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# Exploring the cortical effect of monoclonal antibodies against CGRP ligand: a pilot study of the cortical silent period in migraine

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**ABSTRACT**

**Background:** Evidence from animal studies suggests that monoclonal antibodies targeting the calcitonin gene-related peptide (anti-CGRP mAbs) may only minimally penetrate the blood-brain barrier due to their high molecular weight. However, neuroimaging and electrophysiological studies revealed indirect neuromodulatory effects originating peripherally and moving toward the central nervous system. This pilot study aimed to investigate the cortical inhibitory activity by recording the cortical silent period (SP) triggered by transcranial magnetic stimulation (TMS) in migraine patients before and after anti-CGRP mAbs treatment.

**Methods:** We prospectively recorded 8 individuals with episodic or chronic migraine who had not responded to at least three preventive migraine therapies. We applied high-intensity TMS to the primary motor cortex to evaluate the cortical SP from contracted perioral muscles. Electrophysiological data were gathered at baseline (T0), one month (T1), and two months (T2) before each anti-CGRP mAbs administration.

**Results:** Anti-CGRP mAbs treatment diminished the average monthly headache days (MHD). The duration of SP was reduced at T1 (82.49 ms at T0 *vs.* 66.59 ms at T1, $p<0.001$) but reverted to baseline levels at T2 (82.11 ms). The percentage variations in SP length assessed at T1 and T2 relative to T0 did not correlate with the percentage decrease in MHD measured at T1.

**Conclusions:** Our pilot study findings suggest that anti-CGRP mAbs not only have their known peripheral effects but also influence cortical inhibitory mechanisms in an indirect and transient manner. This provides a valuable foundation for further research, especially studies with larger sample sizes to confirm and expand on these preliminary results.

**Key words:** transcranial magnetic stimulation, monoclonal antibody, CGRP, cortical inhibition, chronic migraine, medication overuse headache.

## Introduction

The pathophysiological processes of migraine remain incompletely elucidated and are currently the subject of extensive research. Research in animal models and humans has highlighted the role of the calcitonin gene-related peptide (CGRP), a vasoactive and proalgesic neuropeptide, in generating neurogenic inflammatory responses underlying migraine pain. (1) The advancement and clinical effectiveness of monoclonal antibodies targeting the ligand or the CGRP receptor (anti-CGRP mAbs) have validated the crucial function of this polypeptide in the pathophysiology of migraine. (2,3) Evidence from animal models has shown only negligible and not pharmacologically active amounts of anti-CGRP mAbs in the central nervous system. Indeed, because of their elevated molecular weight, they cross the blood-brain barrier only in negligible quantities. (4,5) Therefore, their effectiveness is hypothesized to be exclusively linked to their peripheral activity. (1,4,5) Nonetheless, neuroimaging and electrophysiological investigations have found that some brain regions are influenced by the effects of the anti-CGRP mAbs treatment. (6-14) This activity is believed to be of an indirect neuromodulatory nature, originating in the periphery and progressing toward the central nervous system. By reducing the nociceptive discharge from peripheral trigeminal terminals, anti-CGRP mAbs may reduce the sensitization of third-order trigeminal neurons in the thalamus, restoring normal excitability in cortical areas that receive nociceptive signals. (11,15)

