EFFECT OF A HEALTHY MENSTRUAL CYCLE ON GAMMA OSCILLATIONS MEASURED WITH MEG

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Abstract. A balance between neural excitation and inhibition (E-I balance) is pivotal for normal cognitive functioning and is disturbed in neuropsychiatric disorders. Gamma oscillations (30–120 Hz) induced in the visual cortex by moving gratings arise through an interaction of excitatory and inhibitory neurons and are sensitive to the E-I balance. It has been suggested that suppression of the gamma response power caused by increasing the velocity of visual motion ('gamma suppression slope', GSS) can help to assess the E-I balance in neurological disorders (Orekhova et al., 2018a; Orekhova et al., 2018b). However, it is still unknown whether normal fluctuations of excitatory and inhibitory neurotransmission – such as those observed during a healthy menstrual cycle – also affect the GSS. To answer this question, we examined visual gamma oscillations in 18 healthy females during the follicular and luteal phases of their menstrual cycles, using magnetoencephalography. We found that gamma frequency and amplitude were higher in the luteal than in the follicular phase, which suggests their sensitivity to cyclic changes in excitation and inhibition. The GSS, however, remained stable, suggesting stability of the E-I balance in healthy women. Our results have implications for research in disorders characterized by abnormal cyclic fluctuations of the E-I balance, including premenstrual dysphoric disorder and catamenial epilepsy.

Keywords: excitation-inhibition balance, menstrual cycle, progesterone, magnetoencephalography, MEG, gamma rhythm

The excitation-inhibition balance (E-I balance) is an important characteristic of healthy brain functioning and development (Gatto et al., 2010) and its disturbance is thought to contribute to many neuropsychiatric disorders, such as epilepsy, autism, and schizophrenia (Dehghani et al., 2016; Foss-Feig et al., 2017). Detection of the E-I imbalance at early age may assist early diagnostics (Uzunova et al., 2015) and provide important information for clinical trials.

Up to date, the only accurate way to measure the neural E-I balance is to estimate firing rate of the excitatory and inhibitory neurons directly through cell recordings. This method is widely used in animals, but is it not applicable in humans. There is an urgent need for noninvasive biomarkers of the E-I balance in man (Levin & Nelson, 2015), which attracted attention of researchers to elec-

