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Abnormalities in the face primary motor cortex in oromandibular dystonia

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See Editorial, pages 132–133

HIGHLIGHTS

- The excitability and sensorimotor integration of face and hand primary motor cortex in oromandibular dystonia (OMD) was studied.
- In OMD, sensorimotor integration and cortical excitability were altered specifically in face primary motor cortex.
- In OMD, the integration between sensory inflow and motor output is disrupted at cortical level with topographic specificity.

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ABSTRACT

Objective: To comprehensively investigate excitability in face and hand M1 and sensorimotor integration in oromandibular dystonia (OMD) patients.
Methods: Short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), short (SAI) and long (LAI) afferent inhibition were investigated in face and hand M1 using transcranial magnetic stimulation protocols in 10 OMD patients. Data were compared with those obtained in 10 patients with focal hand dystonia (FHD), in 10 patients with blepharospasm (BSP), and 10 matched healthy subjects (HS).
Results: Results demonstrated that in OMD patients SICI was reduced in face M1 ($p < 0.001$), but not in hand M1, compared to HS. In FHD, SICI was significantly impaired in hand M1 ($p = 0.029$), but not in face M1. In BSP, SICI was normal in both face and hand M1 while ICF and LAI were normal in all patient groups and cortical area tested. SAI was significantly reduced ($p = 0.003$) only in the face M1 of OMD patients.
Conclusions: In OMD, SICI and SAI were significantly reduced. These abnormalities are specific to the motor cortical area innervating the muscular district involved in focal dystonia.
Significance: In OMD, the integration between sensory inflow and motor output seem to be disrupted at cortical level with topographic specificity.

1. Introduction

Idiopathic oromandibular dystonia (OMD) is a rare movement disorder characterized by involuntary and sustained contractions of facial, masticatory and lingual muscles, causing involuntary jaw opening or closing (Defazio et al., 2020; Manzo et al., 2022; Yoshida, 2018). OMD symptoms interfere with chewing, speech, swallowing, and facial expressions, resulting in social embarrassment and negatively impacting daily functioning, mood, and quality of life (Defazio et al., 2020; Manzo et al., 2022; Yoshida, 2018). OMD is often associated with blepharospasm (BSP) (Marsden, 1976; Hallett et al., 2017).

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Neurophysiological investigations in patients with OMD, with and without BSP, have demonstrated abnormalities in brainstem and cortical motor areas. The finding of an enhanced recovery cycle of the blink reflex and masseter inhibitory reflex (Berardelli et al., 1985; Cruccu et al., 1991; Thompson et al., 1986; Tolosa et al., 1988) in the absence of structural abnormalities in these pathways (Pauletti et al., 1993) suggests a possible role of increased brainstem interneuron excitability. This may result from altered inhibitory control exerted by the basal ganglia and cortical areas on brainstem reflex circuits. A transcranial magnetic stimulation (TMS) study showed a significantly reduced cortical silent period (Curra et al., 2000) in face muscles after stimulation of the primary motor cortex (M1). The authors proposed that the shortened silent period in OMD reflects cortical inhibitory interneuron hypoactivity in M1 (Curra et al., 2000). Overall, neurophysiological studies have suggested that OMD is characterized by hyperexcitability of motor circuits at the brainstem and cortical level (Berardelli et al., 1985; Cruccu et al., 1991; Curra et al., 2000; Pauletti et al., 1993; Thompson et al., 1986; Tolosa et al., 1988). However, this conclusion was based on studies performed in small samples of OMD patients or in patients with both BSP and OMD. It is still unknown whether loss of inhibition involves all inhibitory cortical circuits or is specific to only some inhibitory interneurons, and whether the loss of inhibition is topographically specific, involving only the face motor area or extending beyond the body parts affected by dystonia in OMD.

In addition to changes in cortical excitability, it is also suggested that altered sensorimotor integration in OMD may play a role in the pathophysiology of this condition (Abbruzzese and Berardelli, 2003; Manzo et al., 2022). In line with this hypothesis, previous studies showed a defective interplay between sensory input and motor output in other forms of idiopathic focal dystonia (Avanzino et al., 2015; Conte et al., 2019; Desrochers et al., 2019).

Therefore, the first aim of this work was to comprehensively investigate excitability changes in the M1 area controlling face muscles (face M1) in patients with OMD. For this purpose, inhibitory and facilitatory intracortical circuit activity, as assessed with short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF), was investigated after stimulation of face M1 and recording from face muscles. To assess whether abnormal sensorimotor integration plays a role in OMD, we also studied short-afferent (SAI) and long-afferent inhibition (LAI) in this condition. To determine whether possible cortical abnormalities in OMD are specific to face M1, we compared the results of SICI, ICF, SAI and LAI obtained after face M1 stimulation with those obtained after hand M1 stimulation in OMD patients. To further study the topography of M1 abnormalities, we also tested the same TMS paradigms in patients with focal hand dystonia (FHD) and BSP since these are models of dystonia that respectively affect body parts that are remote and close to the lower face muscles involved in OMD. Finally, we studied the possible correlations of neurophysiological findings with motor symptom severity in OMD patients. To check for possible abnormalities, data were compared with those obtained from 10 matched healthy subjects (HS).

2. Methods

2.1. Participants

Ten patients with OMD, 10 with FHD, 10 with BSP, and 10 sex- and age-matched HS were enrolled in this cross-sectional study (Table 1). Patients were recruited from the movement disorders outpatient clinic at Sapienza University of Rome and HS were enrolled at the Department of Biomedical Sciences at the University of Sassari.

Exclusion criteria were: duration score $\geq$3.5 and/or a motor severity score of 4 on the Unified Dystonia Rating Scale (UDRS); secondary forms of dystonia; or other diseases of the nervous and/or stomatognathic system. Botulinum toxin injection was performed at least three months before the testing sessions, and patients did not take drugs interfering with central nervous system activity. The study was approved by the local ethics committees (Prot. 2136/CE/15, ASL 1 Sassari and Prot. 329/13 Rif. 2723/14.03.2013 Policlinico Umberto I), and all subjects were required to sign a written informed consent prior to participation in the study.

Clinical evaluation was performed by neurologists expert in movement disorders before the experimental session through the administration of the Oromandibular Dystonia Rating Scale (OMDRS) and Oromandibular Dystonia Questionnaire (OMDQ-25) (Yoshida, 2020) for patients with OMD, the Arm Dystonia Disability Scale (ADDS) for patients with FHD (Albanese et al., 2013), and the Blepharospasm Severity Rating Scale (BSRS) for patients with BSP (DeFazio et al., 2015).

2.2. Transcranial magnetic stimulation (TMS)

TMS was performed through a 70-mm figure-of-eight-shaped coil connected to a Magstim 200 stimulator through a Bistim module (Magstim Co., Whitland, and Dyfed, UK). For the contralateral depressor anguli oris (DAO) and first dorsal interosseous (FDI) muscle, the optimal stimulation site (hot spot) was carefully searched over the left hemisphere and then marked in order to maintain the same coil position throughout the experiments using a soft tip pen. For the DAO, the coil was held to the scalp with the handle pointed posteriorly and laterally, at approximately 30–45 degrees to the interhemispheric line (Pilurzi et al., 2013; Pilurzi et al., 2020), while for the FDI the coil was pointed backwards and laterally at 45 degrees from the midline. The hotspot for the DAO was approximately 4 cm anterior and 8 cm lateral from the Cz with the coil handle pointed posteriorly and laterally, at approximately 30–45 deg to the interhemispheric line (Kujirai et al., 2006; Pilurzi et al., 2013). The resting motor threshold (RMT) was taken as the lowest TMS intensity that elicited MEPs of 0.05 mV in the relaxed muscle in at least 5 out of 10 consecutive trials and was expressed as a percentage of the maximum stimulator output (MSO). In all experiments, at least 10 MEPs for each condition were used for the analysis.

2.3. Electrical stimulation (ES)

Since previous studies have demonstrated that in stimulating face M1, SAI depends on the stimulation of the trigeminal nerve while LAI depends on facial nerve stimulation (Pilurzi et al., 2013; Pilurzi et al., 2020), ES was applied to the mentalis branch of the right trigeminal nerve and to the mandibular branch of the right facial nerve for SAI and LAI recordings, respectively. To elicit SAI and LAI in hand M1, the right median nerve at the wrist was stimulated. ES was delivered using a pair of cup electrodes with distal cathode connected to a constant-current stimulator (model DS7; Digitimer Ltd). Single square-wave pulses (0.2 ms duration) were delivered, with a stimulus intensity set at an intensity of three times the subjective perceptual threshold (PT) for the trigeminal nerve. On the other hand, for both facial and median nerve stimulations, ES was delivered at an intensity able to evoke a small stable compound muscle action potential (CMAP) in the right DAO and FDI, respectively.