Transcranial magnetic stimulation (TMS) is an electrophysiological technique that can examine non-invasively several cerebral functions, including cortical inhibitory networks and their excitability processes. The cortical silent period (SP) is one of the TMS parameters used to investigate the inhibitory function and is defined as the interruption of voluntary motor activity induced by magnetic stimulation. (16) Notably, the SP recorded from facial muscles elucidates pathophysiological mechanisms different from those induced in limb muscles. Spinal and cortical circuits are implicated in the SP induced in limb muscles by TMS, which is primarily facilitated by gamma-aminobutyric acid-B (GABA-B) receptors. In contrast, the SP induced in facial muscles is due to the excitation of cortical inhibitory interneurons surrounding the upper motoneurons, reflecting exclusively the activity of the cortical circuits. (17,18) The SP derived from limb muscles (first dorsal interosseous or abductor pollicis brevis) is found to be shortened in migraine patients with (19) and without aura, (20) suggesting reduced central inhibition between attacks. The shortened SP in migraine patients was confirmed by recording from facial muscles, suggesting that cortical inhibitory interneuronal hypoactivity plays a role in these abnormal cortical inhibitory processes. (21) Interestingly, the SP was found to be prolonged in individuals with chronic migraine (CM), (22) reduced in CM patients overusing triptans, and within normal limits in CM patients who overused non-steroidal anti-inflammatory drugs (chronic migraine with medication overuse headache [CM-MOH]). (23) These changes were hypothesized to be related to the neural adaptation induced by the medications, which can promote changes in central serotonin neurotransmission. (23)

In this pilot study, we aimed to explore whether preventive therapy with anti-CGRP mAbs can influence the level of cortical inhibitory networks in patients with high-frequency episodic migraine (HF-MO, *i.e.*, from 8 to 14 monthly headache days) or CM with or without medication overuse, offering preliminary evidence that can serve as a basis for future research with larger sample sizes. We investigated these effects by applying high-intensity TMS to the primary motor cortex and recording electromyographic (EMG) responses from perioral muscles

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before and 1-month and 2-month post-treatment with galcanezumab or fremanezumab in HF-MO and CM patients and compared them with age- and sex-matched healthy volunteers (HV). Subsequently, we investigated whether changes in electrophysiological features were associated with changes in the monthly headache days (MHD). Based on previous neurophysiological findings that suggest indirect central effects of these drugs, we hypothesized that anti-CGRP mAbs influence cortical inhibitory interneuronal activity within the first month of treatment.

## Results

We enrolled 11 patients with HF-MO (n=4), CM without medication overuse (CM, n=4), or CM with medication overuse (CM-MOH, n=3). For comparison, we recruited 8 age- and sex-matched. Following the preliminary screening, two patients chose not to participate in the recording sessions, and one patient did not complete the study recordings; hence, the final analysis was conducted on 8 patients (4 HF-MO, 3 CM, and 1 CM-MOH). Mean age was 44.4±14.1 in HV, 47.5±9.7 in patients (p=0.615). Of the 8 enrolled patients, 5 received fremanezumab (225 mg) and 3 received galcanezumab (240 mg initial dose and 120 mg the second dose). Due to the small sample size, the patients were not divided into subgroups based on the diagnosis or treatment used. Patients' clinical and demographic characteristics are shown in **Table 1**. No patients experienced treatment-related side effects during the 2-month study period. Assessable TMS recordings were obtained from all participants in the study. Illustrative recordings of the cortical silent period before (T0) and at different time points before each anti-CGRP mAbs administration (T1 and T2) are shown in **Figure 1**.

**Comparison between migraine patients and healthy volunteers.** At baseline, we found no significant differences in electrophysiological variables between the two groups (**Table 2**). No difference was found in SP duration between migraine patients (98.03 ms) and HVs (82.49 ms, Z=0.750, p=0.627).

