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Progesterone modulates theta oscillations in the frontal-parietal network

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Abstract

The neuroactive metabolites of the steroid hormones progesterone (P4) and testosterone (T) are GABAergic modulators that influence cognition, yet, the specific effect of P4 and T on brain network activity remains poorly understood. Here, we investigated if a fundamental oscillatory network activity pattern, often related to cognitive control, frontal midline theta (FMT) oscillations, are modulated by steroids hormones, P4 and T. We measured the concentration of P4 and T using salivary enzyme immunoassay and FMT oscillations using high-density electroencephalography (EEG) during eyes-open resting-state in 55 healthy women and men. Electrical brain activity was analyzed using Fourier analysis, aperiodic signal fitting, and beamformer source localization. Steroid hormone concentrations and biological sex were used as predictors for scalp and source-estimated amplitude of theta oscillations. Elevated concentrations of P4 predicted increased amplitude of FMT oscillations across both sexes, and no relationship was found with T. The positive correlation with P4 was specific to the frontal midline electrodes and survived correction for the background aperiodic signal of the brain. Using source localization, FMT oscillations were localized to the frontal-parietal network (FPN). Additionally, theta amplitude within the FPN, but not the default mode network, positively correlated with P4 concentration. Our results suggest that P4 concentration modulates brain activity via upregulation of theta oscillations in the FPN.

KEYWORDS

aperiodic signal correction, EEG, frontal midline theta, frontal-parietal network, progesterone, source localization, steroid hormones, theta oscillations

1 | INTRODUCTION

The metabolites of the sex steroids, progesterone (P4) and testosterone (T), are allosteric modulators of the gamma-aminobutyric acid ($GABA_A$) receptor and impact cognition (Celec, Ostatníková, & Hodosy, 2015; Schumacher et al., 2014; Zurkovsky, Brown, Boyd, Fell, & Korol, 2007), as well as other biological and affective systems. The

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progestogens (e.g., P4) and androgens (e.g., T) are classes of sex steroids that differentially engage neural activity patterns in functional neuroimaging (Peper, van den Heuvel, Mandl, Hulshoff, & Pol, and Jack van Honk., 2011) and differentially influence cognition (Pletzer, Petasis, & Cahill, 2014). In particular, a recent study found that elevated concentrations of P4 correlated with better performance in the N-back working memory task (Hidalgo-Lopez & Pletzer, 2017) suggesting a role for P4 in boosting cognitive control. Consistent with a role of P4 in cognitive control, increased resting-state connectivity within the frontal-parietal network (FPN) in functional magnetic resonance imaging (MRI) positively correlated with P4 concentrations (Syan et al., 2017). Despite emerging evidence for a role of P4 in cognitive control, there has yet to be an investigation into the electrical brain activity patterns that might underlie this influence. Frontal midline theta (FMT) oscillations (4–7 Hz) are an ideal candidate for how P4 may influence brain activity (see Cavanagh & Frank, 2014 for review).

T concentrations are associated with alterations in social cognition: social decision-making (Eisenegger & Naef, 2011), aggression (Montoya, Terburg, Bos, & Van Honk, 2012), and social status (Eisenegger, Haushofer, & Fehr, 2011). Consistent with the role of T in social cognition, greater concentrations of T are correlated with decreased functional connectivity between the orbitofrontal cortex (critical region for social cognition) and the amygdala (critical region for processing emotionally salient perception) (Ackermann et al., 2012). Frontal theta oscillations also have been shown to play a role in social cognition (Narayanan et al., 2011; Tendler & Wagner, 2015). Therefore, T concentration may also be predictive of the amplitude of FMT oscillations.

We investigated the relationship between the steroid hormones, P4 and T, and the amplitude of FMT oscillations using salivary enzyme immunoassay and recorded high-density electroencephalography (EEG) during the resting-state in men and women. Using source localization, we investigated the neural origin of FMT oscillations and correlated theta activity in the FPN to steroid hormone concentrations.

2 | METHOD

Data from 55 participants were pooled across three experiments (22 from National Clinical Trial 0324450 (Sheffield, Ahn, Alagapan, & Fröhlich, 2019), 14 from NCT03243084 (Ahn, Prim, Alexander, McCulloch, & Fröhlich, 2019), and 19 from NCT03178344). About 23 participants were female and 32 participants were male. Participants were ages 18 to 70 years with an average age of 28.8 years and standard deviation of 12.9 years (Table 1). Seven participants were 50 years of age or older. In each of these studies, we sampled steroid hormone concentrations via saliva sample and collected resting-state electrical brain activity via high-density EEG. All experiments were approved by the institutional review board at the University of North Carolina at Chapel Hill and data were collected at the Carolina Center for Neurostimulation. Participants were screened prior to enrollment with the following inclusion criteria: no personal or immediate family history of neurological or psychiatric illness, no ongoing psychotherapy treatment or use of medication to treat a neurological or psychiatric illness, no major head injury or brain surgery, no brain implants (including cochlear implants), no history of cardiovascular disease. All participants were required to pass a urinary drug test and women were screened with a pregnancy test. Participants were asked to maintain a regular sleep schedule prior to the experimental sessions, as well as abstain from alcohol and caffeine for the 24 hr prior to the visit.

TABLE 1 Sex differences

Mean (SD)	Women (N = 23)	Men (N = 32)	Women and men (N = 55)	Sex difference (w − m)	
				t (53)	*d*
Age (18–70 years)	31.1 (13.7)	27.2 (12.3)	28.8 (12.9)	1.10	0.30
Progesterone (P4) (pg/ml)	142.3 (103.7)	112.4 (76.9)	124.9 (89.5)	0.16	0.04
Testosterone (T) (pg/ml)	20.2 (8.51)	94.3 (38.5)	63.3 (47.3)	**−13.4*****	3.62
Frontal midline theta (μV)	0.994 (0.31)	0.928 (0.24)	0.956 (0.27)	0.13	0.04

Note: Descriptive estimates, mean and standard deviation (*SD*), for all variables are displayed by sex. Data were normalized prior to *t* test according to the description in Methods.

