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The influence of endogenous estrogen on high-frequency prefrontal transcranial magnetic stimulation

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ABSTRACT

Background: The use of repetitive transcranial magnetic stimulation (rTMS) as both therapeutic and experimental tools has grown enormously over the past decade. However, variability in response to rTMS is one challenge that remains to be solved. Estrogen can impact neural plasticity and may also affect plastic changes following rTMS. The present study investigated whether estrogen levels influence the neurophysiological effects of high-frequency (HF) rTMS in the left dorsolateral prefrontal cortex (DLPFC).
Hypothesis: It was hypothesised that individuals with higher endogenous estrogen would demonstrate greater rTMS-induced changes in cortical reactivity.
Methods: 29 healthy adults (15M/14F) received HF-rTMS over left DLPFC. Females attended two sessions, one during a high-estrogen (HE) phase of the menstrual cycle, another during a low-estrogen (LE) phase. Males attended one session. Estrogen level was verified via blood assay. TMS-EEG was used to probe changes in cortical plasticity and comparisons were made using cluster-based permutation statistics and Bayesian analysis.
Results: In females, a significant increase in TMS-evoked P60 amplitude, and decrease in N45, N100 and P180 amplitudes was observed during HE. A less pervasive pattern of change was observed during LE. No significant changes in TEPs were seen in males. Between-condition comparisons revealed higher likelihood of the change in N100 and/or P180 being larger in females during HE compared to both females during LE and males.
Conclusions: These preliminary findings indicate that a greater neuroplastic response to prefrontal HF-rTMS is seen in women when estrogen is at its highest compared to men, suggesting that endogenous estrogen levels contribute to variability in response to HF-rTMS.

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique which can produce neuromodulatory effects when applied repetitively (rTMS). Depending on the frequency of stimulation, rTMS can reduce (low-frequency (LF): ~1 Hz) or increase (high-frequency (HF): 5–20 Hz) corticospinal excitability [1,2] following a single session of stimulation (see review [3]). The ability to modulate brain activity non-invasively has led to substantial interest in rTMS as a therapeutic tool, most often in the treatment of psychiatric illnesses targeting dorsolateral prefrontal cortex (DLPFC) [4–6]. However, there has been a substantial amount of variability in the changes in corticospinal excitability following rTMS [7–9]. Several factors affecting the variability in the neurophysiological response to brain stimulation techniques have been identified, such as age, attention, gender, genetics and time of the day [10].

One of the potential factors that can influence the after-effects of rTMS is estrogen. Estrogen has been shown to have a positive impact on cortical excitability in both animals and humans [11,12].

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For example, a larger increase in corticospinal excitability was observed on day 14 of the menstrual cycle (high estrogen) compared to that of day 1 (low estrogen) measured via motor evoked potentials (MEPs) [13]. In addition, less intracortical inhibition (measured via paired-pulse paradigms [14]) and more facilitation of MEPs were found when the estrogen-to-progesterone ratio was high [12], suggesting estrogen may impact cortical facilitatory mechanism.

Administration of estrogen has also shown to increase the expression of a brain-derived neurotrophic factor in the prefrontal cortex of rodents [15,16], a protein that plays an important role in neuronal plasticity. In addition, we have previously found that estrogen had an impact on the plastic effect of transcranial direct current stimulation (tDCS) applied to the left DLPFC [17], where more consistent changes in TMS-evoked potentials were observed in females during the high estrogen phase. Furthermore, estradiol-to-progesterone ratios are positively associated with depression score improvements in premenopausal women following rTMS treatment, suggesting a potential role of estrogen in the therapeutic response to prefrontal rTMS [18].

While these numerous associations between estrogen and varied aspects of cortical excitability have been described, whether estrogen influences neuroplastic response to HF-rTMS in the DLPFC has not yet been directly investigated. As HF-rTMS over the DLPFC is the most frequent application for neuropsychiatric illnesses, demonstration of an enhanced facilitatory effect of estrogen in response to the stimulation in this brain region would have mechanistic, and potentially therapeutic, implications.

To address this knowledge gap, the present study investigated whether endogenous estrogen levels influence cortical response to HF-rTMS over the left DLPFC in healthy individuals. To achieve this, concurrent recording of TMS and electroencephalography (TMS-EEG) was used to measure cortical reactivity before and after a single session of HF-rTMS delivered to a group of men and a group of women, with the latter participating during both a high estrogen and a low estrogen phase of their menstrual cycle. We hypothesised that higher endogenous estrogen levels would be associated with greater neuroplastic response to HF-rTMS over the DLPFC.

