

# Headache after evaluation with transcranial magnetic stimulation in a healthy participant. Case report

*Cefaleia após avaliação com estimulação magnética transcraniana em participante saudável. Relato de caso*

Julie Azevedo Araújo Valente<sup>1</sup>, Maria José Pedreira Ramalho<sup>2</sup>, Janine Ribeiro Camatti<sup>3</sup>, Abrahão Fontes Baptista<sup>4</sup>

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## ABSTRACT

**BACKGROUND AND OBJECTIVES:** Adverse effects during noninvasive stimulation of the brain are rare events. The objective of this study is to present a patient's case with an intense headache with autonomic signs after single-pulse transcranial magnetic stimulation.

**CASE REPORT:** A 28-year old female patient, volunteered to participate in a study on the evaluation of motor cortical excitability after the injection of lidocaine in the first dorsal interosseous muscle. The resting motor threshold was estimated at four moments: before the procedure, immediately after the procedure, 30 minutes, and one hour after the procedure. At the end of the experiment, 240 pulses were performed. The participant reported mild-intensity headache that rapidly progressed to severe, left hemispheric headache, the same region where the transcranial magnetic stimulation pulses were applied. In association with the pain, she had nausea, vomiting, photophobia, conjunctival hyperemia, lacrimation, and ipsilateral eyelid edema, requiring emergency care.

**CONCLUSION:** It is possible that supraliminal intensities (>100% of resting motor threshold) in single-pulse transcranial magnetic stimulation may predispose to adverse effects. Other factors such as skull anatomy, electrical impedance, age, gender, cognitive and affective status, use of medications, hormone levels, the concentration of neurotransmitters and receptor expression, genetic factors and the circadian cycle may also be involved. There are no well-established safety models to guide assessment

protocols with single-pulse transcranial magnetic stimulation, considered a technique with a low incidence of adverse effects and with little demand for safety studies.

**Keywords:** Case report, Headache, Transcranial magnetic stimulation.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS:** Efeitos adversos durante a estimulação não invasiva do cérebro são eventos considerados raros. O objetivo deste estudo foi apresentar um caso de paciente com cefaleia intensa com sinais autonômicos após estimulação magnética transcraniana de pulso único.

**RELATO DO CASO:** Paciente do sexo feminino, 28 anos, saudável, voluntariamente se apresentou para participar de pesquisa sobre avaliação de excitabilidade cortical motora após a realização de injeção de lidocaína no músculo primeiro interósseo dorsal. O limiar motor em repouso foi estimado em quatro momentos: antes do procedimento, imediatamente após o procedimento, 30 minutos e uma hora após o procedimento. Foram realizados ao final do experimento 240 pulsos. A participante referiu cefaleia, de leve intensidade, que rapidamente progrediu para cefaleia intensa, hemisférica à esquerda, na região onde os pulsos da estimulação magnética transcraniana foram aplicados. Em associação à dor, apresentou náuseas, vômitos, fotofobia, hiperemia conjuntival, lacrimejamento e edema palpebral ipsilaterais, com necessidade de atendimento em unidade de emergência.

**CONCLUSÃO:** É possível que intensidades supraliminares (>100% do limiar motor em repouso) em estimulação magnética transcraniana de pulso único possam predispor a efeitos adversos. Outros fatores como anatomia do crânio, impedância elétrica, idade, sexo, estado cognitivo e afetivo, uso de fármacos, níveis hormonais, concentração de neurotransmissores e expressão de receptores, fatores genéticos e ciclo circadiano também podem ser implicados. Não há modelos de segurança bem estabelecidos para guiar protocolos de avaliação com estimulação magnética transcraniana de pulso único, considerada uma técnica com baixa incidência de efeitos adversos e com baixa demanda de atenção de estudos sobre segurança.

**Descritores:** Cefaleia, Estimulação magnética transcraniana, Relato de caso.

Julie Azevedo Araújo Valente - <https://orcid.org/0000-0001-7417-9961>;  
 Maria José Ramalho - <https://orcid.org/0000-0002-4450-8565>;  
 Janine Ribeiro Camatti - <https://orcid.org/0000-0002-5726-8388>;  
 Abrahão Fontes Baptista - <https://orcid.org/0000-0001-7870-3820>.