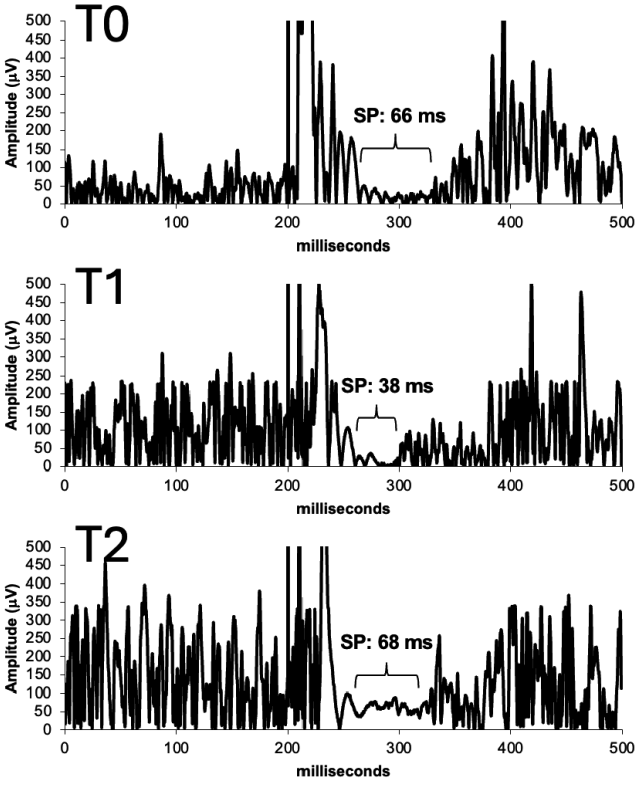


**Figure 1.** Illustrative recordings of the cortical silent period (SP) at baseline (T0) and prior to each new administration of anti-CGRP mAbs (T1 and T2).

**Table 1.** Patients' clinical and demographic features.

| Patient | Sex | Age (y) | Diagnosis | Anti-CGRP mAbs | History of the disease (y) | MHD | MIDAS | HIT-6 | ASC-12 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 29 | CM | FREMA | 8 | 30 | 141 | 72 | 2 |
| 2 | F | 46 | CM-MOH | FREMA | 30 | 20 | 245 | 67 | 8 |
| 3 | F | 65 | HF-MO | FREMA | 50 | 10 | 11 | 68 | 12 |
| 4 | M | 47 | HF-MO | FREMA | 35 | 12 | 50 | 70 | 1 |
| 5 | F | 48 | CM | FREMA | 37 | 20 | 180 | 65 | 14 |
| 6 | F | 51 | HF-MO | GALCA | 35 | 11 | 13 | 63 | 3 |
| 7 | M | 48 | CM | GALCA | 32 | 15 | 72 | 66 | 3 |
| 8 | F | 46 | HF-MO | GALCA | 32 | 14 | 30 | 62 | 5 |
| Mean±SD | | 47.5±9.7 | | | 32.4±11.6 | 16.5±6.6 | 92.7±86.5 | 66.6±3.4 | 6.0±4.8 |

ASC-12, 12-item Allodynia Symptom Checklist; FREMA, fremanezumab; GALCA, galcanezumab; HIT-6, 6-item Headache Impact Test; MIDAS, Migraine Disability Questionnaire; MHD, monthly headache days; SD, standard deviation.

**Table 2.** Recordings from perioral muscles in healthy controls and patients with migraine at the 3-time points.

| Parameter | HCs | T0 | T1 | T2 |
|---|---|---|---|---|
| MEP latency (ms) | 22.24±2.10 | 22.14±1.50 | 22.76±2.45 | 22.41±1.91 |
| MEP amplitude (mV) | 770.54±626.9 | 672.55±786.89 | 906.34±1271.72 | 421.25±411.97 |
| MEP radicular (ms) | 13.60±1.12 | 13.83±1.15 | 13.38±1.15 | 12.95±1.58 |
| SP onset (ms) | 48.50±10.23 | 46.49±11.41 | 50.68±9.21 | 51.63±9.36 |
| SP duration (ms) | 98.03±24.46 | 82.49±36.01 | 66.59±32.1 | 82.11±37.93 |

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**Clinical and electrophysiological effects of anti-CGRP mAbs.** We found a statistically significant repetition effect for the MHD ($c^2$=13.1, p=0.001), which decreased significantly from a mean value of 16.5±6.6 at T0 to 9.1±4.2 at T1 (*post-hoc* test *vs.* T0 t=3.95, p=0.001) and 5.9±2.9 at T2 (*post-hoc* test *vs.* T0 t=7.9, p<0.001) (**Figure 2**).