Material and methods

Participants

Twenty-nine right-handed healthy adults (15 males, M ± SD age: 26.5 ± 5.6 years; 14 females, M ± SD age: 23.4 ± 5.0) participated in this study. Participants reported no history of traumatic brain injury or neurological, psychiatric, or endocrine illness. All were free from implanted pacemakers or metal in the head (excluding dental work), and psychoactive medications (e.g. opioids, antihistamines, benzodiazepines) which could impact cortical excitability. In addition, female participants were free from hormonal contraceptives (minimum wash out = three months), reported no significant premenstrual symptoms, and had a stable pattern of regular menstrual cycles defined as a regular cycle between 21 and 35 days in length, with < seven days difference in average cycle length, and 5–7 day menstruation duration with no more than two days difference per cycle. Cycle regularity over the prior three months was verified via individual tracking strategies (i.e. personal calendar or smartphone app). Additional exclusion criteria for female participants were gynaecological surgery or abnormalities, pregnancy or lactation. The experimental procedures were approved by the Alfred Hospital and Monash University Human Research Ethics Committees, and were registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12615000720516). All participants provided informed consent prior to participation and were compensated $30 for their time. None of the participants had taken part in our prior investigation into estrogen and tDCS [17].

Procedure

This study utilised TMS-EEG to assess DLPFC reactivity following a single session of HF-rTMS (parameters described below). Fifty single TMS pulses were administered before (BL – baseline), 5-min post (T1) and 20-min post (T2) rTMS and EEG recorded throughout. Males attended a single session, and females attended two sessions – one at a low estrogen (LE) phase (2–5 days after the onset of menses), and another at a high estrogen (HE) phase (6–9 days before the onset of menses). Participant availability dictated session order, resulting in a comparable number of first session HE/second session LE versus first session LE/second session HE. The sessions were 13.6 ± 5.76 days apart on average. Estrogen levels were verified by blood assay, and blood collected on the same day as the testing session.

Assessment of endogenous estrogen

A venous blood sample was collected and analysed using a Chemiluminescent Microparticle Immunoassay (ARCHITECT System, USA) at each session to quantify estradiol in human serum plasma. The lower limit of detection for estradiol was 5 pg/mL, and the coefficient of variation was 7%. Ovulation was determined by an increment in estradiol/progesterone above the reference range (estradiol follicular phase: 77–921 pmol/L, luteal phase: 77–1145 pmol/L; progesterone follicular phase: 0.6–4.7 nmol/L, luteal phase 5.3–86 nmol/L).

Due to difficulties drawing blood in two participants (one each from males and LE), the number of participants in which blood samples were obtained differs from that of neurophysiological data – hormonal essay data were available for 14 males, 14 HE and 13 LE whereas TMS-EEG data were available for 15 males, 14 HE and 14 LE.

Transcranial magnetic stimulation

A MagVenture stimulator with a figure-of-eight B-65 fluid-cooled coil (MagVenture A/S, Denmark) was used for both HF-rTMS and single-pulse TMS with biphasic pulse shape (current flow in antero-posterior to postero-anterior direction in the underlying cortex). The coil was positioned at 45° in the sagittal plane with the handle oriented posteriorly, and the edge of the coil was marked on the cap to reliably re-position the coil within 5 mm [19]. We have previously verified the accuracy and reproducibility of this method relative to neuronavigation based targeting in terms of both coil positioning and angle (coil re-positioning within 5.1 ± 0.7 mm, coil angle coefficient of variation = 2% [19]). The resting motor threshold (rMT) from the left motor cortex was identified as the minimum intensity required to evoke at least 3 out of 6 motor-evoked potentials (MEPs) > 0.05 mV in amplitude [20] using Ag/AgCl EMG electrodes attached to the right first dorsal interosseous muscle. The average intensity for each condition was as follows (mean ± SD): HE = 46.6 ± 6.4%; LE = 46.6 ± 6.9%; males = 48.0 ± 7.9%. TMS was delivered to the left DLPFC estimated as F3 electrode using 10/20 method of placement, as it has been shown that DLPFC is approximately at the midpoint between F3 and AF3 electrodes, but closer to F3 [21]. Fifty single TMS pulses (inter-stimulus interval: 5s ± 10% jitter) were administered at 120% rMT before and after HF-rTMS. High frequency rTMS (10 Hz) consisted of 50 trains of 46 pulses (a total of 2300 pulses) with 20.5s inter-train interval given at 120% rMT. While rTMS parameters for

clinical treatment sessions vary substantially (e.g. 600–9000 pulses) [22,23], the parameters used in the current study are in keeping with a single session of therapeutic HF-rTMS [24,25].