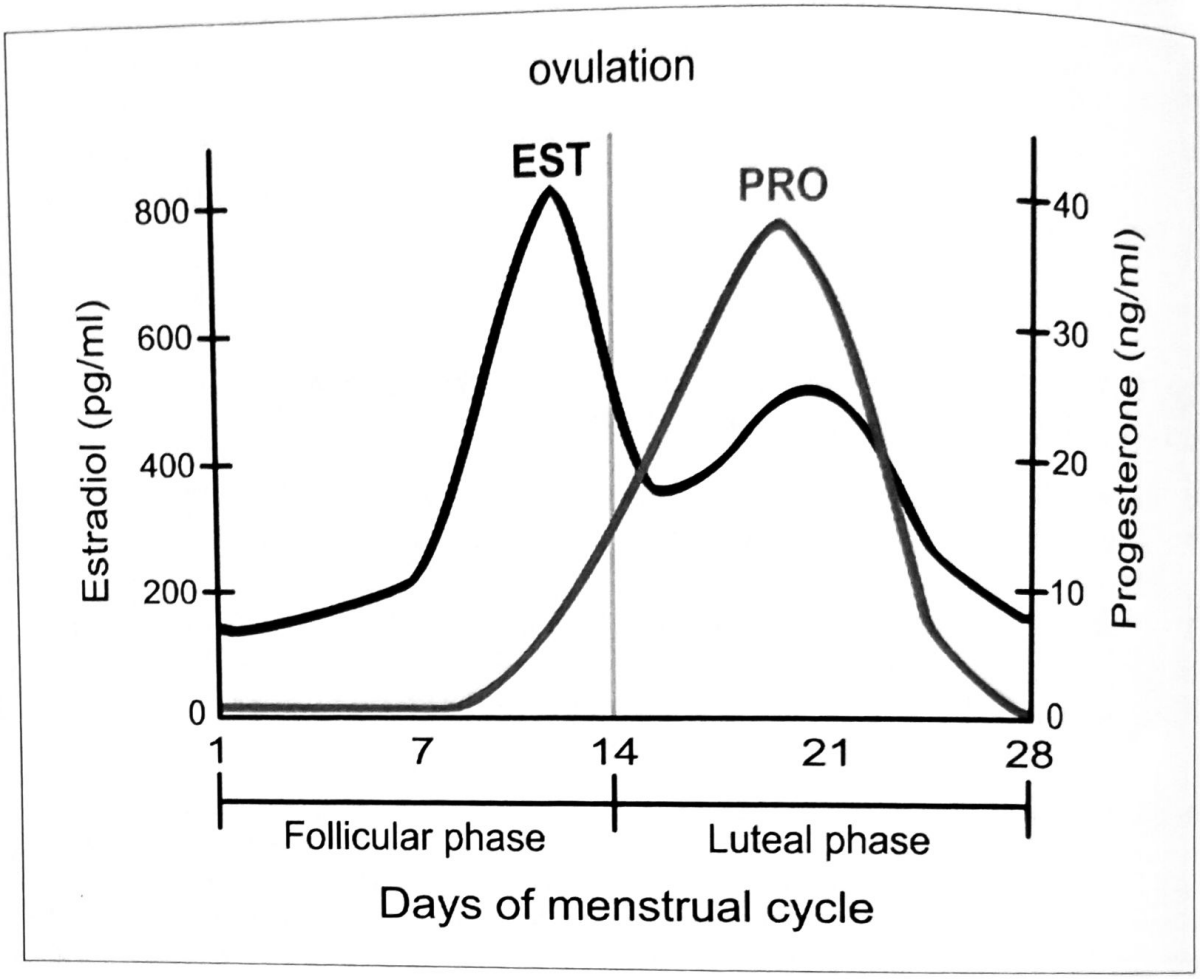

Figure 1. Progesterone (PRO) and estradiol (EST) blood levels during menstrual cycle.

tro-magnetic (MEG/EEG) oscillations in high-frequency range (30 to 120 Hz, gamma) as potentially useful biomarkers of this balance (e.g. Orekhova et al., 2018a).

Gamma oscillations arise through synchronizing influence of inhibitory GABA-ergic interneurons on excitatory pyramidal neurons through $GABA_A$ receptors (Whittington et al., 1995) and properties of these oscillations can help to noninvasively estimate regulation of the E-I balance in neural networks. There is however no agreement on what gamma parameters would be most informative to characterize the E-I balance. The previous findings of our group suggest that changes in gamma response power caused by intensive visual input provide most useful information in this respect, while power or frequency parameters alone are less informative (Orekhova et al., 2018a; Orekhova et al., 2018b). It has been previously found that gamma response power is nonlinearly modulated by intensity of visual input: it initially increases with increasing velocity of moving visual grating and then decreases with yet faster visual motion. We found that the reduced suppression of gamma response with increasing velocity of high-contrast visual gratings (i. e. reduced gamma suppression slope – GSS) is associated with sensory hypersensitivity and may characterize reduced capacity of inhibitory neurons to down-regulate neural excitation in response to increasing excitatory input.

To apply the GSS parameter to characterize the E-I balance it would be important to know whether this characteristic is individually stable or changes with

normal fluctuations in inhibitory and excitatory neurotransmission, as those observed in healthy women during menstrual cycle.

Changes in concentration of estrogen and progesterone hormones during phases of the menstrual cycle (fig. 1) affect excitatory and inhibitory neurotransmission in a complex way (Bäckström et al., 2011). In particular, allopregnanolone – the major progesterone metabolite and an allosteric modulator of $GABA_A$ receptor – increases during luteal phase and potentiates inhibitory neurotransmission. There was only one study that investigated how changes in neurosteroids concentration during menstrual cycle affect parameters of visual gamma oscillations (Sumner et al., 2018). These authors recorded visual gamma in women during early follicular and mid-luteal phases of the menstrual cycle and found increase of gamma peak frequency in luteal phase compared with follicular one.

Our primary aim in the present study was to investigate whether our putative measure of the E-I balance – gamma suppression slope (GSS) – is affected by stage on the menstrual cycle in healthy women. Besides, we thought to verify results of Sumner et al., 2018 using magnetoencephalography (MEG), the method that has higher sensitivity to fast oscillations than the EEG does (Muthukumaraswamy & Singh, 2013) and that is less affected by muscle artifacts (Hipp, Siegel, 2013).

Method

18 females (age: 18 – 40 years, $M = 29.2$, $SD = 6.65$) with regular menstrual cycle took part in our experiment. Their estradiol and progesterone blood level varied in normal range in both follicular and luteal phases. Our participants were observed in follicular (1 – 5 days) and luteal (20 – 25 days) phases of menstrual cycle. Phase affiliation was confirmed by blood tests performed by INVITRO company, underwent by every participant in the morning before an experiment.

In experimental task we measured visually-induced gamma activity. The visual stimulus was a large (18 × 18 degrees of visual angle) 100 % contrast circular sine wave grating, that either remained static or contracted toward the central fixation point. This kind of stimulation has been previously shown to induce strong gamma activity in V1 area (Hoogenboom et al., 2006). Here we used 4 contraction velocities: static stimulus (0 °/s), slow velocity (1.2 °/s), medium velocity (3.6 °/s), high velocity (6.0 °/s).