Additionally, we found a statistically significant repetition effect for the duration of the SP ($c^2$=9.75, p=0.008), which decreased significantly from a mean value of 82.49±36.01 at T0 to 66.59±32.1 at T1 (*post-hoc* test *vs.* T0 t=4.49, p<0.001) but returned to the baseline level at T2 (82.11±37.93, *post-hoc* test *vs.* T0 t=1.12, p=0.281) (**Figure 3**).

**Correlation analysis.** At T0, MHD showed a positive correlation with the SP duration (rho=0.838, p=0.009). In contrast, the duration of the attacks showed a negative correlation with the SP duration (rho=-0.874, p=0.005) (**Figure 4**).

In the patient group, changes in SP duration percentages at T1 and T2, when compared to T0, did not show a significant

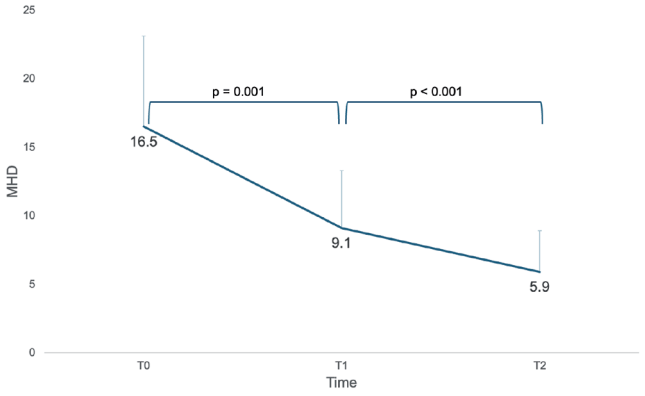


**Figure 2.** Graphs illustrate the substantial decrease in the frequency of monthly headache days (MHD) at baseline (T0) and prior to each new administration of anti-CGRP mAbs (T1 and T2). Data are presented as mean ± standard deviation.