EEG recording and data processing

EEG was recorded using 38 TMS-compatible Ag/AgCl electrodes (AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC5, FC3, FC1, FCz, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, P5, P3, P1, Pz, P2, P4, P6, PO3, POz, PO4, O1, Oz, O2) on a 64-channel EEG cap via SynAmps^2 amplifier on Neuroscan software (Compumedics, Melbourne, Australia). Signals were amplified (1000 x) and low-pass filtered (DC – 2000 Hz) with an acquisition rate of 10,000 Hz (operating window of ±200 mV). Electrodes were referenced to CPz and grounded to FPz. The impedance of the electrodes was kept below 5 kΩ throughout the experiment. During TMS-EEG recordings, the TMS click sound was masked by playing white noise through intra-auricular earphones (Etymotic Research, ER3-14A, USA). The volume was adjusted for each individual until single-pulse TMS at 120% rMT was sufficiently blocked.

EEG preprocessing procedures followed those described previously [26,27]. Data were analysed offline on the MATLAB platform (R2015b, The MathWorks, USA) using the EEGLAB [28], TESA [29], and FieldTrip [30] toolboxes and custom scripts. Data were epoched around the TMS pulse (−1000 to 1000 ms), baseline corrected (−500 to −50 ms) and the TMS pulse artefact was removed and interpolated (−5 to 15 ms). Epoched data were concatenated across three time-points (BL, T1 and T2) to avoid bias in the removal of artefactual components using independent component analysis (ICA). Data were downsampled (1000 Hz) and epochs containing excessive noise (e.g. muscle activity) and/or disconnected electrodes were removed. The average of epoched included in the analyses for each condition was as follows (mean ± SD): HE = 45.8 ± 3.6; LE = 45.6 ± 5.6; males = 47.2 ± 2.5. Two rounds of ICA (FastICA, 'tanh' contrast) were used to remove non-neural components using the TESA toolbox in a semi-automated manner [29]. The first round of ICA was used to remove the remainder of the muscle artefact [31]. Data were then band-pass (Butterworth, second-order, zero-phase, 1–80 Hz) and band-stop (line noise removal, 48–52 Hz) filtered. The second round of ICA was performed to remove artefactual components including eye movement, electrode noise, persistent muscle activity and decay artefacts. Any removed channels were interpolated and data were re-referenced to common average prior to the analysis of averaged TMS-evoked potentials (TEPs) for each time point.

TMS-evoked potentials (TEPs)

TEPs were analysed using a cluster-based global scalp analysis to assess the effect of rTMS in different conditions. As MagVenture stimulator can introduce additional artefacts on electrodes that are in contact with the coil [19], an average of 9 fronto-central electrodes (F1, Fz, F2, FC1, FCz, FC2, C1, CZ and C2) were used for TEP waveform representation in figures. The amplitudes of TEPs were compared within the predetermined time window for each peak of interest; N45 (35–50 ms), P60 (50–75 ms), N100 (90–130 ms) and P180 (160–240 ms) based on previous studies [17,26,27].

The study focused on N45, P60, N100 and P180 as they are reliably induced components of the cortical response to DLPFC stimulation [31,32]. It has been suggested that P60 may be related to cortical excitation both in motor [33–35] and prefrontal cortex [33,36,37], and that N45 and N100 may be related to cortical inhibition [32,38–41]. While the origin of the amplitude of P180 is largely unknown, changes in the P180 amplitude has been observed in various investigative studies using neuromodulation techniques [26,39,42,43], therefore it can be broadly interpreted to reflect the reactivity of the stimulated brain region.