2.4. Electromyography (EMG)

The DAO and FDI muscles were used for TMS investigations as target muscles for face and hand muscles. EMG was recorded using

Table 1
Demographic, clinical and neurophysiological features of the study's participants.

Participants Features		HS	OMD	FHD	BSP	Statistics
Demographic	Age (years)	53.6 ± 5.35	63.5 ± 4.71	48.3 ± 5.05	62.0 ± 3.27	$F_{3,39}$ = 2.369; *p = 0.087*
	Gender	4 M:6F	5 M:5F	5 M:5F	3 M:7F	$F_{3,39}$ = 0.347; *p = 0.791*
Clinic	Disease duration (years)	-	6.89 ± 1.24	14.70 ± 3.30	10.11 ± 0.99	$F_{3,39}$ = 3.108; *p = 0.062*
	OMDRS	-	30.30 ± 15.60	-	-	-
	OMDQ-25	-	33.50 ± 6.67	-	-	-
	ADSS	-	-	69.75 ± 3.36	-	-
	BSRS	-	-	-	7.30 ± 0.84	-
Neurophysiology	RMT DAO (%MSO)	58.20 ± 1.37	58.60 ± 1.86	58.33 ± 1.27	58.80 ± 1.23	$F_{3,39}$ = 0.033; *p = 0.992*
	RMT FDI (%MSO)	45.80 ± 2.55	46.40 ± 1.48	49.89 ± 1.15	50.30 ± 1.20	$F_{3,39}$ = 1.823; *p = 0.161*
	MEP DAO (mV)	0.28 ± 0.04	0.20 ± 0.05	0.21 ± 0.05	0.26 ± 0.05	$F_{3,39}$ = 0.759; *p = 0.508*
	MEP FDI (mV)	1.52 ± 0.50	0.73 ± 0.25	1.22 ± 0.26	0.69 ± 0.16	$F_{3,39}$ = 1.587; *p = 0.201*
	PT median nerve (mA)	2.14 ± 0.23	2.20 ± 0.16	2.16 ± 0.25	2.55 ± 0.25	$F_{3,39}$ = 0.740; *p = 0.535*
	PT mental nerve (mA)	1.03 ± 0.7	1.17 ± 0.09	1.08 ± 0.08	1.09 ± 0.09	$F_{3,39}$ = 0.583; *p = 0.683*
	PT facial nerve (mA)	1.38 ± 0.08	1.67 ± 0.09	1.59 ± 0.07	1.49 ± 0.09	$F_{3,39}$ = 2.329; *p = 0.091*

Abbreviations**:** HS, healthy subjects; OMD, oromandibular dystonia; FHD, focal hand dystonia, BSP, blepharospam; OMDRS, oromandibular dystonia rating scale; OMDQ-25, Oromandibular Dystonia Questionnaire; ADSS, Arm Dystonia Disability Scale; BSRS, Blepharospasm Severity Rating Scale; RMT, resting motor threshold; MSO, MSO, maximum stimulator output; mV, millivolts, depressor anguli oris muscle; FDI, first dorsal interosseus, PT perceptive threshold; mA, milliampère. The table represents means ± standard error of the mean (SEM).

9-mm diameter Ag-AgCl surface electrodes from the right DAO and FDI muscles. For the DAO, the active electrode was positioned at the midpoint between the angle of the mouth and the lower border of the mandible and, the reference electrode above the mandible border and 1 cm below the active electrode, and the ground electrode over the right forehead (Ginatempo et al., 2019a; Ginatempo et al., 2022; Pilurzi et al., 2013; Pilurzi et al., 2020). For the FDI, the active electrode was located over the muscle belly and the reference electrode at the second finger metacarpophalangeal joint and the ground electrode over the forearm. Unrectified EMG signals were recorded (D360 amplifier, Digitimer Ltd, Welwyn Garden City, UK), amplified (x1000), filtered (bandpass 3–3000 Hz), and sampled (5 kHz per channel; window frame length: 250-ms width, 100 and 150 ms pre-stimulus and post stimulus respectively) using a 1401 power analog-to-digital converter (Cambridge Electronic Design, Cambridge, UK) and Signal 6 software on a computer and stored for offline analysis.

Patients with persistent clinical manifestations (i.e., duration ≥75% of the time) and/or patients with extreme lower face, jaw, or tongue motor symptom severity (jaw opening or tongue protrusion >75% of possible range, forced jaw clenching, or intense grimacing) were excluded to minimize possible contamination of resting EMG by involuntary orofacial movements. In addition, each trace was visually inspected during the registration and were rejected online if there present even slight contamination by muscle activity in the pre-stimulus EMG period. Further offline rejection of traces contaminated by EMG activity was performed, when necessary, during data analysis.

2.5. Experimental design

Intracortical excitability as well as the sensorimotor integration of face and hand M1 were studied in OMD, FHD, and BSP patients and HS. During the experiments, subjects sat in a comfortable chair and were asked to stay relaxed but alert. The experimental procedure in patients with OMD and in those with other forms of dystonia was performed by the same researchers.

2.5.1. Experiment 1. Excitability of intracortical inhibitory and facilitatory circuits over face and hand M1 in OMD and FHD patients and HS

Cortical excitability of both face and hand M1 was assessed in OMD and FHD patients and data were compared with those obtained in HS. The experiment was performed with two different blocks for DAO and FDI recordings. SICI and ICF were tested in each block at rest. SICI and ICF were elicited using a standardized paired-pulse TMS protocol delivering a subthreshold conditioning stimulus (CS) that preceded a suprathreshold test stimulus (TS) at an interstimulus interval (ISI) of 3 and 10 ms, respectively. CS intensity was set at 80% of RMT and TS intensity was set at 120% of RMT. Fifteen unconditioned and 15 conditioned MEPs for each ISI were recorded. Both SICI and ICF were expressed as the ratio between conditioned and unconditioned MEP amplitude.

2.5.2. Experiment 2. Sensorimotor integration of face and hand M1 in OMD and FHD patients and HS

Short- and long-latency sensorimotor integration were assessed in both face and hand M1 in OMD and FHD patients and data were compared with those obtained in HS. The experiment was again performed with two different blocks for DAO and FDI recordings. SAI and LAI were tested in each block at rest. Single-pulse TMS on the contralateral M1 was preceded by ES of the peripheral nerve as follows: the median nerve for SAI and LAI of hand M1 at ISIs of 20 ms and 100 ms, respectively; the right mental nerve for SAI of face M1 at an ISI of 15 ms; the facial nerve for LAI of face M1 at an ISI of 100 ms. In each block, TS intensity was set at 120% of RMT. Fifteen unconditioned and 15 conditioned MEPs for each ISI were recorded. Both SAI and LAI were expressed as the ratio of conditioned to unconditioned MEP amplitude.

2.5.3. Experiment 3. Cortical excitability of face and hand M1 in BSP patients compared with OMD patients and HS

Patients with BSP underwent experiments 1 and data were compared with those obtained from OMD patients and HS.

2.5.4. Experiment 4. Sensorimotor integration of face and hand M1 in BSP patients compared with OMD patients and HS

Patients with BSP underwent experiments 2 and data were compared with those obtained from OMD patients and HS.

2.6. Statistical analysis

SPSS 20 software (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis. Student's paired t-test, repeated measures (RM) analysis of variance (ANOVA), and planned post hoc t-test with Bonferroni correction for multiple comparisons were perfomed. Compound symmetry was tested with Mauchly's test, and Greenhouse-Geisser correction was used when essential. Significance was considered when p value <0.05. Unless otherwise stated, values are expressed as mean ± standard error of the mean (SEM). Raw amplitude and amplitude ratio of conditioned to unconditioned MEPs were used as variables. To quantify the mag-

nitude of effect for the observed differences, the partial eta-squared effect size (ηp2) was computed.

Differences in demographic features, RMT intensities, and PT were assessed using one-way ANOVA with group (OMD, BSP, FHD, and HS) as a between-subject factor.

Experiment 1: One-way ANOVAs on the MEP ratios of SICI and ICF were performed separately using group (OMD, FHD, and HS) as a between-subject factor.

Experiment 2: One-way ANOVAs on the MEP ratios of SAI and LAI were performed separately using group (OMD, FHD and HS) as a between-subject factor.

Experiment 3: One-way ANOVAs on the MEP ratios of SICI and ICF were performed separately for each group (OMD, BSP, and HS).

Experiment 4: One-way ANOVAs on the MEP ratios of SAI and LAI were performed separately for each group (OMD, BSP, and HS).