Experimental procedure for this study was previously tested in our laboratory (see fig. 2; Orekhova et al., 2018a). For data preprocessing and processing with sensor-level analysis we used MNE-python toolbox. The spectral power in prestimulus (–0.9 to 0 sec) and stimulation (0.3 to 1.2 sec) intervals has been evaluated using multitaper analysis. Normalized spectrum was obtained for every velocity (V0, V1, V2, V3) for further estimation of gamma power amplitude and frequency at a peak. For every participant and phase we calculated the GSS based on the normalized gamma spectra for V1, V2 and V3 velocities, as previously described (Orekhova et al., 2018a).

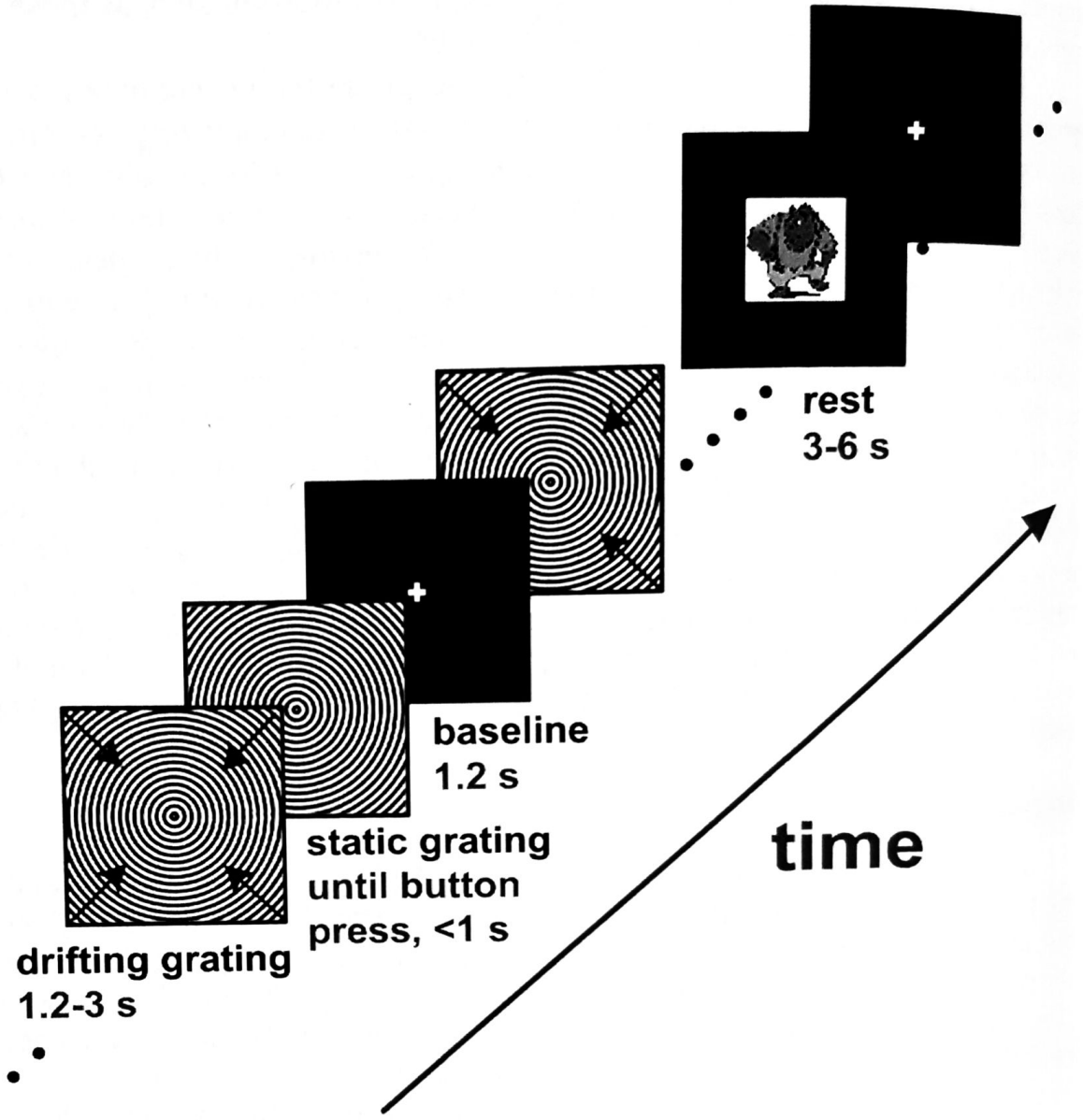

Figure 2. Experimental design. Arrows show direction of 'main stimulus' contraction.