1. Hospital São Rafael, Clínica da Dor, Salvador, BA, Brasil.
2. Hospital São Rafael, Departamento de Anestesiologia, Salvador, BA, Brasil.
3. Universidade Federal do ABC, Departamento de Neurociência e Cognição, São Bernardo do Campo, SP, Brasil.
4. Universidade Federal do ABC, Centro de Matemática, Computação e Cognição, São Bernardo do Campo, SP, Brasil.

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## Correspondence to:

Rua dos Corais, 679, Residencial Estrela do Mar, Alphaville 1  
 41701-080 Salvador, BA, Brasil.  
 E-mail: julieazvalente@gmail.com julie\_az@hotmail.com

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## INTRODUCTION

Transcranial Magnetic Stimulation (TMS) is based on the principle of electromagnetic induction of an electric field on

the skull surface of sufficient magnitude to trigger the depolarization of cortical neurons. Adverse effects during non-invasive brain stimulation are considered rare events<sup>1</sup>, especially during the administration of single- and paired-pulses, techniques used to assess cortical excitability<sup>1,2</sup>. Studies using single-pulse TMS can assess central motor conduction time and causal chronometry in brain-behavior relations<sup>1</sup>. The use of the paired-pulse allows the assessment of intracortical facilitation and inhibition measures, as well as the study of cortico-cortical interactions<sup>1</sup>. The occurrence of mild and transient headache, hearing impairment, neck pain, and toothache are considered possible adverse effects with these techniques<sup>3</sup>. Seizures, acute hypomania, histotoxicity, cognitive, brain and hormonal changes, such as elevated TSH and lactate levels, have not been described in studies with single- and paired-pulse TMS, although they have been reported during high-frequency repetitive transcranial magnetic stimulation (rTMS) and theta-burst protocols<sup>3</sup>.

This study aimed to present a case of severe headache with autonomic signs after single-pulse TMS in a healthy young woman.

## CASE REPORT

Right-handed, white, 28-year-old female patient volunteered to participate in research at the functional electrostimulation laboratory of the Federal University of Bahia (UFBA), to assess the motor cortical excitability after injection of lidocaine in the first dorsal interosseous muscle. After applying a safety questionnaire and signing the Free and Informed Consent Form, this participant was included in the study. She denied a history of comorbidities, drug use, recreational drugs, recent caffeine or cigarette consumption, sleep deprivation, implantable brain devices, seizure history, and pregnancy. When asked about the date of her last period, she could not remember the exact date, but said she was in the ovulatory period. This participant had previously volunteered in other studies involving TMS assessment without any complications.

Cortical excitability and organization were assessed with a TMS device (BISstim, Magstim, Reino Unido). After cleaning with alcohol and abrasive solution, the self-adhesive electromyography (EMG) electrodes (Miotec, Brasil) were placed on the muscular belly of the first dorsal interosseous (FDI), abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles of the participant's right (dominant) hand, which was comfortably seated in a chair, and kept awake throughout the assessment protocol. A polyester cap previously marked with a 1x1cm grid oriented in the Cartesian plane was placed on the participant's head and served as a reference for hotspot marking. An eight-coil was used on the surface of the left frontoparietal region, corresponding to the primary motor cortex. Monophasic paired- and single- pulses were administered every six seconds, and EMG activity was amplified and converted to digital signal (1401 and 1902, CED, Reino Unido) and monitored in real-time using Signal software (CED, Reino Unido). The average of 5 pulses in points under the described region was used to identify the hotspot, aiming to obtain the best response

in motor evoked potential (MEP) size in the FDI muscle. After this step, the resting motor threshold (RMT) was determined, considering the lower intensity of the device to generate a MEP peak-to-peak with an amplitude of 50  $\mu$ Volts. This threshold was estimated at four moments: before the procedure, immediately after, 30 minutes and one hour after the procedure. In each of these moments, 60 pulses were distributed randomly between 20 pulses at 100% of the RMT, related to MEP; 20 pulses at 80% of the RMT, with 2ms intervals, corresponding to the short-term intracortical inhibition measure, and 20 pulses at 120% of the RMT, with 15ms intervals, relative to the Intracortical Facilitation estimates, totaling at the end of the experiment 240 pulses.