In order to understand whether the neurophysiological findings were correlated with clinical features, a correlation analysis was performed with Spearman's correlation between clinical outcomes (demographic features, disease duration, and total clinical scale scores) and neurophysiological parameters that showed a significant difference between patients and HS (RMT, MEP amplitude, SICI, ICF, SAI, LAI).

3. Results

There were no significant differences between groups in demographics features such as age or gender. In addition, analysis of baseline TMS parameters, such as RMT and MEP amplitude of the DAO and FDI, and perceptive thresholds of the stimulated nerves failed to detect any significant differences between groups (Table 1).

3.1. Experiment 1: Excitability of face and hand M1 in OMD and FHD patients and HS

In face M1, SICI was not significantly different between FHD and HS groups, while it was significantly reduced in OMD patients. More specifically, a significant difference between groups was found in the DAO muscle ($F_{1,28}$ = 13.427; $p < 0.001$; ηp2 = 0.995) (Fig. 1A). Post-hoc analysis revealed that the SICI of face M1 in OMD patients was less powerful than in FHD patients ($p = 0.001$) and HS ($p < 0.001$). Conversely, no differences were observed between FHD and HS ($p = 1.00$).

In hand M1, SICI was not significantly different between OMD and HS groups, while it was significantly impaired in FHD patients. In particular, significant differences between groups were found in the FDI muscle ($F_{1,28}$ = 4.265; $p = 0.025$; ηp2 = 0.691) (Fig. 1B). Post-hoc analysis revealed that SICI in FHD patients was less than that in HS ($p = 0.031$) whereas no differences were observed between OMD and HS ($p = 0.128$). Recordings from representative subjects are shown in Fig. 2.

Statistical analysis showed no significant differences between groups for ICF in either the DAO ($F_{1,28}$ = 0.528; $p = 0.596$; ηp2 = 0.128) or FDI muscles ($F_{1,28}$ = 2.279; $p = 0.068$; ηp2 = 0.529) (Fig. 1C and D).

3.2. Experiment 2. Sensorimotor integration of face and hand M1 in OMD and FHD patients and HS

In face M1, SAI was not different in FHD patients compare with HS, whereas SAI was significantly reduced in OMD patients. More specifically, a significant difference between groups was detected in the DAO muscle ($F_{1,28}$ = 7.817; $p = 0.002$; ηp2 = 0.926) (Fig. 3A) and post-hoc analysis revealed that SAI in OMD patients was less than that in FHD patients ($p = 0.013$) and HS ($p = 0.004$). No differences were observed between FHD and HS ($p = 1.00$).

In hand M1, SAI was not different in OMD and FHD patients and HS and no significant differences between the three groups were observed in the FDI muscle ($F_{1,28}$ = 1.435; $p = 0.256$; ηp2 = 0.279) (Fig. 3B).

Statistical analysis showed no significant differences between groups for LAI in either the DAO ($F_{1,28}$ = 0.261; $p = 0.773$ ηp2 = 0.091) or FDI muscle ($F_{1,28}$ = 0.364; $p = 0.699$; ηp2 = 0.102) (Fig. 3C and D).

3.3. Experiment 3. Cortical excitability and sensorimotor integration of face and hand M1 in BSP patients as compared with OMD patients and HS

In face M1, SICI was significantly reduced in OMD patients ($F_{2,28}$ = 12.073, $p < 0.001$; ηp2 = 0.990) in comparison with BSP patients ($p = 0.007$) and HS ($p < 0.001$), while no significant difference was observed between BSP patients and HS ($p = 0.488$) (Fig. 4A). In contrast, there were no significant differences between groups for SICI in the FDI muscle ($F_{2,28}$ = 3.474, $p = 0.05$; ηp2 = 0.598) (Fig. 4B).

ICF did not significantly differ between OMD, BSP, and HS groups in either the DAO ($F_{1,28}$ = 0.600; $p = 0.556$; ηp2 = 0.139) (Fig. 4C) or FDI muscles ($F_{1,28}$ = 0.654; $p = 0.528$; ηp2 = 0.148) (Fig. 4D).

3.4. Experiment 4. Sensorimotor integration of face and hand M1 in BSP patients compared with OMD patients and HS

There were no statistical differences between OMD and BSP patients (Fig. 5) for SAI or LAI in either DAO or FDI representations in M1. However, OMD patients showed reduced SAI of face M1 compared to the HS group. In particular, one-way ANOVA on SAI of face M1 showed a clear effect of group ($F_{2,28}$ = 4.173, $p = 0.026$; ηp2 = 0.709). Post-hoc analysis showed a clear difference between OMD patients and HS ($p = 0.04$). One-way ANOVAs on SAI of the FDI and LAI of the DAO and FDI showed no clear effect of group (SAI-FDI: $F_{2,28}$ = 1.825, $p = 0.181$; ηp2 = 0.347, LAI-DAO: $F_{2,28}$ = 0.260, $p = 0.773$; ηp2 = 0.087; LAI-FDI: $F_{2,28}$ = 1.925, $p = 0.166$; ηp2 = 0.362).

3.5. Correlation analysis

The only significant correlation found was between disease duration and SAI in OMD patients (rho = -0.751, $p = 0.02$).

4. Discussion

The results of the present study show that patients with OMD have abnormal intracortical excitability and sensorimotor integration. Neurophysiological abnormalities were topographically specific, involving the cortical area innervating the body part affected by dystonia. In particular, SICI and SAI were reduced in face M1, but not in hand M1. Notably, the reduced SAI in face M1 of OMD patients inversely correlated with disease duration.

4.1. Intracortical excitability (SICI and ICF)

It can be reasonably excluded that the abnormalities we found were due to involuntary muscle activation during the recordings. Muscle contraction is able to reduce SICI, likely altering the proportion of early and late I-wave contributions to MEP (Di Lazzaro and Rothwell, 2014). For this reason, EMG traces showing even slight muscle activity in the pre-stimulus period were rejected online

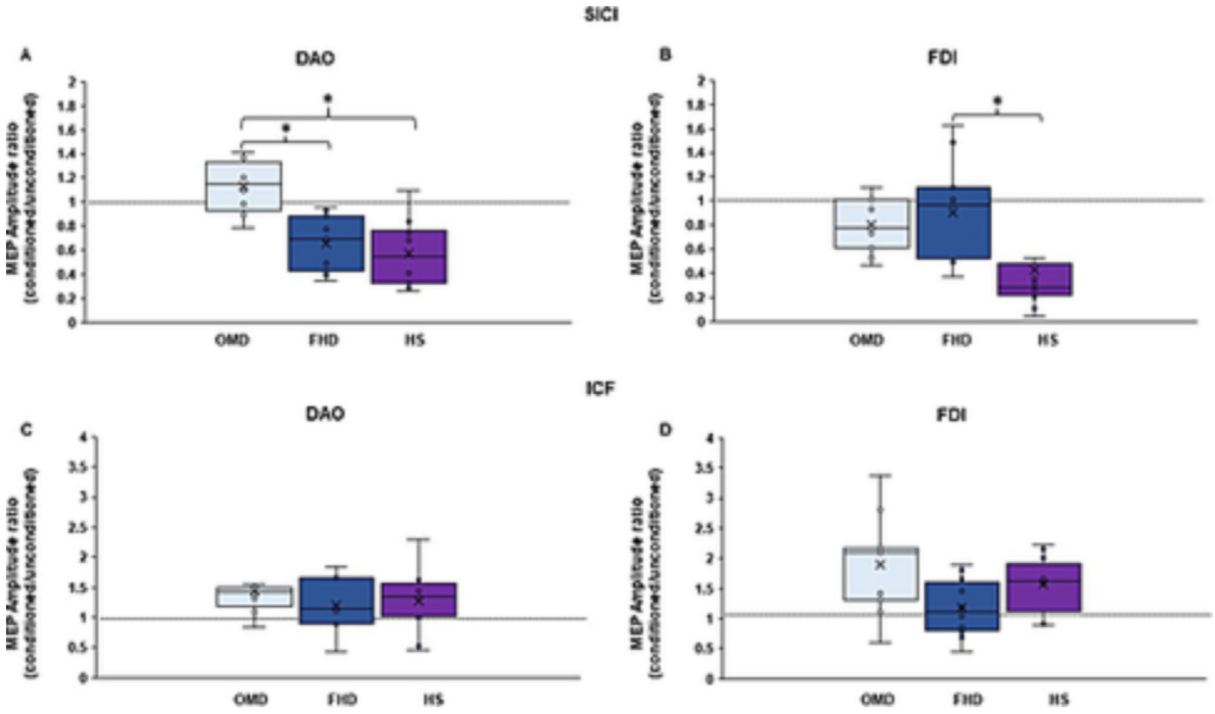

Fig. 1. Short intracortical inhibition (SICI) and intracortical facilitation (ICF) in the depressor anguli oris (DAO) and first dorsal interosseus (FDI) muscles of patients with oromandibular dystonia (OMD) and focal hand dystonia (FHD) and of healthy subjects (HS). The boxplots show the amplitude of the conditioned motor-evoked potential (MEP) (expressed as a ratio of unconditioned MEP) in the DAO (A and C) and FDI (B and D) muscles during SICI (A and B) and ICF (C and D) protocols in OMD, FHD, and HS. The continuous line in the boxplot represents the median value, while the '×' symbol represents the mean value of the group. $*p < 0.05$.