Data were extracted from the average of 9 electrodes mentioned above for the examination of variability in response to HF-rTMS. Each peak was detected within the pre-defined window mentioned above as maximum (positive peaks) or minimum (negative peaks) value and the amplitude of each peak was calculated by averaging the signals between ± 5 ms of the peak latency as previously described [39]. Furthermore, a signal-to-noise ratio (SNR) analysis was performed on each peak to examine the adequacy of the number of pulses included in the study. The SNR was calculated by dividing the amplitude of each peak by the standard deviation of the signals in the pre-stimulus duration (−500 to −50 ms) [39,44,45]. Earlier peaks (N45 and P60) exhibited a moderate-to-good SNR, whereas later peaks (N100 and P180) showed excellent SNR (Supplementary Material Section 1 – Table S1).

Statistical analysis

Statistical analyses were performed in SPSS (IBM Corp, Armonk, NY; Version 22) and MATLAB (FieldTrip toolbox). Data were first tested for normality (Shapiro-Wilk test). Paired (HE vs LE) and independent samples (HE vs males and LE vs males) *t-tests* were performed to compare estrogen levels between conditions. TEPs were analysed using nonparametric cluster-based permutation statistics which provides an effective method of controlling for multiple comparisons across EEG channels and time [46]. This method is commonly used in TMS-EEG research [47,48]. To assess the impact of rTMS on TEPs over time, within condition comparisons were first made across time points (between BL and T1/T2). To assess whether rTMS-induced changes in DLPFC reactivity differed between condition, comparisons were made using change-from-baseline scores (post-pre; Δ). Separate cluster-based permutations were conducted for each peak between conditions. Monte Carlo *p*-values were calculated on 2500 randomisations and clusters were defined as ≥ 2 neighbouring electrodes, controlling for multiple comparisons across space ($p < 0.025$; two-tailed test). The *p*-values were then adjusted to control the false discovery rate across multiple comparisons for an alpha threshold of $p < 0.05$ using the method introduced by Benjamini and Hochberg [49]. To gain insight into the comparisons in a probabilistic way, Bayesian analysis was conducted on the average of 9 electrodes mentioned above (section 2.6). These electrodes were chosen as they displayed maximal differences in the cluster-based analysis. The Bayesian approach allows for the observation of data under each hypothesis from an equal perspective. Bayes Factor (BF_{10} – support in favour of H_1; BF_{01} – support in favour of H_0) denotes how likely comparison is to be true, and provides a quantification of how many times an observation is likely to occur [50]. This differs from the use of *p*-value null-hypothesis significance testing which can portray a binary view of statistical significance in which an observed effect is either real or the null hypothesis must be true [51]. The Bayesian analysis was conducted using JASP (Version 0.9.2.0) software [52], an open-source project which is freely available online (https://jaspstats.org/). Lastly, sensitivity analyses were conducted on TMS-EEG data omitting participants without hormonal assay and the overall pattern of the results did not differ (Supplementary Material Section 2 – Table S2).

Results

Baseline estrogen levels

Table 1 summarises average estrogen levels for each condition at baseline.

Table 1
Estrogen levels (M + SD).

	HE	LE	males	
Oestradiol (E2) (pmol/L)	408.6 ± 188.9	132.8 ± 42.1	89.8 ± 24.2	HE > M ($p = 0.001$) HE > LE ($p = 0.001$) LE > M ($p = 0.003$)

Baseline TEPs

Fig. 1 illustrates TEP waveforms of baseline single-pulse TMS over the left DLPFC. A series of negative and positive peaks (Fig. 1A) was observed with a distinctive pattern in scalp topography (Fig. 1B). It was evident that females (HE and LE) had larger