***$p < .001$.

2.1 | Statistical analysis

Our primary analysis was to test for a correlation (Pearson) between the amplitude of FMT oscillations with P4 or T concentration. To correct for multiple comparisons, we used the Bonferroni method and consider a correlation significant at alpha of .025. Upon finding a significant correlation, we tested for the specificity of this relationship by comparing correlations between steroid hormones. For this analysis, we used Pearson and Filon's comparison of correlations with an overlapping variable (Pearson & Filon, 1898) implemented by the "cocor" toolbox (Diedenhofen & Musch, 2015) in R (The R Foundation).

Steroid hormone concentration of P4 and T is known to decrease with age (Ukkola et al., 2001). Therefore, to control for age, we investigated if the difference in correlations between steroid hormones was still significant after removing the variance that was explained by age (Pearson partial-correlation). The physiological impact of steroid hormones is also known to be mediated by sex. Therefore, we also investigated if the relationship was sex-specific by comparing correlations between women and men for each steroid hormone to FMT amplitude (Pearson and Filon). If no difference was found, then, follow-up analyses were run on the full group. However, given the relevance of sex to the function of steroid hormones, we report sex-specific effects as an exploratory analysis.

We ran three control analyses that tested for the frequency specificity of the relationship (see Section 2.3), scalp specificity of the relationship (see Section 2.3), and addressed a confound to interpreting neural oscillations (see Section 2.4). Frequency specificity was evaluated using a difference in correlation with neighboring oscillations (Pearson and Filon). Spatial specificity was quantitatively investigated in a control site and qualitatively assessed via an exhaustive topographic correlation analysis (Pearson). A confound that theta oscillations may be an artifact of the aperiodic signal (described in Section 2.4) was assessed by correlation (Pearson) after aperiodic signal removal. Finally, we ran a follow-up analysis that investigated the network origin of the theta oscillation using source localization (see Section 2.5). The relationship of source localized theta amplitude to steroid hormone concentration was investigated by comparing correlations between steroid hormones (Pearson and Filon) and using post hoc correlation analysis (Pearson).

2.2 | Steroid hormone enzyme immunoassay

Steroid hormone concentrations were assessed via four saliva samples taken throughout a single day: before breakfast, before lunch, before dinner, and before bed. Participants were instructed not to eat for an hour before giving the sample. By sampling across four timepoints in a single day, we controlled for the known diurnal fluctuation in salivary hormone concentration (Konishi, Brindle, Guyton, & O'Connor, 2012). In each experiment, participants were provided with the saliva sample kit in their first session and returned the kit in their second session that was scheduled for a week later. EEG data were used from the first session of each experiment. Thus, the saliva samples reflect hormone concentrations in the week following the EEG. Samples were sent to Labrix for assay (Clackamas, OR, USA). Labrix pooled the four samples into a single sample estimate and conducted enzyme immunoassays for P4 and T. The P4 (4-pregnen-3,20-dione) enzyme immunoassay kit was provided by Salimetrics Inc (State College, PA, USA) with a limit of detection of 5 pg/ml, a strong correlation between salivary P4 and serum P4 ($r(35) = .80$), and no detectable (<.004%) cross-reactivity with T (Salimetrics Salivary Progesterone Enzyme Immunoassay Kit Item No. 1-2502). The kit measured free P4 in the saliva that was not bound to serum proteins and was considered biologically active. The T enzyme immunoassay kit was the Pantex Salivary Direct Testosterone EIA Kit by Pantex Division of Bio-Analysis (Santa Monica, CA, USA) with a limit of detection of 2.1 pg/ml and low cross-reactivity with P4 (0.28%) (Pantex Salivary Direct Testosterone EIA Kit Catalog No. 635). One to two percent of T is free in plasma, and this concentration is highly correlated with free T in saliva. Like P4, the kit measured only biologically active T. The immunoassays have an exponential distribution. Therefore, raw values were log-transformed prior to all statistical analysis. Range and descriptive metrics are provided in Table 1.

2.3 | High-density EEG

EEG data were collected with a high-density 128-channel electrode net at 1,000 Hz (HydroCel Geodesic Sensor Net) and EGI system (NetAmps 410, Electrical Geodesics Inc., OR, USA). The impedance of each electrode was ensured to be below 50 kΩ at the start of each session. Four-minutes (5 min in 19 participants from NCT03178344) of eyes-open resting-state EEG was collected.

The resting-state EEG data were preprocessed using custom scripts in MatLab and the EEGLAB toolbox (Delorme & Makeig, 2004). All EEG data were downsampled to 250 Hz with antialiasing filtering and band-pass filtered from 1 to 50 Hz. The data were then preprocessed using an artifact subspace reconstruction algorithm to remove high-variance signal and reconstruct missing data (Mullen et al., 2013). Channels that were found in the previous step to contain above threshold noise were interpolated.

All data were common average referenced. An infomax independent component analysis (ICA) was performed to separate plausible neural activity from eye blinks, eye movement, muscle activity, heartbeats, and channel noise (Jung et al., 2000). All ICA components were visually inspected and components corresponding to noise were manually rejected. Resting-state EEG data were epoched into two-second windows.