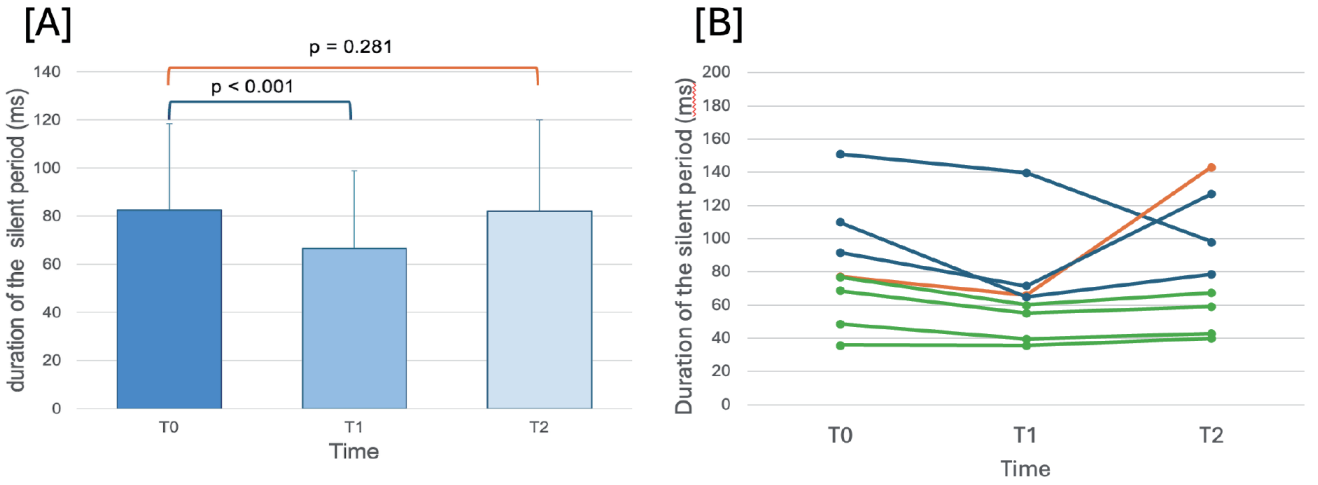


**Figure 3.** Graphs illustrate the duration of the cortical silent period at T0 and prior to each subsequent injection of anti-CGRP mAbs. High-frequency episodic migraine patients: green line; chronic migraine without medication overuse: blue line; chronic migraine with medication overuse: orange line. Data is shown as the mean ± standard deviation of numerous individuals (A) and for individual patients (B).

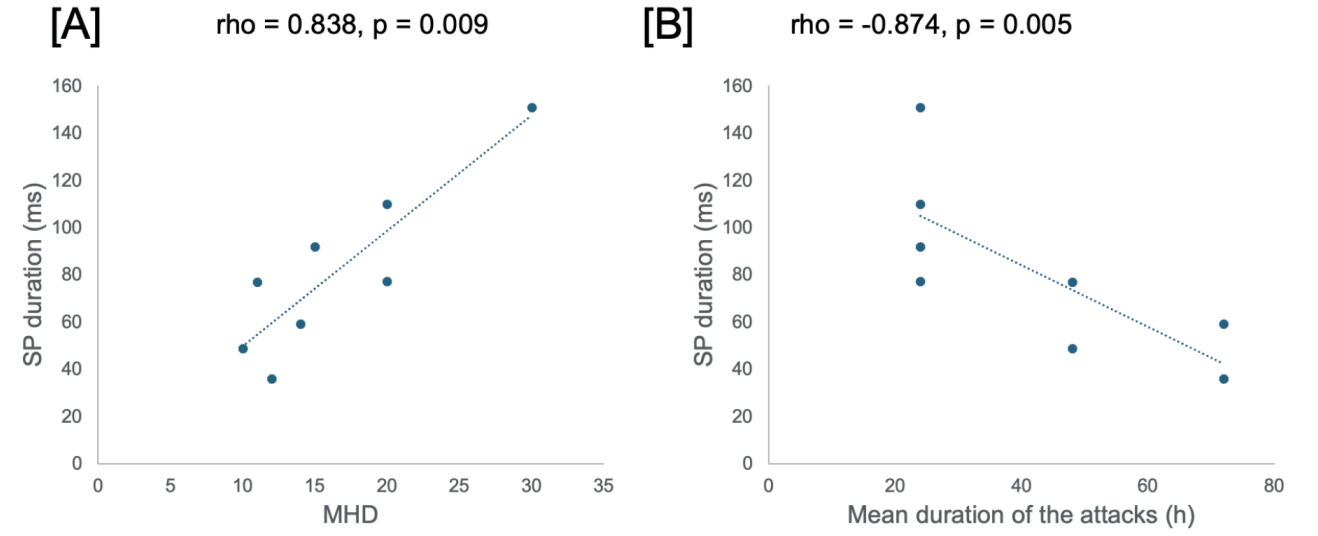


**Figure 4.** (A) Correlation between the duration of the silent period (SP) and the monthly headache days (MHD) at T0. (B) Correlation between the duration of SP and mean duration of attacks (hours) at T0.


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correlation with the percentage reduction in MHD at T1 (rho=-0.221, p=0.59) and T2 (rho=0.052, p=0.90), again compared to T0 (**Figure 5**).

## Discussion

The findings of this pilot study indicate that anti-CGRP mAbs can modify cortical inhibitory activity in migraine patients, as assessed by facial SP induced by TMS. This influence appears to be transient, occurring only during the first month of anti-CGRP mAbs treatment. Notably, there was a significant reduction in SP length at T1, which returned to baseline levels at T2. However, our data reveal no correlation between the percentage changes in SP length assessed at T1 and T2 relative to T0 and the percentage decrease in MHD measured at T1. In contrast, we found that the length of the inhibitory SP at baseline (before treatment) increases with headache frequency and decreases with prolonged attack duration.