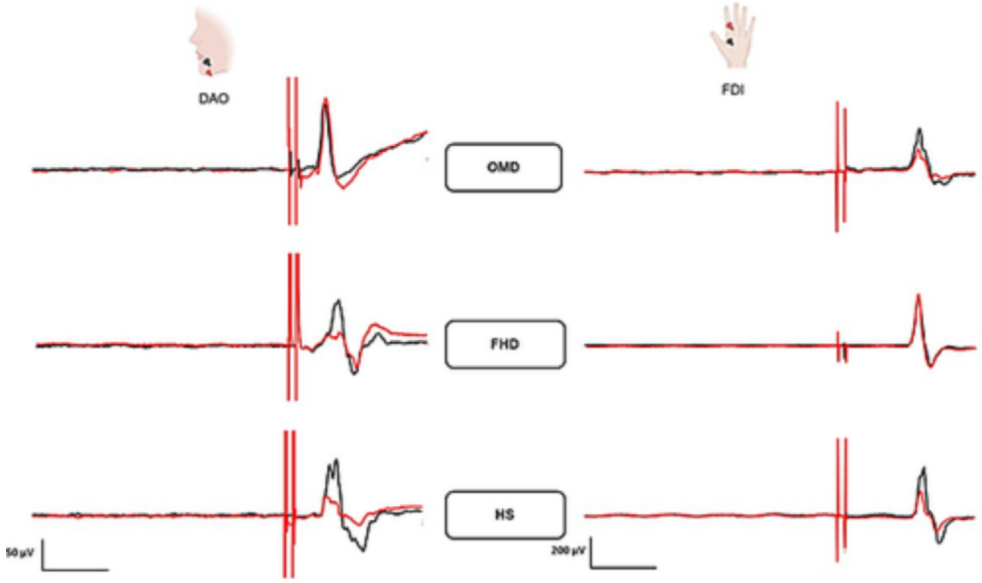

Fig. 2. Short intracortical inhibition (SICI) in the motor cortical representation of the depressor anguli oris (DAO) and first dorsal interosseus (FDI) muscles of patients with oromandibular dystonia (OMD) and focal hand dystonia (FHD) and of healthy subjects (HS). Recordings from a representative subject from each group (OMD, FHD, and HS) are reported for each muscle at an interstimulus interval of 3 ms. The unconditioned motor evoked potential (MEP), elicited by the test stimulus (120% of the resting motor threshold, RMT) is represented by the black line; the conditioned MEP (conditioning stimulus intensity 80% RMT) is represented by the red line. In the DAO, clear SICI was detected in the FHD and HS groups, but not in the OMD group. In the FDI, clear SICI was observed in the OMD and HS groups, but not in the FHD group.

and offline, thus minimizing the possibility that the observed reduction in SICI was due to involuntary muscle activation. A previous work demonstrated that SICI is normal in patients with hemifacial spasm, a neurological condition characterized by involuntary facial muscle contractions, but whose aetiology is linked to increased excitability of the peripheral nerve (Park et al., 2018). This observation, suggests that long-term abnormal facial contractions per se have no effect on SICI, supporting the lack of contamination of our results by involuntary muscle contractions during the recordings.

The evidence of altered SICI in both OMD and FHD patients is in line with previous evidence showing reduced SICI in patients with different forms of idiopathic focal dystonia compared to HS (Berardelli et al., 2008; McCambridge and Bradnam, 2021). The

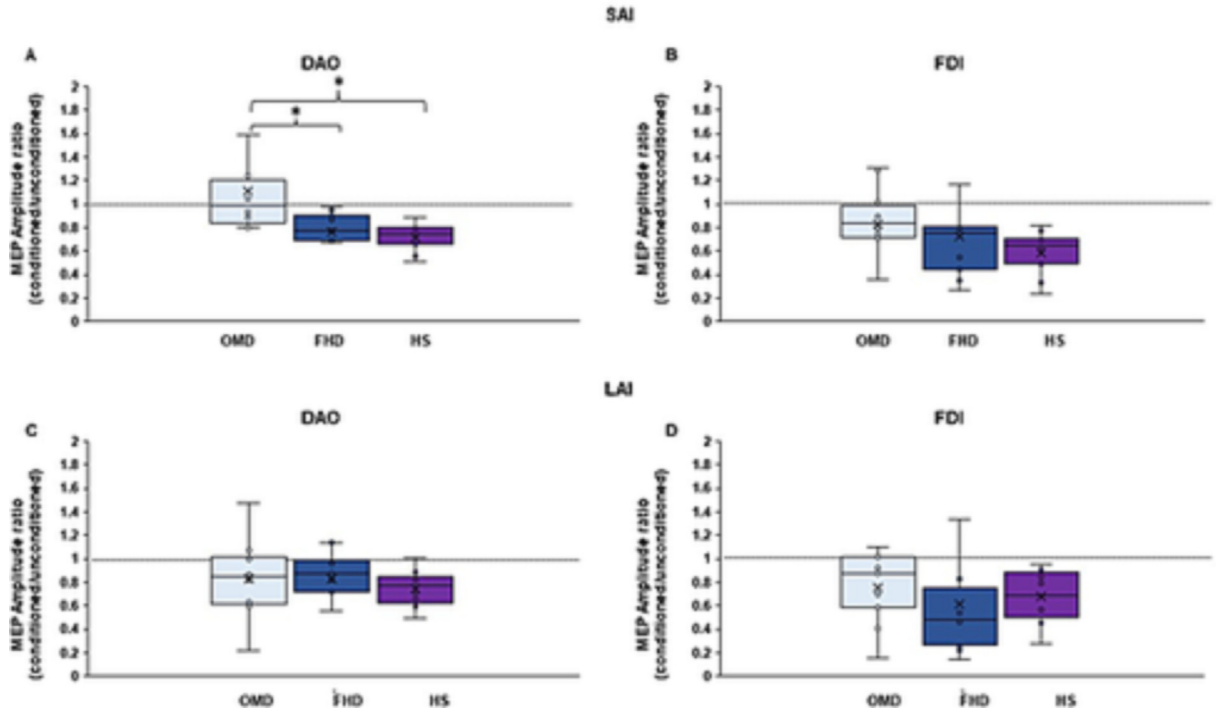

Fig. 3. Short-afferent inhibition (SAI) and long-afferent inhibition (LAI) in the depressor anguli oris (DAI) and first dorsal interosseus (FDI) muscles of patients with oromandibular dystonia (OMD) and focal hand dystonia (FHD) and of healthy subjects (HS). The boxplots show the amplitude of the conditioned motor-evoked potential (MEP) (expressed as a ratio of unconditioned MEP) in the DAO (A and C) and FDI (B and D) muscles during rest SAI (A and B) and LAI (C and D) protocols in OMD, FHD, and HS. The continuous line in the boxplot represents the median value, while the '×' symbol represents the mean value of the group. $*p < 0.05$.