Our analysis was restricted to the 90 channels on the scalp, referred to as data channels. The fast Fourier transform was applied to each two-second epoch and the average spectral amplitude was calculated by median to reduce spurious amplitude fluctuations from outlier epochs. FMT amplitude was calculated as the average amplitude from 4 to 7 Hz, the canonical theta band, for the FCz channel. The range and descriptive metrics for the amplitude of FMT oscillations is provided in Table 1. To reduce multiple comparisons, we restricted our primary analysis to this single channel. We were interested in the frequency specificity of our effects. Thus, as a control analysis, we calculated the amplitude of alpha oscillations (8–12 Hz) and beta (15–30 Hz) oscillations and compared the correlation of these bands with steroid hormone concentrations with that of FMT amplitude. As an additional control analysis, we also estimate spectral amplitude in an occipital-midline electrode, Oz, that is known to be dominated by alpha, but not theta, oscillations, and correlated these estimates with steroid hormone concentration.

Furthermore, we hypothesized that theta amplitude, and thus, its correlation with steroid hormone concentration would be spatially localized to the frontal midline. To estimate the spatial distribution of theta amplitude across the scalp, we log-transformed theta amplitude for each of the 90 data channels and applied a spatial normalization using the *z*-transformation for each participant. We hypothesized that a genuine correlation with FMT oscillations would be confined to a cluster of electrodes surrounding FCz.

2.4 | Correction for aperiodic signal

Recent evidence suggests that the aperiodic signal in the background brain activity may play a meaningful role in modulating cognition and predicting healthy aging (Voytek et al., 2015). As the aperiodic signal of the brain, a $1/f$ power distribution, steepens, there will be an increase in theta and delta power (2–7 Hz). The change in slope could lead to the erroneous conclusion that theta oscillations are increasing, when the more parsimonious explanation is a steepening of the aperiodic signal slope (Gao, Peterson, & Voytek, 2017). A true oscillation under this framework is defined as a band-limited increase in spectral power over and above the aperiodic background spectra (He, 2014). Therefore, we calculated the aperiodic signal for each participant and subtracted it in order to confirm that the measured theta oscillations represent true oscillations. We calculated the aperiodic signal as a linear fit to the log(amplitude) and log(frequency) of each participant. As the alpha oscillation is prominent in EEG during the resting state, we calculated the aperiodic signal as the linear fit to amplitude values from 2 to 4 Hz and 40 to 50 Hz (see Voytek et al., 2015 for a similar method). After fitting the data for each participant, we subtracted the fit amplitude across all frequencies in order to calculate theta amplitude after aperiodic signal correction.

2.5 | Network analysis

Our large sample size and use of a 128-channel EEG system provided a methodological foundation for source localization analysis to investigate the spatial origination of FMT oscillations. Source localization was run using the Dynamical Imaging of Coherent Sources (DICS) beamformer algorithm implemented in the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). For each two-second epoch of resting-state data, we calculated the spectral amplitude for each channel via 5-cycle Morlet wavelet convolution at 6 Hz. Next, we calculated the cross-spectral density matrix to estimate the phase difference and shared amplitude of each channel pair for source localization. The beamformer algorithm was run using a lead field calculated in the Montreal Neurological Institute (MNI) space using standard skull, skin, and brain tissue estimates provided in the FieldTrip toolbox. Theta amplitude was source localized into MNI space for each two-second epoch, and then, averaged across epochs. The theta amplitude estimates from source localization were not normally distributed. Therefore, the data were log-transformed. We applied spatial normalization using the z-transformation for all voxels within a grey-matter mask in MNI space derived from tissue segmentation estimates provided by the SPM12 toolbox (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011). For display purposes, an independent *t* test between participants with high and low FMT amplitude in sensor-space (median split) was run on theta amplitude for every voxel in source-space.

Investigation into the temporal and spatial engagement of the human brain during cognitive control has found two primary signals: one spatial and one temporal. Electrophysiology researchers find increased amplitude of FMT oscillations and hypothesized that these signals originate from the anterior cingulate cortex or medial prefrontal cortex directly beneath the scalp sensors with peak FMT amplitude (see Cavanagh & Frank, 2014 for review), whereas functional neuroimaging

researchers find increased functional connectivity and activation within the FPN as a function of increased cognitive control as driven by task demands (see Badre & Nee, 2018 for review). When dipoles in homologous brain regions are aligned in opposite directions (e.g., medial to lateral), the resulting electric field is found in the space between the two dipoles where the field inverts. This principle of electric field modeling is found in task-evoked electrical activity. For example, in auditory tasks, peak auditory-evoked electrophysiological signal is found in central midline electrode, Cz; but via source localization auditory activity is found to be driven by bilateral auditory cortex (Stropahl, Bauer, Debener, & Bleichner, 2018). Therefore, we hypothesized that source localization of FMT oscillations would reveal greatest theta amplitude in bilateral frontal cortex (Sasaki, Tsujimoto, Nambu, Matsuzaki, & Kyuhou, 1994; Sasaki, Tsujimoto, Nishikawa, Nishitani, & Ishihara, 1996) and not in superior frontal gyrus or medial prefrontal cortex.

Bilateral middle frontal gyri have network membership in the task-positive FPN, whereas anterior superior frontal gyrus and medial prefrontal cortex have network membership in the default mode network (DMN) (Yeo et al., 2011). To quantify the degree to which theta oscillations were source localized to the FPN as opposed to the DMN, we averaged theta amplitude in grey-matter voxels of the FPN and DMN. FPN and DMN were defined as the sixth and seventh network from the seven-network Yeo atlas derived from resting-state functional connectivity analysis (Yeo et al., 2011). This network analysis provides a critical dimensionality reduction by which 10,000s of voxels are reduced to two networks; and therefore, addresses the multiple comparisons problem. Analyses were run using custom code written in MatLab using functions from SPM12 and Fieldtrip.