Due to their high molecular weight, anti-CGRP mAbs are unlikely to cross the blood-brain barrier, indicating that their target is primarily the peripheral sensory terminals of the trigeminovascular system, most likely at the level of the dura mater. (1) In rats, about 10% of the fremanezumab or galcanezumab found in plasma was measured in peripheral tissues, including the trigeminal ganglion, while trace amounts (thousandths) were found in the central nervous system, such as hypothalamic parenchyma, prefrontal cortex, and cerebellum. (4) Anti-CGRP mAbs reduce the activation of high-threshold trigeminovascular neurons by dural afferents in the animal model. (24) Furthermore, the CGRP receptor antagonist BIBN4096BS diminishes the firing of central trigeminovascular neurons, which are stimulated by the superior sagittal sinus and receive input from wide dynamic range neurons or nociceptive specific neurons in facial cutaneous receptive regions. (25) Based on these considerations, continuous and sustained inhibition of the CGRP signaling pathway in peripheral trigeminal nerve fibers and ganglia may reduce the discharge to second-order brainstem trigeminal neurons. This may result in reduced sensitivity of trigeminovascular nociceptors and the ensuing excitatory inputs to third-order trigeminal neurons in the ventroposteromedial thalamic nucleus. We propose that such indirect anti-CGRP mAbs action may explain the reduced duration of SP after the first month of therapy. It is also possible that the SP shortening observed in patients at T1 may result from thalamo-cortical disfacilitation akin to that reported for the sensorimotor cortices. (26-28) The thalamo-cortical loops may control both the excitability of sensory cortices and modulate the activation of excitatory and inhibitory interneurons in the motor cortices. (29) Considering that thalamo-motor cortical facilitation predominantly relies on neuronal pathways in the basal ganglia, (30) the shortened SP may be associated with lessened thalamo-cortical facilitation of inhibitory motor interneurons originating from the basal ganglia. Accordingly, diminished functional thalamic (14) and augmented putamen connectivity (12) have been observed following the administration of the anti-CGRP receptor erenumab, while reduced somatomotor cortical thickness has been reported after galcanezumab administration in prior MRI analysis. (11) However, these investigations are only partially comparable to our study, as the first follow-up recording session was performed after 2 or 3 months. Notably, shorter SP duration has been previously reported in attack-free periods in episodic migraine in comparison with HVs. (20,21) Thus, anti-CGRP mAbs, producing a significant effect in reducing headache frequency, may transiently restore the interictal migraine electrocortical state. This hypothesis is partially supported by the observation that baseline SP duration depends upon migraine frequency, being shorter with fewer MHDs. The electrophysiological effect of anti-CGRP mAbs on sensory processing returned to baseline after two months of treatment, suggesting that peripheral blockade of the CGRP signaling pathway only transiently alleviates the central mechanisms associated with migraine recurrence.

The study's most evident weakness is the small sample size. This prevented us from dividing the patients into subgroups based on the diagnosis, which could explain the absence of baseline differences between migraine patients and healthy controls. However, electrophysiological data were consistent across all participants except for one (**Figure 3B**). Despite the absence of an association between electrophysiological and clinical alterations generated by anti-CGRP mAbs, the limited sample size precludes assessing whether cortical inhibitory activity varies with treatment response. Another limitation of our study is that we did not record the patients' parameters after three months of therapy. As a result, we cannot exclude that changes in the central nervous system produced by anti-CGRP mAbs need a longer time to influence pain modulation.

