conditioned primary motor hand area.

IHI was tested at interstimulus intervals (ISIs) of 6, 7, 8, 9 and 10 ms. These six conditions (test pulse was given alone for 20 times and five conditioning pulse at different ISIs 10 times each) were applied randomly in a block of 70 trials.

2.4. Data analyses

Measurements were made on individual trials. Mean peak-to-peak MEP amplitudes were determined. IHI was calculated for