2.6 | Code accessibility

Scripts used for these analyses can be found in our code repository for this study on the Open Science Framework (https://osf.io/6j253/).

3 | RESULTS

The goal of the study was to test for a possible relationship between P4 or T concentration and the amplitude of FMT oscillations. We applied the Bonferroni method for multiple comparisons and considered an alpha of .025 to be significant. P4 concentration was positively correlated with FMT amplitude for all participants ($r(54) = .370$, $p = .005$) (Figure 1a), and T concentration was not correlated with FMT amplitude ($r(54) = -.003$, $p = .981$; Figure 1b). The correlation between FMT amplitude and P4 concentration was significantly greater than the correlation with T concentration (Pearson and Filon, $z(54) = 2.462$, $p = .014$). Thus, the relationship of FMT amplitude to P4 concentration was hormone specific. Furthermore, the correlation between FMT amplitude and P4 concentration explained unique variance when controlling for T concentration (partial-correlation, $r(54) = .386$, $p = .004$) despite a positive relationship between P4 and T concentration ($r(54) = .279$, $p = .039$). P4 and T concentration are known to decrease with age (Ukkola et al., 2001), and indeed this was the case within our data set for both P4 ($r(54) = -.352$) and T ($r(54) = -.355$). When controlling for age, the correlation between P4 concentration and FMT amplitude was still greater than the correlation with T concentration (partial-correlation Pearson and Filon, $z(54) = 3.301$, $p = .001$).

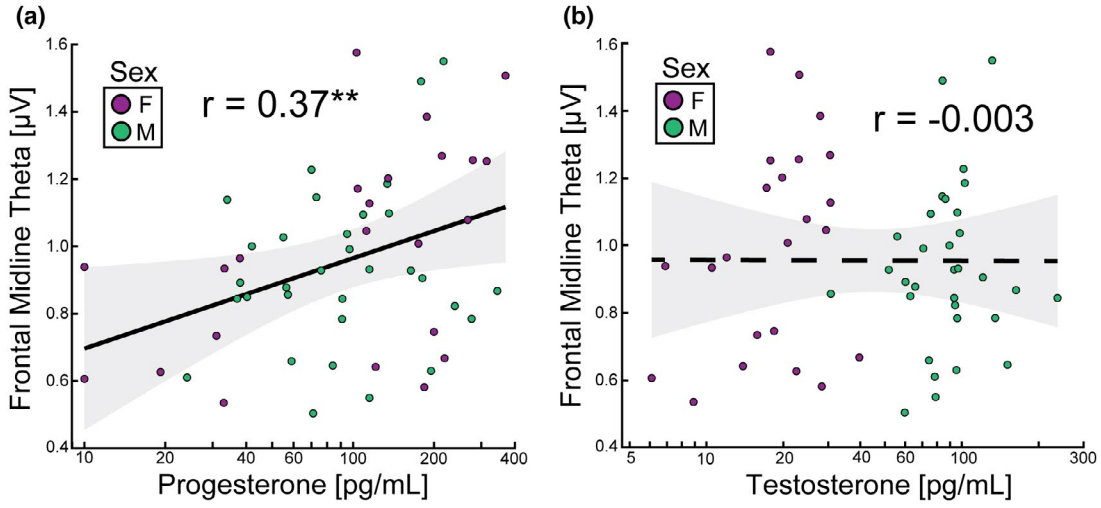

FIGURE 1 Frontal midline theta (FMT) amplitude to steroid hormone correlation analysis. Correlation analysis (Pearson; $N = 55$) of progesterone (a) and testosterone (b) concentration to FMT oscillatory amplitude. Solid line depicts significant relationship, dotted line is nonsignificant. Shaded area is 95% confidence interval. $^{**}p < .01$. F, female; M, male

As a follow-up analysis, we investigated a potential sex difference between these findings. Critically, the difference in correlation of P4 concentration to FMT amplitude between women and men was not significant (Fisher, $z(53) = 1.240$, $p = .215$), nor was the difference significant for T concentration (Fisher, $z(53) = 0.824$, $p = .410$). As there was no difference in correlation between women and men, all follow-up and control analyses were run ignoring sex as a factor. However, given the relevance of sex as a biological factor in the action of steroid hormones, we include the separate analyses for women and men as uncorrected exploratory analyses in Table 2, and qualitative differences between the sexes are reviewed in the discussion section.

TABLE 2 Exploratory analysis by sex

	Women (N = 23)		Men (N = 32)	
R-values	**P4**	***T***	**P4**	***T***
Raw FMT amplitude	**0.498***	0.322	0.184	0.094
FMT w/o aperiodic	0.383˜	0.201	0.104	−0.018
Theta [FPN–DMN]	0.380˜	0.284	0.217	0.127

Note: Exploratory correlation analysis (Pearson) between steroid hormone concentrations and the amplitude of theta oscillations for each primary analysis (see Section 2.3, 2.4, and 2.5) independently for both sexes.

Abbreviations: DMN, default-mode network; FMT, frontal midline theta; FPN, frontal-parietal network; w/o, without.

*$p < .05$; ˜$p < .1$.