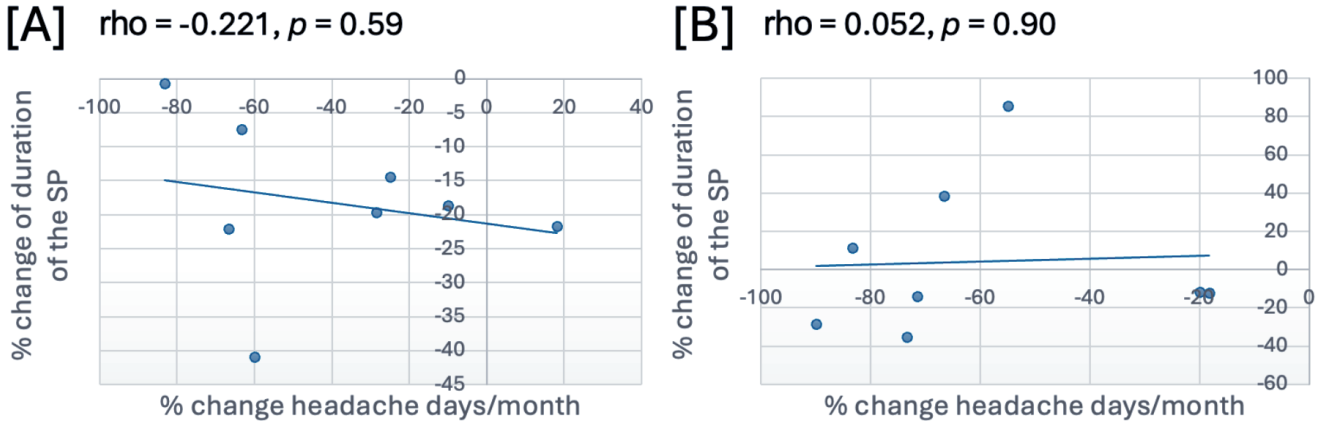


**Figure 5.** Scatter plots show no correlation between the percentage change in silent period (SP) duration and the percentage change in monthly headache days (MHD) at T1 (A) and T2 (B).

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## Conclusions

This pilot study revealed a transient reduction in cortical inhibitory activity following one month of treatment with anti-CGRP mAbs in patients with HF-MO or CM. Although these findings need confirmation in placebo-controlled studies with larger sample sizes and longer follow-up, they establish a basis for future research to investigate inhibition levels and cortical excitation following anti-CGRP mAbs therapy.

## Materials and Methods

**Subjects.** This was a pilot observational study. Migraine patients who were eligible for anti-CGRP mAbs according to our national criteria (*i.e.*, at least 8 monthly migraine days with MIDAS score ≥11 and failure to respond to a minimum of three prophylactic migraine treatments) were prospectively recruited from our headache center (Sapienza Università di Roma, Polo Pontino, Latina, Italy). We included only patients on stable migraine prophylaxis (n=3) or those who had not received any treatment for at least 2 months (n=5). Exclusion criteria included contraindications to the TMS, less than 8 monthly headache days per month in the previous three months, previous treatment with mAbs or oral anti-CGRP drugs, and previous use of botulinum toxin as a preventive therapy. Patients were instructed to complete a paper headache diary for at least one month before T0 and to continue to complete the diary throughout the study. Additionally, at T0, patients completed the Migraine Disability Questionnaire (MIDAS), the 6-item Headache Impact Test (HIT-6), and the 12-item Allodynia Symptom Checklist (ASC-12). We collected clinical characteristics, including disease duration (years), MHD (migraine-like or tension-type) (n/month), average monthly attack duration (h), attack severity (0-10 visual analogue scale), total monthly acute medication intake (n/month), and number of days with acute medication intake (n/month). For comparison, we recruited 8 HV, matched for age (44.4±14.1 for HV, 47.5±9.7 for patients, p=0.615) and sex (6 females in both groups), without any significant medical conditions, including personal or first-degree familiar history of migraine or any other primary headache. All participants were aware of the study's objective and provided written informed consent. The study protocol (Studio 23.20) received approval from the Lazio 2 Ethics Committee.