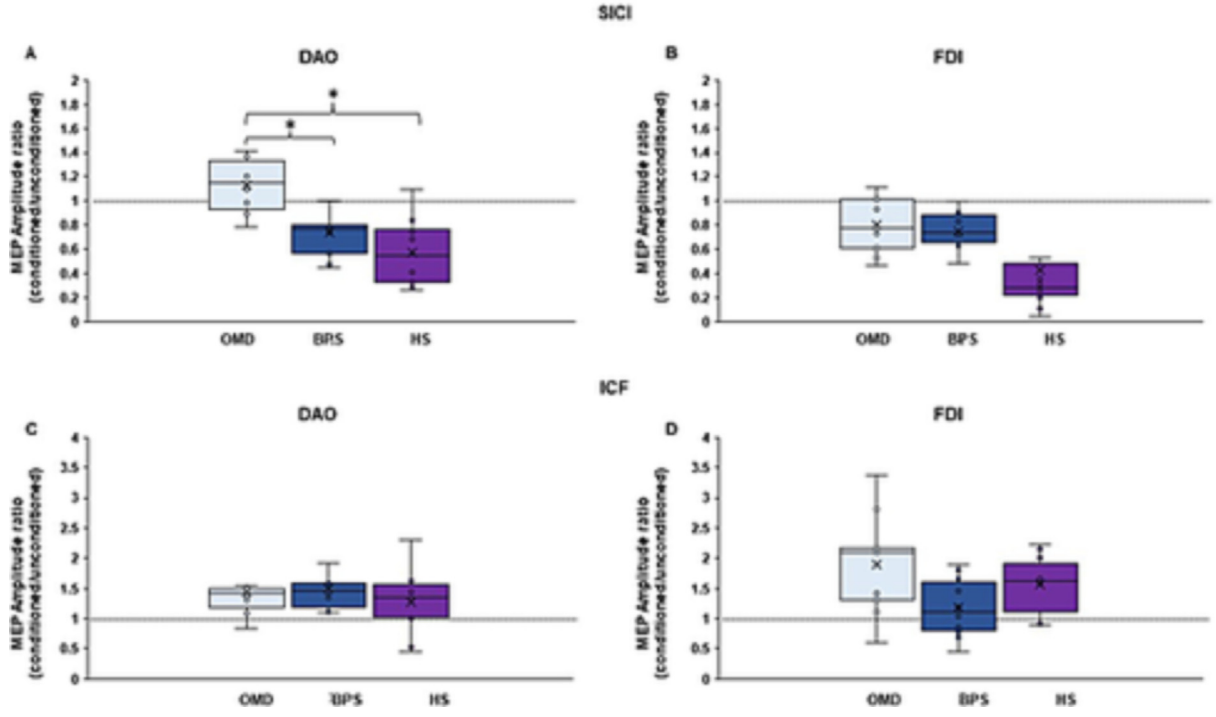

Fig. 4. Short intracortical inhibition (SICI) and intracortical facilitation (ICF) in the depressor anguli oris (DAO) and first dorsal interosseus (FDI) muscles of patients with oromandibular dystonia (OMD) and blepharospasm (BSP) and of healthy subjects (HS). The boxplots show the amplitude of the conditioned motor-evoked potential (MEP) (expressed as a ratio of unconditioned MEP) in the DAO (A and C) and FDI (B and D) muscles during SICI (A and B) and ICF (C and D) protocols in OMD, BSP, and HS. The continuous line in the boxplot represents the median value, while the '×' symbol represents the mean value of the group. $*p < 0.05$.

observations that SICI is reduced in OMD patients only after face M1 stimulation while it is normal after hand M1 stimulation and that SICI is reduced after hand M1 stimulation but not after face M1 stimulation in FHD patients provides novel evidence of topographic specificity of SICI abnormalities in idiopathic focal dystonia. Our results are consistent with and extend the findings of a

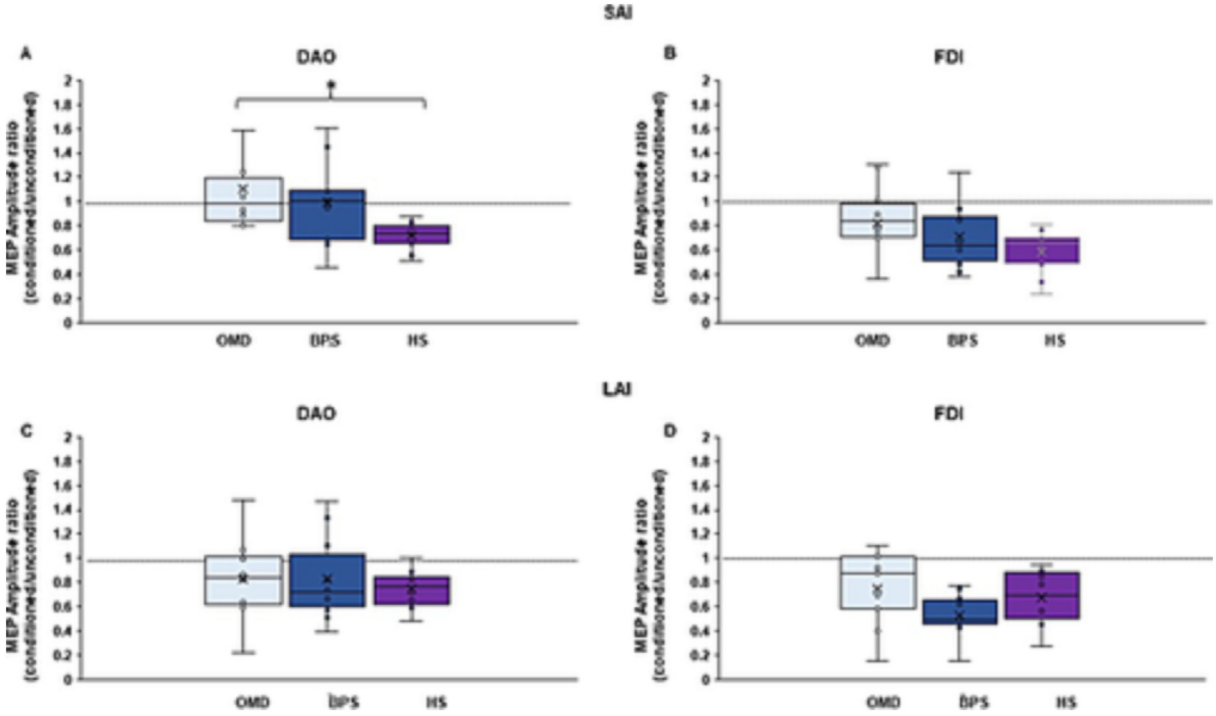

Fig. 5. Short-afferent inhibition (SAI) and long-afferent inhibition (LAI) in the depressor anguli oris (DAO) and first dorsal interosseus (FDI) of patients with oromandibular dystonia (OMD) and blepharospasm (BSP) and of healthy subjects (HS). The boxplots show the amplitude of the conditioned motor-evoked potential (MEP) (expressed as a ratio of unconditioned MEP) in the DAO (A and C) and FDI (B and D) muscles during SAI (A and B) and LAI (C and D) protocols in OMD, BSP, and HS. The continuous line in the boxplot represents the median value, while the '×' symbol represents the mean value of the group. $*p < 0.05$.

recent meta-analysis on studies investigating SICI in "isolated" dystonia that concluded that SICI is reduced after hand M1 stimulation in patients with FHD (Beck et al., 2008; Hubsch et al., 2013; McCambridge and Bradnam, 2021; Quartarone et al., 2003; Ridding et al., 1995; Simonetta-Moreau et al., 2006), but not in patients with cervical dystonia (CD) (Amadio et al., 2014; Kaňovský et al., 2003; McCambridge and Bradnam, 2021) as compared to HS.

Consistent with topographic specificity, SICI was normal in both lower face M1 and hand M1 in BSP patients, as compared with OMD patients and HS, despite the dystonic region in BSP, *i.e.*, the orbicularis oculi (OO) muscles, being close to the investigated one. The anatomy of the facial nucleus and its cortical control can help explain these results. Cell bodies innervating face muscles are spatially arranged in a musculotopic pattern. Motoneurons innervating the same muscles are grouped together in longitudinal columns oriented cranio-caudally (Cattaneo and Pavesi, 2014). Holstege (2002) demonstrated that the dorsal subgroup of the facial nucleus contains motoneurons innervating the muscles around the eye, while the lateral subgroup innervates muscles of the mouth. M1 sends corticofacial fibres bilaterally to all musculotopical subdivisions of the facial nucleus (Jenny and Saper, 1987; Morecraft et al., 2001) with a significant portion of the projections innervating the contralateral lower facial musculature (Morecraft et al., 2001). Considering that we investigated SICI in lower face M1, it is possible that the somatotopic specificity of cortical control of motoneurons in the facial nucleus is responsible for the different SICI results we observed in BSP and OMD patients. Based on these considerations, the findings of the present study suggest that future investigations should consider the stimulation area when assessing SICI in dystonia patients.

ICF in all patient groups was normal in both face and hand M1. These results contrast with previous data demonstrating increased ICF in patients with FHD, BSP, and CD (Amadio et al., 2014; Furuya et al., 2018; Sommer et al., 2002). Differences between these studies and ours may be explained by several technical differences, such as the coil employed (single vs. double coil) (Sommer et al., 2002) or the ISI used (10 ms vs. 15 ms) (Amadio et al., 2014). Differences in the features of patients studied can also explain the contrasting results (idiopathic focal dystonia vs. task-specific musician's dystonia) (Furuya et al., 2018). Finally, since ICF is a facilitatory protocol, it is possible that our experimental set up was able to evoke the maximum facilitation of M1, determining a ceiling effect that prevented observing an alteration in ICF.