To assess the frequency specificity of the relationship between P4 and peak theta amplitude, we analyzed the difference in correlation from peak alpha (8–12 Hz) and peak beta (15–30 Hz) amplitude (Figure 2a and Table 3). The increased correlation from FMT amplitude to P4 concentration was greater than alpha amplitude at a trend-level (Pearson and Filon, $z(54) = 1.812$, $p = .070$), and the difference in correlation from beta amplitude was significant (Pearson and Filon, $z(54) = 2.059$, $p = .040$). These findings provide evidence

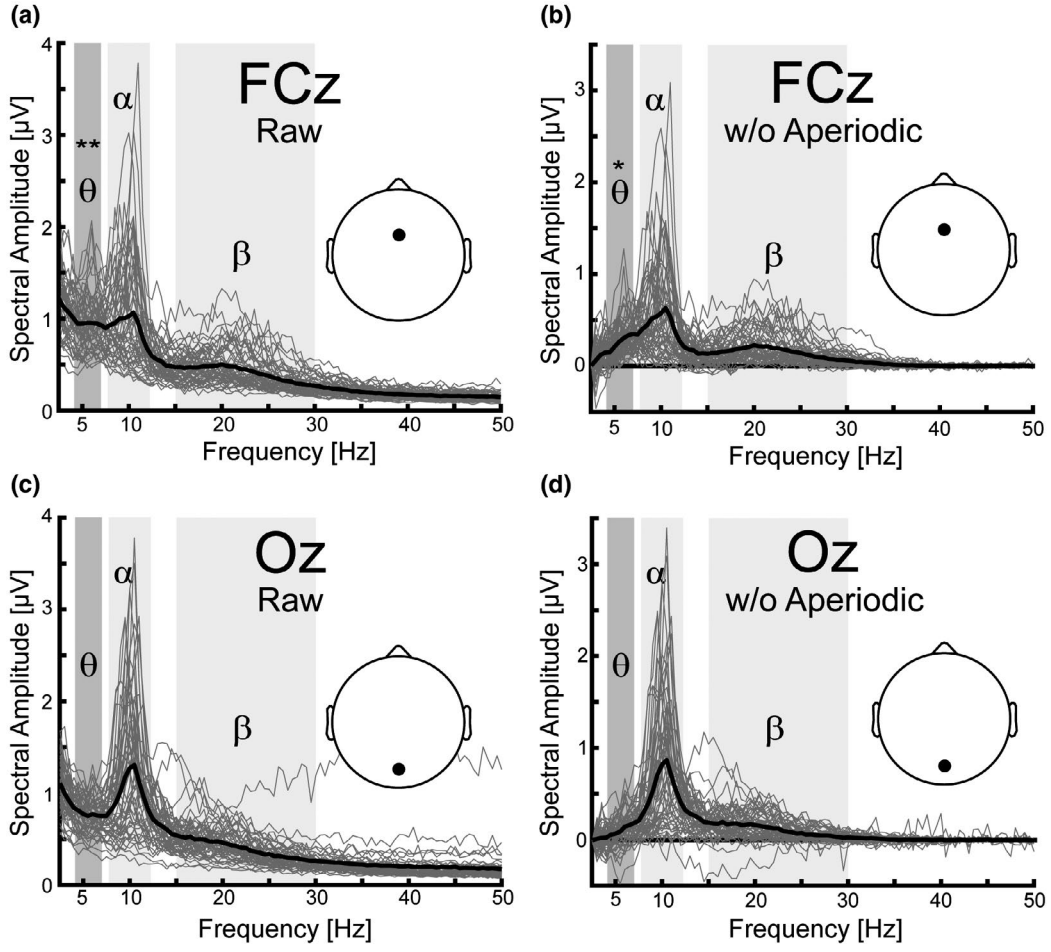

FIGURE 2 Spectral analysis and aperiodic signal correction. Frontal midline theta (FMT) oscillations survive aperiodic signal correction. Raw spectral amplitude for (a) FCz and (c) Oz electrode. Aperiodic signal was estimated by linear regression of the log(amplitude) and log(frequency) values for each participant. Then, aperiodic signal was removed from the data for (b) FCz and (d) Oz electrode. Individual participants are display in light grey and the group average is displayed in black. Theta band is highlighted in a dark grey box. Alpha and beta band are highlighted in a light grey box. FCz and Oz are depicted on the scalp. Correlation to P4: **$p < .01$, *$p < .05$, no asterisks $p > .05$. w/o, without

that the correlation of FMT amplitude with P4 concentration is not widespread across all frequencies, but is band-limited to canonical theta frequency.

The aperiodic signal, or background noise, of the human brain is a biologically relevant signal independent of neuronal oscillations (Voytek et al., 2015). With a sharper slope in the background noise, low frequency power is increased, despite no band-specific increase in power. In order to confirm that our results are specific to the amplitude of theta frequency neuronal oscillations and not a result of a difference in aperiodic signal, we fit and removed the aperiodic signal (Figure 2b). We found that our initial correlation between FMT amplitude and P4 concentration across all participants was still significant after correction for aperiodic signal ($r(54) = .284$, $p = .035$). The correlation of FMT amplitude after aperiodic signal correction with P4 concentration was greater than the correlation with T concentration (Pearson and Filon, $z(54) = 2.118$, $p = .034$). Therefore, the relationship between P4 concentration and the amplitude of FMT oscillations in our data is likely due to the modulation of a genuine neuronal oscillation by P4.

As a control analysis, we analyzed peak theta amplitude in a scalp location that displays elevated alpha oscillations, electrode Oz at the occipital-midline (Table 3). Theta amplitude in Oz was neither significantly correlated with P4 concentration in the raw spectra ($r(54) = .198$, $p = .148$) (Figure 2c) nor after aperiodic signal correction ($r(54) = .057$, $p = .667$) (Figure 2d). There was no difference in correlation with P4 concentration for alpha or beta amplitude in Oz in the raw spectra or after aperiodic signal correction. This control analysis demonstrates that the frequency-specific relationship of theta amplitude to P4 concentration was limited to the frontal midline.