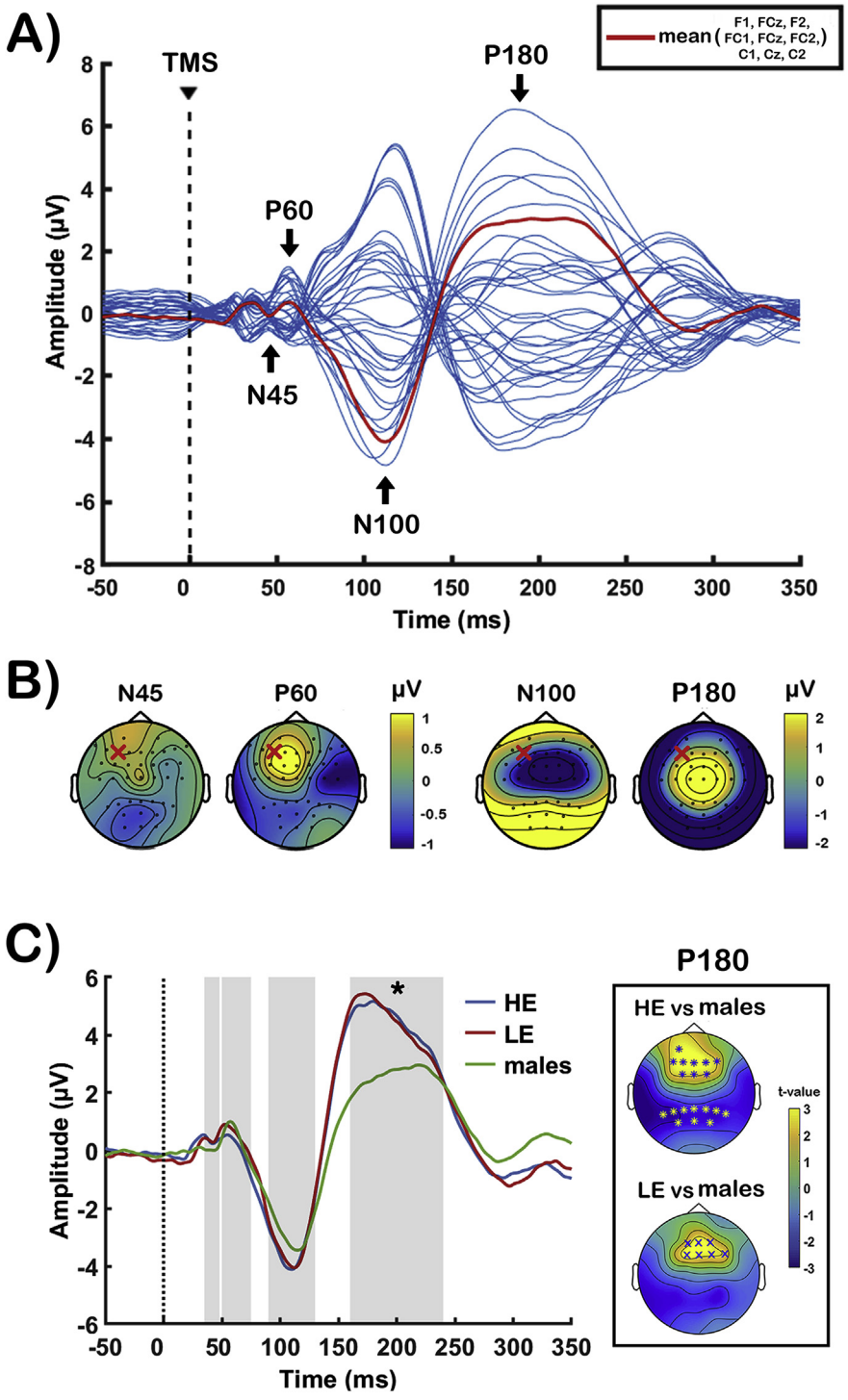

Fig. 1. Baseline TEPs over the left DLPFC (F3 electrode). Data were combined across three different conditions at baseline. (A) Butterfly plot of all electrodes with peaks of interest indicated in the text. The waveform in red is drawn using the average of 9 fronto-central electrodes (F1, Fz, F2, FC1, FCz, FC2, C1, Cz and C2) for graphical representation. (B) Topographical distribution of voltage. 'X' on the topoplots indicated stimulation site (F3 electrode). (C) Grand average TEP waveforms for females during HE (blue), females during LE (red) and males (green). Scalp map represents t-values for comparison of P180 amplitude between conditions. Asterisks and 'X's on topoplots indicate significant electrodes between comparisons (cluster-based statistics, $^{*}p < 0.01$, $^{X}p < 0.025$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

amplitude TEPs compared to males (Fig. 1C). The cluster-based permutation tests for the peaks of interest revealed significant differences in the amplitude of P180 between females during HE and males (frontal – $p = 0.0064$, parietal – $p = 0.0094$), and between females during LE and males (frontal – $p = 0.0125$). The estimated Bayes factors were found to be $BF_{10} = 6.802$ and $BF_{10} = 7.407$, respectively, suggesting that P180 were approximately 7 times more likely to be larger in females than males. No significant differences were observed between females during HE and LE at any peak ($p > 0.025$). Order effect analysis on the baseline TEPs confirmed the effectiveness of the counter balancing and indicated that repeated effects were not present (Supplementary Material Section 3 – Fig. S1).