We propose that the increased excitability in OMD is mainly due to impaired activity of intracortical inhibitory interneurons mediating SICI, rather than to increased activity of excitatory interneurons mediating ICF. This is not surprising since separate neuronal populations are likely to mediate SICI and ICF (Ziemann et al., 1996). Pharmacological studies showed that SICI is related to the activity of γ-aminobutyric acid type A ($GABA_A$) connections (Di Lazzaro et al., 2007; Rothwell et al., 2021; Ziemann et al., 1996) and that ICF is mediated by glutamatergic cortical interneurons (Ziemann et al., 1996). Based on the above considerations, we suggest that impaired $GABA_A$ interneuron activity plays a major role in the pathophysiology of focal dystonia. From a mechanistic point of view, the investigation of SICI and ICF in OMD and, for comparison, in other forms of focal dystonia (FHD and BSP) involving body parts other than the lower facial muscles, indicates that cortical excitability is increased in M1 with musculotopic specificity.

4.2. Sensorimotor integration (SAI and LAI)

Sensorimotor integration was impaired in OMD patients but not in FHD and BSP patients. Abnormalities were present for SAI but not for LAI. In OMD patients, SAI was reduced only for face, but not for hand M1, showing the same topographical specificity as SICI. The finding of normal SAI in FHD and BSP patients is consistent with data from previous studies (Avanzino et al., 2008;

Kessler et al., 2005). The SAI reduction observed in OMD may be due to an alteration in cutaneous afferents from the orofacial district. Although it has been shown that the contribution of peripheral acute trauma to idiopathic dystonia is negligible (Defazio et al., 2020), it has been consistently reported that oral trauma is a peculiar feature of OMD (Kreisler et al., 2016; Manzo et al., 2022; Page and Siegel, 2017; Raoofi et al., 2017; Sankhla et al., 1998), where dystonic movements frequently determine oral trauma. Jaw deviation and involuntary tongue protrusion often result in persistent grinding of the teeth, tongue biting, wearing away of the enamel, early loss of teeth, and trauma of the lips or gums (Page and Siegel, 2017). Notably, in the present OMD sample, eight out of 10 patients reported oral trauma due to dystonic movements. It is possible that the related altered sensory inputs and their processing at the cortical and subcortical level determine prominent changes in corticobulbar tract excitability in OMD patients. The different result between OMD and FHD may be due to the combination of two processes: a prominent contribution of subcortical inhibitory systems in the modulation of corticobulbar excitability (Ginatempo et al., 2019a,b) and the consequences of dystonic movements, *i.e.,* the occurrence of repetitive oral trauma in OMD patients. Moreover, SAI evoked in face M1 has a different origin than SAI of hand M1. In particular, the former is elicited by the stimulation of pure cutaneous fibres (trigeminal nerve) (Pilurzi et al., 2013; Pilurzi et al., 2020), while the latter is elicited by the stimulation of a mixed nerve (median nerve), including both cutaneous and proprioceptive fibres. We argue that the increased exposure and susceptibility to repetitive trauma of cutaneous trigeminal fibres in OMD may determine their facilitation, which may in turn be responsible for the abnormal SAI observed in this condition, but not in FHD or BSP, where these characteristics are not common. SAI increases with greater nerve stimulation intensity, and it has been demonstrated that increasing nerve stimulation intensity from the minimum intensity for perception to the minimum intensity for muscle twitch determines an increase in SAI (Turco et al., 2018). However, a reduction in SAI was observed immediately after the removal of pain-inducing hypertonic saline infusion (Ginatempo et al., 2019b). It is therefore possible that the facilitation of sensory fibres and the activation of pain fibres due to peripheral trauma could induce the reduction in SAI observed in the present work.

In addition, as described above, several factors can influence SAI and LAI, including the intensities of nerve stimulation, nerve composition, recorded muscle and receptor activated (Turco et al., 2018). In this light, differently from the hand muscle, in the DAO, SAI depends on the activity of low threshold, presumably cutaneous, afferents, whereas LAI requires activity in sensory afferents, activated by the muscle twitch evoked by electrical stimulation of the motor nerve (Pilurzi et al. 2013, 2020). According to this view, cutaneous inputs may exert a paucisynaptic inhibitory effect, namely SAI, on face M1, while proprioceptive information is likely to target inhibitory polysynaptic circuits involved in LAI. SAI was reduced only in OMD, which makes it likely that only the alteration of cutaneous fibres is able to induce an alteration of SAI. In the hand district, the later could be compensated by muscle spindle activation, that is instead lacking in face muscles, because they are devoid of these receptors (Cattaneo and Pavesi, 2014).

On the other hand, LAI was normal in all patients after stimulation of both face and hand M1. These results are in line with a previous study on LAI in FHD patients (Avanzino et al., 2008). In contrast with our observation, another previous study showed a reduction in LAI in focal dystonia, but the parameters used for LAI differed from those used in our study, *i.e.*, an ISI of 200 vs. 100 ms (Abbruzzese et al., 2001).

Previous pharmacological studies have demonstrated that SAI and LAI activate different mechanisms. In particular, it has been demonstrated that $GABA_A$ receptor agonists are able to reduce SAI (Rossini et al., 2015; Turco et al., 2018) and there is strong evidence supporting the role of acetylcholine (Ach) in the generation of SAI since intravenous injection of a muscarinic antagonist is able to reduce it (Oliviero et al., 2005). Conversely, LAI could result from $GABA_B$ modulation (Sailer et al., 2002, 2003; Turco et al., 2018).

In conclusion, our investigation of sensorimotor integration in OMD evidenced impaired SAI, suggesting a dysfunction in $GABA_A$ and Ach interneuron activity in face M1.

4.3. Intracortical excitability and sensorimotor integration interactions

Overall, the topographic specificity of the reduced SICI and SAI in OMD patients provides novel insights on the pathophysiological mechanisms of OMD. Although previous studies hypothesized abnormal sensorimotor integration as well as reduced inhibition in different forms of focal idiopathic dystonia, whether these abnormalities play a causal role or are secondary to motor symptoms is still debated, and their relationship with dystonic symptoms is unclear (Berardelli, 2006; Conte et al., 2019; Manzo et al., 2022). Based on our results, it is likely that somatosensory input alterations, which occur even at early stages of OMD (Manzo et al., 2022), may lead to alterations in sensorimotor integration processes, as suggested by the inverse correlation between disease duration and the reduction in SAI observed in our study. We suggest that the abnormal processing of sensory inputs and the subsequent abnormal sensorimotor integration at the cortical level may be responsible for SICI abnormalities. A previous humans work investigating how somatosensory inputs modulate motor output at the cortical level (Tokimura et al., 2000) showed that both I2 and I3 waves were reduced at an interval appropriate for SAI, while the I1 wave remained unaffected (Reis et al., 2008). Similar results were showed for mixed nerve stimulation and digit nerve stimulation of separate fingers. Taking into account these findings, it seems likely that reduced corticofugal output may result in reduced MEPs amplitude. Similar evidence have been shown for cutaneous stimulation of digital nerves. MEPs were inhibited when a TMS pulse was delivered 25–50 ms after homotopic stimulation of a digital nerve (Classen et al., 2000; Tamburin et al., 2005). When a cutaneous stimulus was applied ~35 ms before a conditioning TMS pulse, a reduction in SICI was described (Ridding and Rothwell, 1999). This finding suggests that the afferent input activated by the digital stimulus directly affect the circuits involved in SICI, most likely due to interference with later I-waves and thus weakening the efficacy of cortical CS. In this light, we suggest that repeated peripheral trauma, which results in abnormal sensory inputs, may lead to a reduction in SICI through modulation of late I-waves.

It should be also considered that the altered intracortical inhibitory circuits may affect the control exerted by motor cortical areas on brainstem reflex circuits. This could result in the enhanced recovery cycle of the blink reflex and masseter inhibitory reflex observed by previous works (Berardelli et al., 1985; Cruccu et al., 1991; Thompson et al., 1986; Tolosa et al., 1988), which suggests a possible secondary role of altered brainstem interneuron excitability in the pathophysiology of OMD.