To confirm that the correlation between FMT amplitude and P4 concentration is spatially specific to the frontal midline electrodes, we correlated P4 concentration with the spatial-normalized theta amplitude across the scalp (Figure 3a). Consistent with the canonical distribution of FMT oscillations, the positive correlation with P4 was specific to FCz and its surrounding electrodes. To better understand the neural origin of theta oscillations, we ran source localization on theta oscillations and performed a median split of our participants based on FMT amplitude in sensor-space to analyze the spatial distribution of theta amplitude in source-space (Figure 3b). As hypothesized, participants with the greatest FMT amplitude showed increased theta amplitude in bilateral prefrontal cortex and not in medial prefrontal cortex or superior frontal gyrus (Figure 4a,b). We hypothesized that FMT oscillations originated in the FPN and not the DMN. The FPN and DMN are visualized in Figure 4c,d to illustrate the spatial consistency between the spatial distribution of theta amplitude in source-space and the independently

TABLE 3 Spectral analysis correlated to P4 concentration

	FCz		Oz	
R-values	**Raw**	**w/o Aperiodic**	**Raw**	**w/o Aperiodic**
Theta band (4–8 Hz)	**0.377****	**0.284***	0.198	0.057
Alpha band (8–12 Hz)	0.165	0.115	0.080	0.062
Beta band (15–30 Hz)	−0.004	−0.131	−0.031	−0.124

Note: Correlation analysis (Pearson; $N = 55$) between steroid hormone concentrations and peak spectral amplitude in three frequency bands (theta, alpha, and beta) in the frontal-midline (FCz) and the occipital-midline (Oz) in the raw power spectra and after correction for the aperiodic signal.

Abbreviation: w/o, without.

**$p < .01$; *$p < .05$.

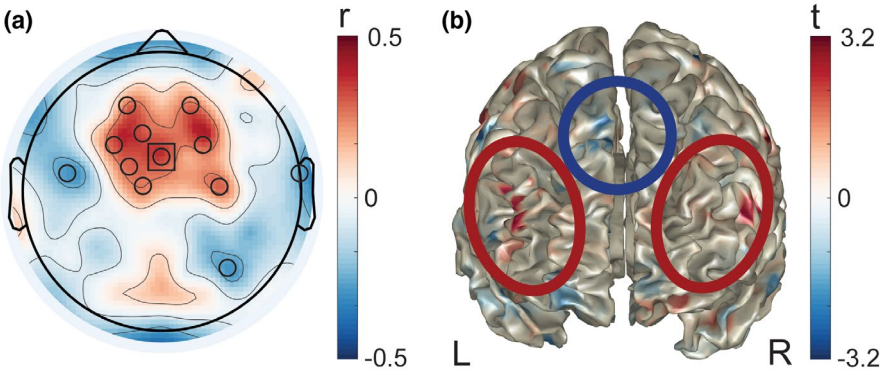

FIGURE 3 Spatial distribution of frontal midline theta (FMT) oscillations. (a) Sensor-space correlation (Pearson; $N = 55$) between theta amplitude and P4 across women and men revealed the canonical distribution of FMT. FCz is outlined with a black square. A black circle depicts a correlation with significance of $p < .05$. (b) Source localization of theta amplitude. For display purposes, voxel-wise independent t-values ($df = 53$) between participants median split on sensor-space FMT amplitude. Theta oscillations localized to bilateral prefrontal cortex. Anterior-to-posterior axial view of prefrontal cortex. L, left; R, right. The red ellipses highlight increased theta oscillations in the lateral prefrontal cortices, and the blue circle highlights decreased theta oscillations in the superior frontal gyri

