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# Intermittent theta-burst stimulation for memory modulation in a patient with mild cognitive impairment and trigeminal neuralgia

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## Dear Sir,

Theta burst transcranial magnetic stimulation (TBS) is a noninvasive approach to modulate brain activity. A growing number of studies have focused on whether TBS can be used to improve memory in healthy older adults and those with incipient Alzheimer's Disease (AD) pathology using both intermittent (iTBS) and continuous TBS (cTBS)[1]. However, one important factor for neuromodulation in AD is the range of potential comorbid conditions and the landscape of inclusion or exclusion criteria based on pre-existing neurological and psychiatric conditions that is still being established.

Here we report an attack of ipsilateral trigeminal neuralgia that followed iTBS transcranial magnetic stimulation (TMS). The participant was a 74-year-old woman recruited into this study because of her diagnosis of mild cognitive impairment (MCI) with Alzheimer's Disease (AD) pathology based on cerebrospinal fluid biomarkers, who carried an additional history of trigeminal neuralgia (TN) and migraines. She has no brain abnormalities beyond mild hippocampal and lateral parietal lobe atrophy and mild to moderate periventricular leukoaraiosis associated with aging and AD-neuropathological changes. She was screened using a self-report questionnaire for contraindications to TMS, which revealed no cardiac or psychiatric conditions, family history of epilepsy, sleep deprivation, or drug abuse. Undisclosed substance use was ruled out by a urine drug test on the day of the event.

Trigeminal neuralgia is characterized by abrupt, recurrent, unilateral, and brief electric-shock-like pains triggered by innocuous stimuli. The participant was diagnosed with TN in the maxillary branch (V2) of the trigeminal nerve on the left side six years prior to

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enrolling in the study. Her condition is pharmacologically managed by regular Gabapentin and occasional Carbamazepine when attacks persist. The participant is not aware of any specific TN event triggers but believes that pain might be triggered by stress. TMS applied to the facial control region of primary motor cortex contralateral to pain has been studied as a possible treatment for TN[2] and there are no reports of worsening of TN after TMS. Nonetheless, we proceeded with caution, and a member of the research team (NBP) reviewed this participant's medical record and the existing studies on TMS in TN patients and found this participant eligible.

At the time of enrollment, this participant had not experienced a TN episode in six months. On the day of her visit, participant took 200 mg of a nonsteroidal anti-inflammatory drug (Advil). Participant was also prescribed: Aspirin (81 mg), Atorvastatin (40 mg), Donepezil (10 mg), Gabapentin (100 mg), Lisinopril (5 mg) and Carbamazepine (100 mg, every hour as needed) but patient reported not taking it up to one week preceding or during the TN event. Participant consumed approximately 140 mg of caffeine (coffee) and had slept 6.5 hours prior to this visit, which was approximately one hour less than usual.

The current study design seeks to improve memory through iTBS targeted to a participant-specific cortico-hippocampal network site in parietal cortex, in an NIA-sponsored research protocol approved by the Institutional Review Board of Duke University, to whom this incident was reported. After written informed consent and participants complete a baseline memory task during fMRI to identify the optimal target for stimulation based on subsequent memory differences in lateral parietal cortex. The stimulation site for this participant was ipsilateral to the side of her TN pain. Neuromodulation via iTBS then proceeds on three consecutive visits, and structural and functional MRI are collected immediately after iTBS to assess the time course of treatment effects.

## Event.

On the participant's first day of TMS, she arrived at 1 pm and completed resting motor threshold (RMT) determination, iTBS, and fMRI scan without event. RMT was 69% of maximum simulator output of a MagPro X100 machine with a MagVenture Cool-B65 figure-eight coil. Our use of this product was investigational. After motor threshold determination and target localization, iTBS was delivered at 80% RMT using the same coil positioned over the left angular gyrus using Brainsight (Rogue Research) for neuronavigation. Stimulation parameters for iTBS comprised of 50 Hz triplets at 5 Hz applied for 2 s with an inter-train interval of 8 s; 40 trains were delivered, lasting a total of 4.5 minutes. Approximately 1 hour and 10 minutes after iTBS concluded, participant experienced a 10–15 second attack of TN. Participant described this attack as occurring in the usual location and at the usual intensity, but at a shorter duration than her typical TN attacks. Participant experienced one more TN attack within 20 minutes of the first attack. Participant did not experience additional attacks that day or the next. Participant was evaluated via telehealth on the subsequent day by her neurologist (AL) who described this as a "lip twitching event". It is therefore possible that TBS targeted to the ipsilateral side could have irritated the trigeminal nerve and contributed to the subsequent TN attack.

## Discussion.

There are other reports of similar mouth twitches and pain during TMS including an instance of “dental pain” ipsilateral to stimulation during standard DLPFC rTMS treatment for depression[3]. One participant experienced this type of discomfort under treatment from a Magstim sham coil[4] that induces an electric field in the periphery as high as 25% of its peak active strength. This electric field may have superficially stimulated the trigeminal nerve resulting in efferent activation that irritated the mouth. However, in both instances, the pain occurred during stimulation and resolved with its termination. The effects of TBS on motor evoked potential (MEP) have been observed to last 25–60 minutes after the offset of stimulation[5]. Thus in our case, the participant experienced TN attacks within the possible window of time in which TBS effects are thought to last.

Future TMS studies that include individuals with TN should consider the stimulation target and location of TN attacks when determining eligibility since ipsilateral stimulation has the potential to irritate constricted or otherwise disrupted branches of the trigeminal nerve. It is possible that the effects on the trigeminal nerve emerged over an hour after stimulation concluded due to the longer-lasting impacts of TBS, but more work is necessary to determine the effects of TBS on peripheral nerve activity. In order to recognize adverse events after TBS and assess off-target effects, participants should be monitored well after stimulation concludes.

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