Results

Visual motion induced strong and reliable gamma activation in visual cortex in all participants. Gamma peak frequency increases with the velocity growth regardless of the phase of the menstrual cycle (paired *t*-test, all $p < .05$). This result corresponds to previous findings (Orekhova et al., 2018a; Orekhova et al., 2018b). In accordance with these earlier studies, we observed that increase of contraction velocity resulted in bell-shaped changes of gamma response power. We found that gamma peak frequency significantly increases in luteal phase (paired *t*-test, all $p < .05$) and gamma power amplitude increases (V0, V2; Wilcoxon signed-rank test, all $p < .05$) or tends to increase (V1, Wilcoxon signed-rank test, all $p < 0.1$) in luteal phase of the menstrual cycle, too. Next, we compared GSS estimation in luteal and follicular phases and found no significant difference (paired *t*-test, $p > .5$).

Discussion and conclusions

Using MEG we observed in healthy women fluctuations in peak frequency of gamma oscillation, similar to those described by Sumner et al., 2018 using EEG. Specifically, the gamma frequency increased during luteal as compared with follicular phase. These frequency changes were paralleled by changes in gamma power: the power was higher in the luteal than in the follicular phase. Together these findings point to higher excitation of both excitatory and inhibitory visual cortical neurons in the luteal than in the follicular phase. Although counterintuitive, these phasic changes may be explained by paradoxical effects of allopregnanolone (Bäckström et al., 2011).

Most importantly, we found that despite the phase-related changes of gamma frequency and amplitude, modulation of the gamma response power (i.e. GSS) by velocity of visual motion remained stable across phases. Considering our previous findings pointing to the GSS as a possible biomarker of the E-I balance, this result suggests that despite cyclic changes in neurotransmission during menstrual cycle, the neural excitation and inhibition in healthy women remained well-balanced.

Our findings have important implications for studies in cyclic disorders related to the phase of menstrual cycle, such as catamenial epilepsy and premenstrual dysphoric disorder (Halbreich et al., 2003; Herzog, 2016). It has been suggested that women suffering these disorders may have abnormal neural responses to changes in neurosteroids concentration during menstrual cycle (Bäckström et al., 2011). Examination of cyclic changes in parameters of gamma brain waves may help to unravel neural mechanisms of these abnormalities and potentially facilitate development of treatments aimed to improve life quality of life in women suffering these disorders.

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ИЗУЧЕНИЕ ВЛИЯНИЯ МЕНСТРУАЛЬНОГО ЦИКЛА НА ГАММА ОСЦИЛЛЯЦИИ МЕТОДОМ МАГНИТОЭНЦЕФАЛОГРАФИИ (МЭГ)

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Аннотация. Оптимальное соотношение возбуждения и торможения в нейронных сетях головного мозга необходимо для поддержания когнитивных функций, в то время как нарушения этого баланса ассоциированы с многими психическими заболеваниями. Гамма осцилляции (30 – 120 Гц), вызванные в зрительной коре движущимся стимулом-решеткой, возникают вследствие взаимодействия между возбуждающими и тормозными нейронами и чувствительны к балансу между возбуждением и торможением. Исследования нашей группы показали, что увеличение скорости движения стимула-решетки вызывает снижение мощности гамма (СМГ), а также, что СМГ может использоваться для оценки соотношения между возбуждением и торможением у пациентов с различными расстройствами (Orekhova et al., 2018a; Orekhova et al., 2018b). В то же время, остается неясным, влияют

ли на этот показатель колебания в активности возбуждающих и тормозных нейромедиаторных систем, как то наблюдается при нормальном менструальном цикле у женщин. Чтобы проверить это, мы регистрировали зрительную гамма-активность у 18 здоровых женщин в фолликулярной и лютеальной фазах менструального цикла с помощью магнитоэнцефалографии (МЭГ). Мы обнаружили, что частота и амплитуда гамма осцилляций были выше в лютеальной фазе по сравнению с фолликулярной, что предполагает чувствительность гамма-активности к фазе менструального цикла. Однако показатель СМГ остался неизменным в обеих фазах, что предполагает сохранность баланса между возбуждением и торможением у здоровых женщин. Проведенное исследование имеет приложение в области исследования заболеваний, связанных с патологическими циклическими изменениями в балансе между возбуждением и торможением (предменструальное дисфорическое расстройство, катаменциальная эпилепсия).

Ключевые слова: баланс возбуждения и торможения, менструальный цикл, прогестерон, магнитоэнцефалография, МЭГ, гамма-ритм