The effect of estrogen levels on TEPs following HF-rTMS

Within-condition comparisons

HE: For women during the HE phase of the menstrual cycle, a significant increase in the amplitude of P60 ($p = 0.0132$) and significant decreases in N45 ($p = 0.0208$), N100 ($p = 0.0093$) and P180 ($p = 0.0036$) were observed at T1 across fronto-central electrodes. These changes remained significant for N100 ($p = 0.0056$) and P180 ($p = 0.0184$) at T2 (Fig. 2A).

LE: A less pervasive pattern of change was observed during the LE phase of the menstrual cycle, with a decrease observed for P180 amplitude ($p = 0.0244$; FDR uncorrected) alone at T1 across fronto-central electrodes (Fig. 2B), however, this did not survive correction for multiple comparisons between peaks.

Males: For men, no significant change from baseline in any peak was observed following HF-rTMS, at either T1 or T2 ($p > 0.025$) (Fig. 2C).

The estimated Bayes factors for within-condition comparisons are summarised in Table 2. The results largely corroborate the outcome of cluster-based statistics.

Between-condition comparisons

When between condition comparisons were conducted, females during HE showed a larger change in the amplitude of the TEPs following HF-rTMS compared to males at T1 across fronto-central electrodes (N45 – $p = 0.0512$; P60 – $p = 0.0288$; N100 – $p = 0.0336$; P180 – $p = 0.0112$). When adjusted for FDR, only N100 and P180 survived the correction for multiple comparisons between peaks. No other significant differences were found between females during HE and LE, and between females during LE and males in the amplitude of any peak at any time point ($p > 0.025$).

The estimated Bayes factors for between-condition comparisons are summarised in Table 3. Similar trends were observed between Bayesian and cluster-based analysis. However, Bayesian analysis suggested that the change in HF-rTMS-induced N100 amplitude was approximately 7 times more likely to be larger in females during HE compared to both females during LE and males at T1.

Table 2
Comparisons of TEPs within conditions using Bayesian method.

Across time	N45				P60			
	< T1 vs BL >		< T2 vs BL >		< T1 vs BL >		< T2 vs BL >	
	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}
HE	**4.720**[a]	0.212	0.310	3.221	**6.111**[a]	0.164	0.278	3.598
LE	0.676	1.479	0.328	3.047	0.525	1.910	0.424	2.358
males	0.264	3.786	0.273	3.660	0.323	3.097	0.262	3.811
	N100				**P180**			
	< T1 vs BL >		< T2 vs BL >		< T1 vs BL >		< T2 vs BL >	
	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}
HE	**54.626**[a]	0.018	**10.095**[a]	0.095	**16.468**[a]	0.061	2.906	0.344
LE	0.330	3.032	0.270	3.703	**4.474**[a]	0.224	0.460	2.175
males	0.266	3.765	0.295	3.385	0.279	3.589	0.442	2.260

[a] More likely to be under H_1 than under H_0.

Examination of variability in HF-rTMS-induced changes in TEPs

Figs. 3 and 4 illustrate individual variability and group variance, respectively, in response to HF-rTMS in each group for TMS-evoked Δ N100 and Δ P180. We focused our analysis on the N100 and P180 as these peaks were modulated by tDCS and demonstrated