4.4. Limitations of the study

We acknowledge some limitations of this study. First, we recorded from a face muscle rather than from masticatory muscles, which are prominently involved in OMD. The reason for choosing the DAO muscle was due to the presence of standardized TMS protocols for face muscles (Cattaneo and Pavesi, 2014; Pilurzi et al., 2013; Pilurzi et al., 2020), which do not exist with masticatory muscles. In addition, TMS-induced MEPs in the DAO are elicitable

in the resting condition, as opposed to the masseter muscles where pre-innervation is necessary to elicit MEPs. Second, due to technical limitations we did not investigate the representation area of the OO muscle. Since in the present study, TMS protocols were tested at rest, patients with a duration score of $\leq$3.5 and with severe and constant symptoms were excluded, which could have influenced our results. Furthermore, OMD, FHD and BPS patients were evaluated as symptom severity, using three different scales (specific for each disease) which could not allowed a direct clinical comparison among the three groups thus it cannot be excluded that one group was more affected than the other. Finally, the role of interhemispheric processing (Bocci et al., 2016, 2020) and brainstem excitability in OMD pathophysiology, which has been already demonstrated by several authors (Berardelli et al., 1985; Cruccu et al., 1991; Curra et al., 2000; Pauletti et al., 1993; Thompson et al., 1986; Tolosa et al., 1988), it has not been tested in the present study.

5. Conclusions

In conclusion, the results of this study suggest that an abnormal sensory processing, possibly related to frequent oral trauma, which is a peculiar feature of OMD, may alter the integration between sensory input and motor output, thus inducing excitability changes at the cortical level in OMD. This may in turn be responsible for the abnormal intracortical inhibition observed in the face but not the hand motor area in patients with OMD, thus supporting a crucial role of sensory input processing in the pathophysiology of OMD.

The results of the present study may have clinical implications for the treatment of focal dystonia. In this regard, both peripheral (*e.g.,* trigeminal nerve) and central (*e.g.,* non-invasive brain) stimulation may modulate the altered function of both cortical and brainstem circuits.

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Competing interests

The authors do not have any competing interest in this research.

References

Abbruzzese G, Berardelli A. Sensorimotor integration in movement disorders. Mov Disord 2003;18(3):231–40. https://doi.org/10.1002/mds.10327.

Abbruzzese G, Marchese R, Buccolieri A, Gasparetto B, Trompetto C. Abnormalities of sensorimotor integration in focal dystonia: A transcranial magnetic stimulation study. Brain 2001;124(3):537–45. https://doi.org/10.1093/brain/124.3.537.

Albanese A, Sorbo FD, Comella C, Jinnah HA, Mink JW, Post B, et al. Dystonia rating scales: critique and recommendations. Mov Disord 2013;28(7):874–83. https://doi.org/10.1002/mds.25579.

Amadio S, Houdayer E, Bianchi F, Tesfaghebriel Tekle H, Urban I, et al. Sensory tricks and brain excitability in cervical dystonia: A transcranial magnetic stimulation study. Mov Disord 2014;29(9):1185–8. https://doi.org/10.1002/mds.25888.

Avanzino L, Martino D, van de Warrenburg BPC, Schneider SA, Abbruzzese G, Defazio G, et al. Cortical excitability is abnormal in patients with the “fixed dystonia” syndrome. Mov Disord 2008;23(5):646–52. https://doi.org/10.1002/mds.21801.

Avanzino L, Tinazzi M, Ionta S, Fiorio M. Sensory-motor integration in focal dystonia. Neuropsychologia 2015;79:288–300. https://doi.org/10.1016/j.neuropsychologia.2015.07.008.

Beck S, Richardson SP, Shamim EA, Dang N, Schubert M, Hallett M. Short intracortical and surround inhibition are selectively reduced during movement initiation in focal hand dystonia. J Neurosci 2008;28(41):10363–9. https://doi.org/10.1523/JNEUROSCI.3564-08.2008.

Berardelli A, Rothwell JC, Day BL, Marsden CD. Pathophysiology of blepharospasm and oromandibular dystonia. Brain 1985;108(3):593–608. https://doi.org/10.1093/brain/108.3.593.

Berardelli A. New advances in the pathophysiology of focal dystonias. Brain 2006;129(1):6–7. https://doi.org/10.1093/brain/awh717.

Berardelli A, Abbruzzese G, Chen R, Orth M, Ridding MC, Stinear C, et al. Consensus paper on short-interval intracortical inhibition and other transcranial magnetic stimulation intracortical paradigms in movement disorders. Brain Stimul 2008;1(3):183–91. https://doi.org/10.1016/j.brs.2008.06.005.

Bocci T, Baloscio D, Ferrucci R, Briscese L, Priori A, Sartucci F. Interhemispheric Connectivity in Idiopathic Cervical Dystonia and Spinocerebellar Ataxias: A Transcranial Magnetic Stimulation Study. Clin EEG Neurosci 2020;53(5):460–6. https://doi.org/10.1177/1550059420957487.

Bocci T, Hensghens MJM, Di Rollo A, Parenti L, Barloscio D, Rossi S, et al. Impaired interhemispheric processing in early Huntington's Disease: A transcranial magnetic stimulation study. Clin Neurophysiol 2016;127(2):1750–2. https://doi.org/10.1016/j.clinph.2015.10.036.

Cattaneo L, Pavesi G. The facial motor system. Neurosci Biobehav Rev 2014;38:135–59. https://doi.org/10.1016/j.neubiorev.2013.11.002.

Classen J, Steinfelder B, Liepert J, Stefan K, Celnik P, Cohen LG, et al. Cutaneomotor integration in humans is somatotopically organized at various levels of the nervous system and is task dependent. Exp Brain Res 2000;130(1):48–59. https://doi.org/10.1007/s002210050005.

Conte A, Defazio G, Hallett M, Fabbrini G, Berardelli A. The role of sensory information in the pathophysiology of focal dystonias. Nat Rev Neurol 2019;15(4):224–33. https://doi.org/10.1038/s41582-019-0137-9.

Cruccu G, Pauletti G, Agostino R, Berardelli A, Manfredi M. Masseter inhibitory reflex in movement disorders. Huntington's chorea, Parkinson's disease, dystonia, and unilateral masticatory spasm. *Electroencephalography and Clinical Neurophys./.* Evoked Potentials 1991;81(1):24–30. https://doi.org/10.1016/0168-5597(91)90100-C.

Curra A, Romanielo A, Berardelli A, Cruccu G, Manfredi M. Shortened cortical silent period in facial muscles of patients with cranial dystonia. Neurology 2000;54(1):130–5. https://doi.org/10.1016/j.pain.2007.05.009.

Defazio G, Fabbrini G, Erro R, Albanese A, Barone P, Zibetti M, et al. Does acute peripheral trauma contribute to idiopathic adult-onset dystonia? Parkinsonism Relat Disord 2020;71:40–3. https://doi.org/10.1016/j.parkreldis.2020.01.002.

DeFazio G, Hallett M, Jinnah HA, Stebbins GT, Gigante AF, Ferazzano G, et al. Development and validation of a clinical scale for rating the severity of blepharospasm. Mov Disord 2015;30(4):525–30. https://doi.org/10.1002/mds.26156.Development.

Desrochers P, Brunfeldt A, Sidiropoulos C, Kagerer F. Sensorimotor control in dystonia *Brain Sci* 2019;9(4):1–18. https://doi.org/10.3390/brainsci9040079.

Di Lazzaro V, Pilato F, Dileone M, Profice P, Ranieri F, Ricci V, et al. Segregating two inhibitory circuits in human motor cortex at the level of GABAA receptor subtypes: A TMS study. Clin Neurophysiol 2007;118(10):2207–14. https://doi.org/10.1016/j.clinph.2007.07.005.

Di Lazzaro V, Rothwell JC. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J Physiol 2014;592(19):4115–28. https://doi.org/10.1113/jphysiol.2014.274316.

Furuya S, Uehara K, Sakamoto T, Hanakawa T. Aberrant cortical excitability reflects the loss of hand dexterity in musician's dystonia. J Physiol 2018;596(12):2397–411. https://doi.org/10.1113/JP275813.

Ginatempo F, Loi N, Manca A, Rothwell JC, Deriu F. Is it possible to compare inhibitory and excitatory intracortical circuits in face and hand primary motor cortex? J Physiol 2022;600(15):3567–83. https://doi.org/10.1113/JP283137.

Ginatempo F, Manzo N, Rothwell JC, Deriu F. Lack of evidence for interhemispheric inhibition in the lower face primary motor cortex. Clin Neurophysiol 2019a;130(10):1917–25. https://doi.org/10.1016/j.clinph.2019.07.027.

Ginatempo F, Spampinato DA, Manzo N, Rothwell JC, Deriu F. Exploring the connectivity between the cerebellum and facial motor cortex. Brain Stimul 2019b;12(6):1586–7. https://doi.org/10.1016/j.brs.2019.07.012.

Hallett MA, Jinnah HA, Conte A, Berardelli GD. Blepharospasm 40 Years Later. Mov Disord 2017;32(4):498–509. https://doi.org/10.1002/mds.26934.

Holstege G. Emotional innervation of facial musculature. Mov Disord 2002;17(SUPPL:2). https://doi.org/10.1002/mds.10050.