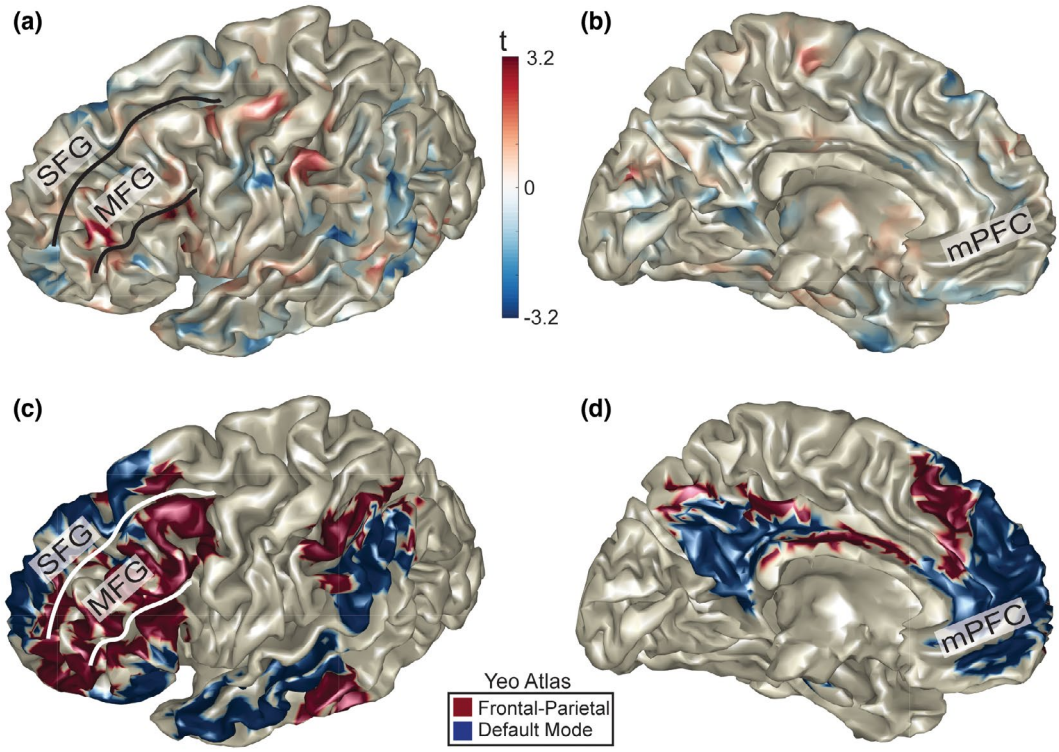

FIGURE 4 Network analysis of source localized theta amplitude. Source localization analysis of frontal midline theta (FMT) amplitude reveals activation in bilateral middle frontal gyrus (MFG), and not in superior frontal gyrus (SFG) or medial prefrontal cortex (mPFC). Lateral (a) and medial (b) view of the spatial distribution of increased theta amplitude (source-space) with increased FMT amplitude (sensor-space) in left hemisphere. Lateral (c) and medial (d) view of the frontal-parietal (red) and default mode (blue) networks from an atlas that was independently derived from resting-state functional connectivity in fMRI (Yeo et al., 2011)

TABLE 4 Network analysis correlated with steroid hormones

	Progesterone (P4)	Testosterone (T)
FPN − DMN	**0.310***	−0.079
FPN	**0.343***	−0.019
DMN	−0.024	0.096

Note: Correlation analysis (Pearson; $N = 55$) between steroid hormone concentrations and theta amplitude within the frontal parietal network (FPN) and default mode network (DMN). FPN and DMN were independently derived from fMRI analysis.

*$p < .05$.

derived FPN network from the seven-network Yeo atlas (Yeo et al., 2011).

As hypothesized, a one-tailed t test between participants with high and low FMT amplitude found that theta amplitude was greater in the FPN relative to the DMN (one-tailed, $t(53) = 1.798$, $p = .039$, $d = 0.485$). Post hoc t tests between the high and low FMT groups revealed that this effect was driven by an increase in theta amplitude within the FPN (one-tailed, $t(53) = 1.697$, $p = .048$, $d = 0.460$), but not the DMN (one-tailed, $t(53) = -0.501$, $p = .691$, $d = 0.136$). Finally, we ran a correlation between theta amplitude derived from source localization and steroid hormone concentrations. As expected, we found a significant positive correlation between P4 concentration and theta amplitude in the FPN relative to DMN (Table 4). Post hoc correlation analysis revealed that this effect was driven by a significant correlation between theta amplitude in the FPN and P4 concentration, but there was no relationship between theta amplitude in the DMN and P4 concentration (Table 4). Furthermore, P4 concentration showed a significantly greater correlation to source localized FMT amplitude in the FPN relative to DMN than T concentration (Pearson and Filon, $z(54) = 2.546$, $p = .011$). Post hoc analysis revealed that this effect was driven by a significant increase in correlation for P4 concentration to theta amplitude in the FPN relative to T concentration (Pearson and Filon, $z(54) = 2.373$, $p = .018$), and there was no difference in correlation between steroid hormones to theta amplitude in the DMN (Pearson and Filon, $z(54) = -0.745$, $p = .456$). These findings provide evidence that P4 is positively related to theta amplitude within the FPN, and that this relationship is hormone and network specific.

4 | DISCUSSION

We investigated if the amplitude of FMT oscillations were related to the concentration of steroid hormones P4 or T.

We found that P4, but not T, concentrations correlated positively with FMT oscillatory amplitude. The relationship with P4 concentration was frequency specific to the theta band and spatially specific to the frontal midline scalp electrodes. We found supporting evidence that theta frequency oscillatory amplitude in frontal midline electrodes represented a genuine neuronal oscillation by removing the aperiodic signal, or background spectra, of the brain for each participant. Source localization analysis found that FMT oscillations originated in the FPN, not the DMN, and source localized theta amplitude in the FPN correlated with P4 concentration. Together, these findings suggest a role for P4 to specifically increase the amplitude of theta oscillations in the FPN that is measured from the scalp at the frontal midline.

P4 has been found to play a neuroprotective role in both women and men and readily passes through the blood–brain barrier (see Schumacher et al., 2014 for review). P4, particularly its neuroactive metabolite allopregnanolone (ALLO), is critical to downregulation of hypothalamic-pituitary-adrenal (HPA) activation following stress by facilitating GABAergic inhibitory signaling; and this compensatory response to stress is impaired in depression (Schumacher et al., 2014) (see Girdler & Klatzkin, 2007 for review). ALLO is a potent, positive allosteric modulator of the $GABA_A$ receptor, and it is through this mechanism that P4 exerts antidepressant, antianxiety, and HPA-axis modulatory effects. This research culminated in FDA approval for ALLO as a treatment of postpartum depression (Kanes et al., 2017; Osborne et al., 2017). Although we did not directly measure ALLO in this study, concentrations of P4 and ALLO are highly correlated in blood and in the CNS (e.g., correlation strength in serum ranging from .80 to .95) (Andréen et al., 2005; Freeman, Purdy, Coutifaris, Rickels, & Paul, 1993; Palliser, Kelleher, Tolcos, Walker, & Hirst, 2015). In some cases, such as postpartum, P4 showed a reduced correlation with ALLO and a lower concentration of ALLO predicted increased depressive symptoms (Nappi et al., 2001). This finding suggests an additional mechanism by which P4, a steroid hormone, is converted into its neuroactive metabolite ALLO, despite their strong correlation in most studies with healthy participants.