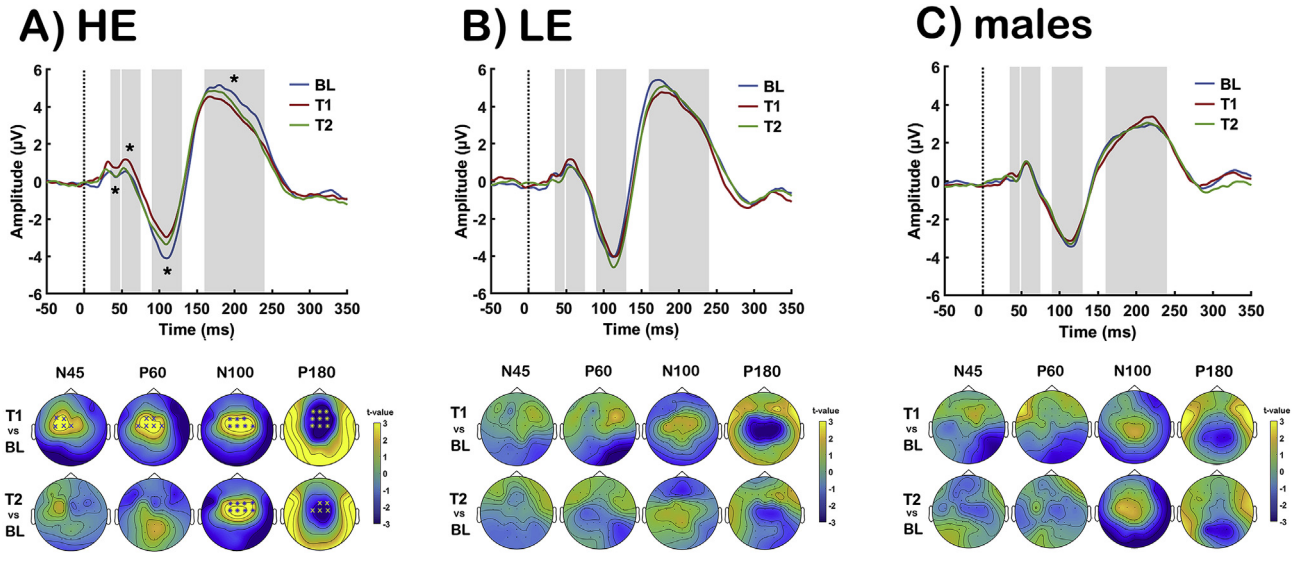

Fig. 2. Effect of estrogen level on the outcome of repetitive transcranial magnetic stimulation (rTMS) in modulating cortical activity assessed via TMS-evoked potentials (TEPs) in different conditions (A: High estrogen, B: Low estrogen, C: males). Grand average TEP waveforms at BL (blue), T1 (red), and T2 (green) using the average of 9 fronto-central electrodes (F1, Fz, F2, FC1, FCz, FC2, C1, Cz and C2). Scalp map represents t-values for comparison between time points. Asterisks and 'X's on topoplots indicate significant electrodes between comparisons (cluster-based statistics, $^{*}p < 0.01$, $^{X}p < 0.025$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Comparisons of TEPs between conditions using Bayesian method.

Across condition	Δ N45				Δ P60			
	< T1 >		< T2 >		< T1 >		< T2 >	
	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}
HE vs males	0.586	1.706	0.354	2.829	2.272	0.440	0.352	2.845
LE vs males	0.520	1.924	0.424	2.360	0.707	1.414	0.385	2.598
HE vs LE	0.272	3.680	0.420	2.381	0.335	2.982	0.293	3.411
	Δ N100				**Δ P180**			
	< T1 >		< T2 >		< T1 >		< T2 >	
	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}	BF_{10}	BF_{01}
HE vs males	**7.982**[a]	0.125	2.437	0.410	**4.298**[a]	0.233	0.615	1.627
LE vs males	0.410	2.438	0.372	2.685	2.375	0.421	0.353	2.831
HE vs LE	**6.923**[a]	0.144	1.300	0.769	0.273	3.660	0.408	2.451

[a] More likely to be under H_1 than under H_0.

sensitivity as a metric for inter- and intra-individual variability in our previous study [17].,. Females during the HE phase showed greater consistency in the number of subjects responding to HF-rTMS in these peaks, leading to smaller variance in the group data. Increased individual variability was seen in females during LE and males with larger group variances, particularly in Δ N100. In-depth examinations can be found in the Supplementary Material Section 4 (Figs. S2 and S3, and Table S3).

Discussion

The current study examined whether endogenous estrogen levels influence the modulatory effect of HF-rTMS over the left DLPFC. The data indicate that estrogen can play a role in the magnitude and the variance of neuroplastic effects following HF-rTMS, thus contributing to inter-individual variability in rTMS outcomes.

Our previous research demonstrated a larger and more consistent response to anodal tDCS over the left DLPFC in women during the high estrogen phase of the menstrual cycle compared with men [17]. Findings in the current study are therefore in line with these findings in that the magnitude of rTMS-induced changes were influenced by endogenous estrogen. The largest change was observed during the high estrogen phase of the menstrual cycle, which may have been driven by the reduced interindividual variability in response to HF-rTMS.