Hubsch C, Roze E, Popa T, Russo M, Balachandran A, Pradeep S, et al. Defective cerebellar control of cortical plasticity in writer's cramp. Brain 2013;136(7):2050–62. https://doi.org/10.1093/brain/awt147.

Jenny AB, Saper CB. Organization of the facial nucleus and corticofacial projection in the monkey: a reconsideration of the upper motor neuron facial palsy. Neurology 1987;37(6):930. https://doi.org/10.1212/wnl.37.6.930.

Kaňovský P, Bareš M, Streitová H, Klajblová H, Daniel P, Rektor I. Abnormalities of cortical excitability and cortical inhibition in cervical dystonia: Evidence from somatosensory evoked potentials and paired transcranial magnetic stimulation recordings. J Neurol 2003;250(1):42–50. https://doi.org/10.1007/s00415-003-0942-2.

Kessler KR, Ruge D, Ilić TV, Ziemann U. Short latency afferent inhibition and facilitation in patients with writer's cramp. Mov Disord 2005;20(2):238–42. https://doi.org/10.1002/mds.20295.

Kreisler A, Verpraet A-C, Veit S, Pennel-Ployart O, Behal H, Alain D, et al. Clinical Characteristics of Voice, Speech, and Swallowing Disorders in Oromandibular Dystonia. J Speech Lang Hear Res 2016;59(5):940–9. https://doi.org/10.1044/2016.

Kujirai K, Kujirai T, Sinkjaer T, Rothwell JC. Associative plasticity in human motor cortex during voluntary muscle contraction. J Neurophysiol 2006;96 (3):1337–46. https://doi.org/10.1152/jn.01140.2005.
Manzo N, Ginatempo F, Belvisi D, Defazio G, Conte A, Deriu F, et al. Pathophysiological mechanisms of oromandibular dystonia. Clin Neurophysiol 2022;134:73–80. https://doi.org/10.1016/j.clinph.2021.11.075.
Marsden CD. Blepharospasm-oromandibular dystonia syndrome (Brueghel's syndrome). A variant of adult-onset torsion dystonia? J Neurol Neurosurg Psychiatry 1976;39(12):1204–9. https://doi.org/10.1136/jnnp.39.12.1204.
McCambridge AB, Bradnam LV. Cortical neurophysiology of primary isolated dystonia and non-dystonic adults: A meta-analysis. Eur J Neurosci 2021;53 (4):1300–23. https://doi.org/10.1111/ejn.14987.
Morecraft RJ, Louie JL, Herrick JL, Stilwell-Morecraft KS. Cortical innervation of the facial nucleus in the non-human primate: A new interpretation of the effects of stroke and related subtotal brain trauma on the muscles of facial expression. Brain 2001. https://doi.org/10.1093/brain/124.1.176.
Oliviero A, Molina León A, Holler I, Florensa Vila J, Siebner HR, Della Marca G, et al. Reduced sensorimotor inhibition in the ipsilesional motor cortex in a patient with chronic stroke of the paramedian thalamus. Clin Neurophysiol 2005;116 (11):2592–8. https://doi.org/10.1016/j.clinph.2005.07.015.
Page AD, Siegel L. Perspectives on the Psychosocial Management of Oromandibular Dystonia. Semin Speech Lang 2017;38(3):173–83. https://doi.org/10.1055/s-0037-1602836.
Park JS, Lee S, Park SK, Lee JA, Park K. Facial motor evoked potential with paired transcranial magnetic stimulation: prognostic value following microvascular decompression or hemifacial spasm. J Neurosurg 2018;131(6):1780–7. https://doi.org/10.3171/2018.8.JNS18708.
Pauletti G, Berardelli A, Cruccu G, Agostino R, Manfredi M. Blink reflex and the masseter inhibitory reflex in patients with dystonia. Mov Disord 1993;8 (4):495–500. https://doi.org/10.1002/mds.870080414.
Pilurzi G, Hasan A, Saifee TA, Tolu E, Rothwell JC, Deriu F. Intracortical circuits, sensorimotor integration and plasticity in human motor cortical projections to muscles of the lower face. J Physiol 2013;591(7):1889–906. https://doi.org/10.1113/jphysiol.2012.245746.
Pilurzi G, Ginatempo F, Mercante B, Cattaneo L, Pavesi G, Rothwell JC, et al. Role of cutaneous and proprioceptive inputs in sensorimotor integration and plasticity occurring in the facial primary motor cortex. J Physiol 2020. https://doi.org/10.1113/JP278877.
Quartarone A, Bagnato S, Rizzo V, Siebner HR, Dattola V, Scalfari A, et al. Abnormal associative plasticity of the human motor cortex in writer's cramp. Brain 2003;126(12):2586–96. https://doi.org/10.1093/brain/awg273.
Raoofi S, Khorshidi H, Najafi M. Etiology, diagnosis and management of oromandibular dystonia: an update for stomatologists. J Dent 2017;18 (2):73–81. PMID: 28620630.
Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 2008;586(2):325–51. https://doi.org/10.1113/jphysiol.2007.144824.
Ridding MC, Rothwell JC. Afferent input and cortical organisation: A study with magnetic stimulation. Exp Brain Res 1999;126(4):536–44. https://doi.org/10.1007/s002210050762.
Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. J Neurol Neurosurg Psychiatry 1995;59(5):493–8. https://doi.org/10.1136/jnnp.59.5.493.
Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015;126(6):1071–107. https://doi.org/10.1016/j.clinph.2015.02.001.
Rothwell J, Antal A, Burke D, Carlsen A, Georgiev D, Jahanshahi M, et al. Central nervous system physiology. Clin Neurophysiol 2021;132(12):3043–83. https://doi.org/10.1016/j.clinph.2021.09.013.
Sailer A, Molnar GF, Cunic DI, Chen R. Effects of peripheral sensory input on cortical inhibition in humans. J Physiol 2002;544(2):617–29. https://doi.org/10.1113/jphysiol.2002.028670.
Sailer A, Molnar GF, Paradiso G, Gunraj CA, Lang AE, Chen R. Short and long latency afferent inhibition in Parkinson's disease. Brain 2003;126(8):1883–94. https://doi.org/10.1093/brain/awg183.
Sankhla C, Lai EC, Jankovic J. Peripherally induced oromandibular dystonia. J Neurol Neurosurg Psychiatry 1998;65(5):722–8. https://doi.org/10.1136/jnnp.65.5.722.
Simonetta-Moreau M, Lourenço G, Sangla S, Mazieres L, Vidailhet M, Meunier S. Lack of inhibitory interaction between somatosensory afferent inputs and intracortical inhibitory interneurons in focal hand dystonia. Mov Disord 2006;21(6):824–34. https://doi.org/10.1002/mds.20821.
Sommer M, Ruge D, Tergau F, Beuche W, Altenmüller E, Paulus W. Intracortical excitability in the hand motor representation in hand dystonia and blepharospasm. Mov Disord 2002;17(5):1017–25. https://doi.org/10.1002/mds.10205.
Tamburin S, Fiaschi A, Andreoli A, Marani S, Zanette G. Sensorimotor integration to cutaneous afferents in humans: the effect of the size of the receptive field. Exp Brain Res 2005;167(3):362–9. https://doi.org/10.1007/s00221-005-0041-y.
Thompson PD, Obeso JA, Delgado G, Gallego J, Marsden CD. Focal dystonia of the jaw and the differential diagnosis of unilateral jaw and masticatory spasm. J Neurol Neurosurg Psychiatry 1986;49(6):651–6. https://doi.org/10.1136/jnnp.49.6.651.
Tokimura H, Di Lazzaro V, Tokimura Y, Oliviero A, Profice P, Insola A, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol 2000;523(2):503–13. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00503.x.
Tolosa E, Montserrat L, Bayes A. Blink reflex studies in patients with focal dystonias. Adv Neurol 1988;50:517–24.
Turco CV, El-Sayes J, Savoie MJ, Fassett HJ, Locke MB, Nelson AJ. Short- and long-latency afferent inhibition; uses, mechanisms and influencing factors. Brain Stimul 2018;11(1):59–74. https://doi.org/10.1016/j.brs.2017.09.009.
Yoshida K. Sensory trick splint as a multimodal therapy for oromandibular dystonia. J Prosthodont Res 2018;62(2):239–44. https://doi.org/10.1016/j.jpor.2017.09.004.
Yoshida K. Development and Validation of a Disease-Specific Oromandibular Dystonia Rating Scale (OMDRS). Front Neurol 2020;11. https://doi.org/10.3389/fneur.2020.583177 583177.
Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: A transcranial magnetic stimulation study. Ann Neurol 1996;40(3):367–78. https://doi.org/10.1002/ana.410400306.