**Neurophysiological procedures.** All patients were recorded on days when they were headache-free. During the recording session, study participants underwent recording of their cortical silent period using a Digitimer D360 amplifier (band-pass 0.05–2000 Hz, gain 1000) and CED™ power1401 digital-to-analog converter (Cambridge Electronic Design Ltd, Cambridge, UK). The study participants were seated on an armchair in a quiet room and instructed to relax with their eyes open. The recording sessions were all carried out in the afternoon from 2 p.m. to 6 p.m. by two experienced neurophysiologists (FC and GS). Recordings were made at baseline (T0), 1 month (T1), and 2 months (T2) before each new anti-CGRP mAbs administration.

**Transcranial magnetic stimulation.** Stimuli were administered using a Magstim Super-Rapid device linked to a figure-of-eight coil (outside diameter 90 mm) positioned over the facial muscle hotspot. The coil was positioned with the handle facing rearward to elicit the maximum motor-evoked potential (MEP) amplitude. The stimulation intensity for eliciting the SP was either the highest level the participants could endure or the maximum output of the stimulator (ranging from 95 to 100%).

**Recording technique.** EMG responses were obtained from surface electrodes positioned across the left and right perioral muscles. (18) The active electrode was positioned 2 cm lateral to the midline in the mental area, whereas the reference electrode was situated 0.5 cm lateral to the ipsilateral labial commissure. These electrode placements capture EMG activity from the perioral muscles, specifically the orbicularis oris, risorius, and triangularis muscles. Subjects were instructed to "protrude their mouth vigorously", resulting in the recorded EMG activity primarily emanating from the orbicularis oris muscle.

EMG activity was captured and preserved for subsequent analysis using a CED™ power1401 device (Cambridge Electronic Design Ltd). EMG signals were amplified and filtered using Digitimer™ D360 pre-amplifiers (Digitimer Ltd, UK) with a band-pass of 200-5000 Hz and a gain of 1000, followed by full-wave rectification. Background EMG activity was documented for 200 ms prior to the administration of magnetic stimulation. Patients and controls were instructed to engage the target muscles at maximal strength by forcefully extending their mouths.

**Measurements.** The neurophysiologist and other personnel engaged in data recording and analysis were blind to the basal diagnosis. Given that TMS characteristics indicate cortical excitability, we assessed MEP latency and amplitude, as well as the length of the perioral muscular SP. We also assessed the background EMG activity during the 100 ms before TMS. All factors were assessed in six individual trials. The data were averaged to yield a single mean value for each variable, categorized by side and participant, for statistical analysis. The background pre-stimulus EMG activity was quantified as the area (mV×s) under the signal during the 100 ms before the stimulus. The MEP was measured as the area (mV×s) under the signal during the interval from the commencement of the MEP (*i.e.*, MEP latency) until the onset of the SP. The duration of the SP was measured from the conclusion of the MEP to the latency at which the EMG activity reverted to its mean pre-stimulus level.

**Statistical analysis.** The Statistical Package for the Social Sciences (SPSS) for Windows, version 21.0, was used for all the analyses (Armonk, New York, USA). Because of the limited sample size, we decided to use nonparametric tests. A Mann-Whitney U test was used to compare baseline neurophysiological data between migraine patients and the control group. The changes in the electrophysiological parameters pre- (T0) and post- (T1, T2) anti-CGRP mAbs administration were analyzed by Friedman repeated measures analysis of variance (ANOVA) on ranks. Tukey's test was used for *post-hoc* analyses.

Spearman's correlation tests were performed between the percentage changes in the MHD and percentage changes in SP duration at T1 and T2 compared with T0. Results were considered significant at $p<0.01$.

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Availability of data and materials: data supporting the findings of this study are reported in the article. The data collected and analyzed for this research are available from the corresponding author upon reasonable request.

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