The neural target of ALLO, $GABA_A$ receptors, are found throughout the brain, but are found in the greatest concentration in the striatum (Brittain & Brown, 2014). The striatum plays a critical role in cognitive control from operant-conditioning (Pagnoni, Zink, Read Montague, & Berns, 2002) to decision-making (Balleine, Delgado, & Hikosaka, 2007) due to its primary function in inhibiting motor output (Grillner, Hellgren, Menard, Saitoh, & Wikström, 2005). The FPN and the striatum have reciprocal anatomical projections that contribute to a dynamic hierarchically organized system for cognitive control (Badre & Nee, 2018; Jarbo & Verstynen, 2015). Although the current study did not directly measure cognitive control processes, facilitation of GABAergic signaling by P4 may facilitate the FPN in exerting inhibitory control.

Furthermore, FMT oscillations are an emerging biomarker relevant to the treatment of depression. Previous observational studies have found decreased amplitude of theta oscillations (Pizzagalli, Oakes, & Davidson, 2003; Saletu, Anderer, & Saletu-Zyhlarz, 2010) and decreased theta frequency functional connectivity (Linkenkaer-Hansen et al., 2005) during the resting-state in patients with major depressive disorder. A recent experiment found that depressed patients with increased amplitude of FMT oscillations during a working memory task were more likely to respond to non-invasive brain stimulation treatment (Bailey et al., 2018). Variability in recruitment of FMT oscillations during rest also serves as a predictor for pharmaceutical intervention for major depressive disorder (Mulert et al., 2007). Therefore, elucidating contributing factors to FMT oscillations may be of critical importance to future interventions.

As in any scientific study, the work presented here has limitations. We only measured peripheral concentrations of P4 and T. Therefore, we cannot draw inferences about concentrations in the brain. However, P4 readily crosses the blood–brain barrier and significantly contributes to central P4 and ALLO concentrations (Hu, Li, Fang, Wai, & Yew, 2009). Another important factor that mediates steroid hormone concentration is age (Ukkola et al., 2001). Our effects were robust when accounting for variance explained by the age-related decrease in P4 and T concentration. Sex differences were not captured in the current data set, although our exploratory analysis found that P4 concentration shows a qualitatively greater correlation with FMT amplitude in women relative to men. Exogenous administration of P4 results in a sedative effect in both men and women (Söderpalm, Lindsey, Purdy, Hauger, & De Wit, 2004) suggesting that there may be a common mechanism for P4 action on neural activity across sexes. It should be noted that although women had a numerically higher concentration of P4, this difference was not significant. Therefore, the women in our sample must have been by majority preovulatory (follicular phase), using oral contraception (low P4 concentration across the menstrual cycle), or in menopause, although these data were not collected. None of the women in our study were pregnant. Under these conditions, men display comparable P4 concentration to women (Oettel & Mukhopadhyay, 2004). The particular reasons for a similar concentration between women and men does not invalidate the correlation of P4 concentration to FMT amplitude. Future research needs to be conducted to remove any nonlinear effects introduced by reproductive events, such as the menopause transition or the postpartum period, where there may be a breakdown in relationship between P4 concentration and FMT amplitude.

In our cross-sectional study, we were unable to conclude that within a participant FMT amplitude tracks fluctuations in P4 concentration over time. Recent evidence suggests that

change in hormone concentration is most critical for predicting its impact on mood (Gordon, Rubinow, Eisenlohr-Moul, Leserman, & Girdler, 2016; Schmidt et al., 2017). Therefore, future research should employ a within-participant design that investigates the relative change in P4 concentration and FMT amplitude. Additionally, emerging experimental evidence suggests that some women are more sensitive to changes in hormone concentration than others and these women are more likely to develop reproductive mood disorders (Schiller, Meltzer-Brody, & Rubinow, 2015). For example, the late luteal phase is characterized by a sharp decrease in P4 concentration and women with hormone sensitivity experience this withdrawal with mood disturbances (Farage, Osborn, & MacLean, 2008; Schmidt, Nieman, Danaceau, Adams, & Rubinow, 1998). Future research is required to investigate whether the relationship between P4 concentration and FMT amplitude breaks down in women with hormone sensitivity.

A recent review on the effect of P4 in the menstrual cycle found that P4 concentration was a key predictor of emotional reactivity in women with premenstrual dysphoric disorder (PMDD) (Sundström-Poromaa, 2018). P4 concentration during the late luteal phase positively correlated with increased activity in the amygdala and increased symptoms of anxiety (Gingnell et al., 2014; Gingnell, Morell, Bannbers, Wikström, & Poromaa, 2012). Consistent with our prediction, previous research using functional neuroimaging found that connectivity in the FPN was modulated in the late luteal phase as a function of P4 concentration (Syan et al., 2017) and treatment with ALLO during the luteal phase reduced symptoms of PMDD (Bixo et al., 2017). While speculative, the decrease in P4 during the late luteal phase may downregulate theta oscillations in the FPN resulting in hyperactivity of the amygdala in PMDD (Gingnell et al., 2012). Causal investigation using double-blinded administration of P4 or ALLO with EEG is required to establish a causal link between P4 concentration and FMT amplitude. Furthermore, the use of a task that drives FMT oscillations as a function of cognitive control demands would further elucidate the functional role of FMT oscillations with respect to P4.

Finally, noninvasive brain stimulation is a promising new therapeutic that has been used to target the lateral prefrontal cortex in depression (Perera et al., 2016), and can be tailored to target-specific brain networks in a frequency-specific manner (Ahn et al., 2019; Alexander et al., 2019). In cognitive neuroscience, transcranial alternating current stimulation (tACS) that synchronizes theta oscillations in frontal and parietal regions increases performance during cognitive control tasks (Jaušovec & Jaušovec, 2014; Polanía, Nitsche, Korman, Batsikadze, & Paulus, 2012; Reinhart & Nguyen, 2019; Vosskuhl, Huster, & Herrmann, 2015). Future research should investigate the application of theta frequency tACS targeted to the FPN as a potential treatment for reproductive mood disorders typified by P4 withdrawal.

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