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## Transcranial Magnetic Stimulation Across the Menstrual Cycle: What Do Hormones Have To Do With It?

### Are Patterns of Cortical Hyper-Excitability Altered in Catamenial Epilepsy?

Badawy RA, Vogrin SJ, Lai A, Cook MJ. [published online ahead of print May 18, 2013]. *Ann Neurol*. doi: 10.1002/ana.23923.

**OBJECTIVE:** We used transcranial magnetic stimulation to determine menstrual cycle-related changes in cortical excitability in women with and without catamenial epilepsy and investigated whether these changes differed between ovulatory and anovulatory cohorts. **METHODS:** Healthy nonepilepsy women and women with generalized and focal epilepsy were investigated during ovulatory ( $n = 11, 46,$  and  $43,$  respectively) and anovulatory ( $n = 9, 42,$  and  $41$ ) cycles. Patients were divided based on seizure pattern into catamenial (C1 = perimenstrual, C2 = periovulatory, C3 = luteal seizure exacerbation), noncatamenial, and seizure free. Cortical excitability was assessed using motor threshold (MT) and paired pulse stimulation at short (2-15 milliseconds) and long (100-300 milliseconds) interstimulus intervals twice, at the (1) late follicular and (2) mid luteal phases of the menstrual cycle. **RESULTS:** In controls, cortical excitability was greatest in the follicular study, where intracortical facilitation was increased ( $p < 0.05$ ). The opposite was seen in women with epilepsy, where intracortical facilitation was greatest and intracortical inhibition was least in the luteal studies ( $p < 0.05$ ). There were no differences between the ovulatory and anovulatory groups in any of the cohorts. No changes were observed in MT. **INTERPRETATION:** Nonhormonal factors are involved in the cyclicity of cortical excitability across the menstrual cycle. Normal menstrual cycle variations in cortical excitability are altered in a similar pattern in ovulatory and anovulatory women with epilepsy regardless of seizure patterns. The underlying neural changes associated with epilepsy may alter responses to sex hormones. This may be an important underlying mechanism for catamenial seizure clustering.

### Commentary

The authors have performed a beautiful study of transcranial magnetic stimulation (TMS) in the follicular and luteal phases of the menstrual cycles of a small group of healthy nonepilepsy women ( $n = 20$ ) and a much larger group of women with epilepsy ( $n = 171$ ) and found some controversial results. Both groups were evaluated during either ovulatory or anovulatory cycles; it appears data were used for only one cycle per subject. The epilepsy group was divided into mutually exclusive multiple endocrinological and neurological categories: generalized versus partial epilepsy, and type of catamenial seizure pattern (C1-3) if any and ovulatory versus anovulatory. Most of the epilepsy group were highly refractory, having on average 6 seizures per month, with a minimum of 2 per month. However, a subset of the epilepsy group ( $n = 36$ ) were seizure free for at least 1 year.

The findings presented in this study are counterintuitive according to current conceptions of reproductive neurosteroid activity yet extremely thought-provoking about brain excitability in epilepsy assessed by TMS. The authors found no

differences in cortical excitability when comparing ovulatory versus anovulatory cycles in any groups, including healthy nonepilepsy controls. This lack of difference therefore includes women who reported catamenial seizure patterns, women with seizures or without seizures and, most importantly, women with low, normal, or high estrogen or progesterone levels, depending on the ovulatory status for the cycle studied. The hormone levels reported were consistent with the ovulatory status; indeed, an anovulatory cycle was defined as a midluteal progesterone level of  $<5$  ng/ml.

By way of background, TMS techniques such as central motor conduction time, the threshold and amplitude of motor evoked potentials allow the evaluation of motor conduction in the central nervous system. Advanced TMS applications used in epilepsy research include evaluation of brain excitability by deriving the cortical silent period length after motor stimulation, as well as paired-pulse stimulation that allows assessment of intracortical facilitation, generally thought to be glutamate-mediated activity, and intracortical inhibition, generally attributed to GABAA mediated-inhibition (1).

Reproductive hormones have little to do with TMS variation across the menstrual cycle according to these data. The authors have summarized previous studies nicely and presented those results that differ from their own: Hattemer et al. in 2006 reported an increase in excitability (decreased inhibition)



in the luteal phase as measured by TMS cortical silent period in 5 women with catamenial epilepsy; however, there was much overlap with the results in the follicular phase (2). In another finding contrasting with the current study, Hattemer et al. in 2007 did find differences in TMS parameters in a small number of healthy control women when comparing ovulatory versus anovulatory cycles (3). The authors acknowledge but do not explain these inconsistencies; one contributing reason may be that the investigators of the study under discussion did not perform cortical silent period assessment. However, the more important reason is that the current study is much larger than the previous studies, suggesting a Type 1 error in the previous work. Therefore, the results in more study subjects may bring us closer to the truth.

Intriguing findings are present here, though, indicating that TMS responses are altered due to having seizures in the setting of epilepsy, if not due to having ovulatory versus and anovulatory menstrual cycles. Healthy nonepilepsy women had increased cortical excitability evidenced by higher intracortical facilitation in the follicular phase compared to the luteal phase; this finding now meets the bar of being reproducible in that it was previously reported (4). One important finding in the current study is that in epilepsy patients, this gradient in cortical excitability is reversed: The luteal phase shows increased cortical excitability compared to the follicular phase. In fact, if one looks closely at the graphs of both the short and long interstimulus recovery curves for the epilepsy subjects, there is very little difference in responses when comparing phases of the menstrual cycle, as previously shown (2). Further observation of these graphs reveals that the responses in women with refractory epilepsy are very different than in control subjects. The responses in the long-term seizure-free group, however, are not dissimilar to controls. The graphs herein clearly show a luteal phase short response ISI curve in the seizure-free group not deviating from the normal curve, where as it is markedly increased from normal in all other epilepsy groups. Since the authors state they have excluded anti-epileptic drug (AED) effects by correlating AED type and levels with the responses, that leaves the epilepsy itself and seizure activity as possible causes of this finding. (These data are not shown, but the rest of the methodology is so painstaking that I tend to believe it.) This finding suggests a “dose effect” of seizures on TMS disruption, although the authors reported that in this study, seizure frequency had no effect on the results. In a slight contradiction of themselves, the lead authors’ previous work published this year shows that achieving seizure freedom with use of an AED decreases cortical excitability, indicating that seizure occurrence does play a role in the brain excitability parameters measured by TMS (5).

The authors’ previous work also shows that as measured by ISI, increased cortical excitability is present with new onset

generalized epilepsy prior to treatment, with decreases in excitability occurring with response to treatment (6). The seizure frequency in the new onset drug-naïve patients prior to TMS evaluation is unclear from this paper. In this work (6), motor threshold was lower in new onset drug-naïve subject while the motor threshold was higher in treatment responders; lower values indicate increased cortical excitability. Notably, no differences in motor threshold were found across groups in the current study.

So, what conclusions can we draw from the plethora of information revealed by TMS studies in persons with epilepsy compared to controls? An attempt to summarize from available research follows.

1. There is some inconsistency in the TMS data across studies.
2. Consistent findings include:
  - a. Estrogen and progesterone levels and, in turn, ovulatory versus anovulatory cycles do not have an influence on TMS-measured cortical excitability.
  - b. Epilepsy patients in general have measurably different TMS responses than healthy nonepilepsy controls.
  - c. Effective treatment decreases TMS cortical excitability.

The question as to whether epilepsy itself produces TMS alterations that are significantly different from normal remains unclear from the available data and provides opportunity for further exploration.

by Cynthia L. Harden, MD

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