The procedure, performed by an anesthesiologist, was chosen randomly by drawing sealed envelopes. The participant underwent dry needling in the FDI muscle of the dominant hand, and no substance was injected (Table 1).

**Table 1.** Electrophysiological measurements obtained by transcranial magnetic stimulation before and after dry needling in the first dorsal interosseous muscle of the dominant hand

	Baseline	Immediately after needling	30 min after needling	1h after needling
RMT	50	52	51	48
80% of RMT	40	42	41	38
120% of RMT	59	63	61	58

RMT = resting motor threshold.

During pulse application, the participant did not report any complaints. However, in the first minute after the end of the last data collection, the participant reported a mild headache that rapidly progressed to severe, left hemispheric headache. In association with headache, she presented nausea, photophobia, conjunctival hyperemia, tearing, and ipsilateral eyelid edema. She denied similar previous episodes, but reported an irregular history of premenstrual headache (mean of three to four episodes per year), however, without medical follow-up. Two anesthesiologists and two physical therapists were present during the collection and provided care to the participant, who was placed in a horizontal supine position on a stretcher and had vital signs checked within normal limits. Dipyron was administered orally. The participant was observed for approximately 60 minutes, until she reported headache improvement, and was then released and advised to contact the medical team involved in the research if symptoms returned. A few hours after being released, the participant presented headache return, with the same characteristics as before, but at this moment, accompanied by nausea and vomiting. She was instructed to use naproxen (500mg), cyclobenzaprine (5mg) and ondansetron (4mg) orally, with complete relief of symptoms, as well as outpatient follow-up with a neurologist. Two days after the event, the participant had her menstrual flow. The investigation was performed by cranial nuclear magnetic resonance and electroencephalogram without changes.

## DISCUSSION

The use of TMS devices has become increasingly common in both basic research and clinical therapies<sup>2</sup>. In the application of repetitive transcranial magnetic stimulation (rTMS), many safety parameters are suggested, such as the total number of pulses, duration, and intervals between pulses, intervals between stimulation sessions, coil type, and stimulation site<sup>3</sup>. In the application of single-pulse TMS, the pulse amplitude, in theory, does not cause therapeutic changes. Therefore, there are no well-established safety models to guide assessment protocols with single-pulse TMS, considered a technique with a low incidence of adverse effects and low attention demand from safety studies<sup>4</sup>. However, there are studies reporting adverse effects when supraliminal intensities (>100% of the RMT) are used in single-pulse TMS<sup>5</sup>. Moreover, more than just technical requirements, other factors can influence the response of TMS, being much more difficult to control, but no less important: skull anatomy, electrical impedance, age, gender, cognitive and affective state, drug use, hormone levels, neurotransmitter concentration and receptor expression, genetic factors and circadian cycle<sup>5</sup>.

Headache in single-pulse TMS protocols is considered a rare occurrence and little described in the literature<sup>6</sup>. In the last study on the safety and TMS, it was described that the presence of neck pain, toothache, and discomfort under the region where the coil is positioned are possible to occur with single pulses<sup>1</sup>. A study published in 2013 compared the incidence of adverse effects between single-pulse TMS and rTMS with results different from those described in the literature<sup>7</sup>. In this work, the incidence of adverse effects was more frequent in single-pulse protocols. The suggested explanation for this occurrence is the participant profile of single-pulse TMS protocols, often naive or with fantasies regarding the mechanism of action of TMS<sup>8</sup>. In the case of headache occurring in this case report, this argument cannot be applied since the participant had already participated in other study protocols, and she was aware of the TMS effects. The occurrence of trigeminal headache, with signs and symptoms very similar to those presented by the participant in this study, was described after the application of rTMS<sup>9</sup> protocol.

In this specific case, the etiology can be established by a therapeutic test performed with the administration of oxygen and immediate relief of symptoms. The diagnosis of the type of headache presented by the participant, whether trigeminal headache or migraine with autonomic signs<sup>10</sup> was impaired in this report since the data collection was performed in an out-of-hospital unit and without the presence of a neurologist. Thus, there was impairment in the assessment of the case, since the differential diagnosis was made retrospectively.

## CONCLUSION

Although rare, adverse effects are possible with the use of single-pulse TMS. It is critical that researchers be familiar with the most common occurrences to identify and follow up with each case.

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