Modulation of TEPs following HF-rTMS was most evident in females during HE, where a significant post-stimulation increase was observed in TMS-evoked P60 amplitude, and significant decreases seen in N45, N100 and P180 amplitudes. The change in TEPs, particularly the increase in P60 peak, following HF-rTMS over DLPFC in females during HE is consistent with the outcome of anodal tDCS [36] and individualised intermittent theta burst stimulation [53] over DLPFC, which are also excitatory paradigms. It

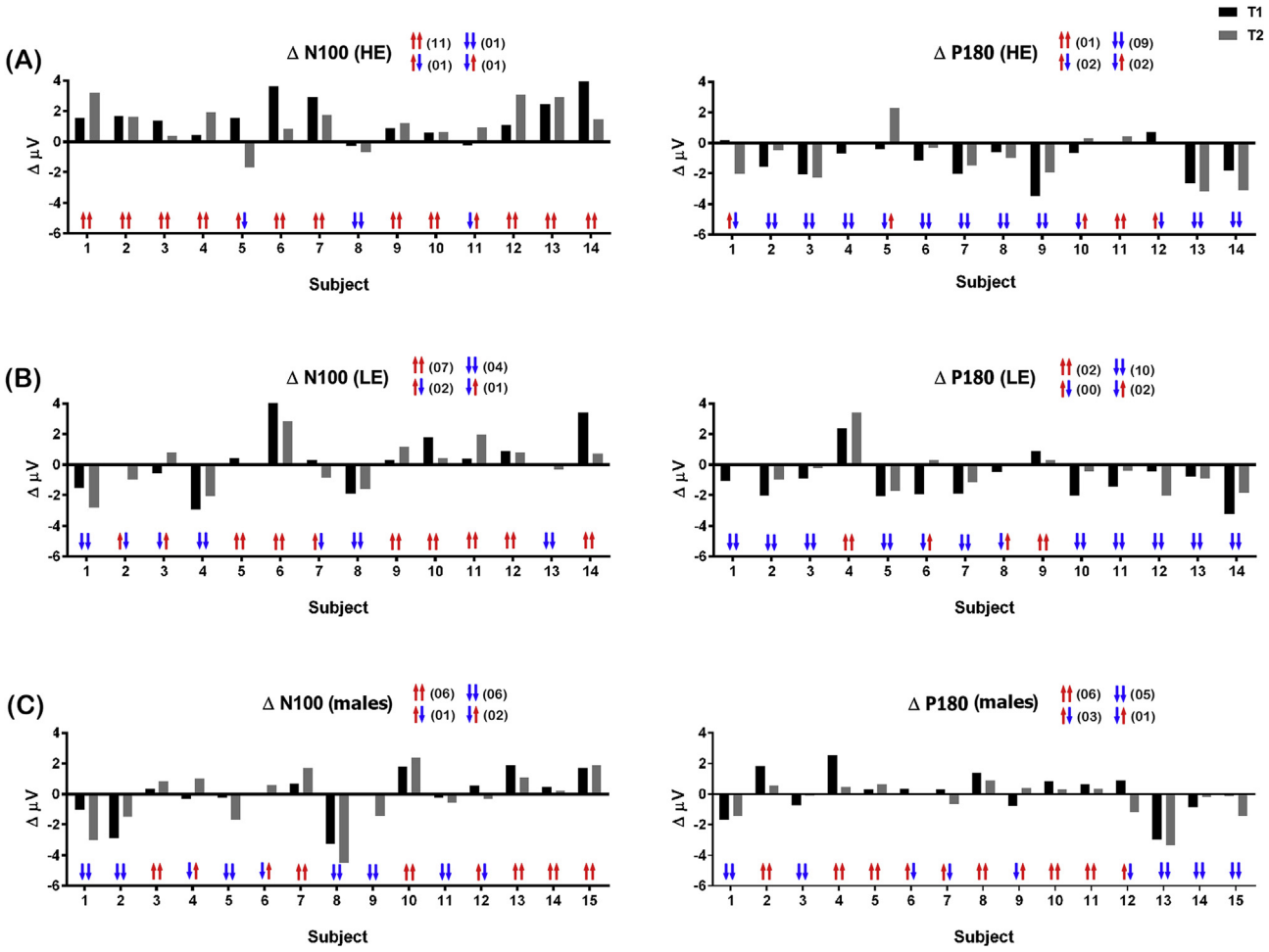

Fig. 3. Within-condition examination of the variability in rTMS-induced change in TMS-evoked N100 and P180 in different conditions (A: High estrogen; B: Low estrogen; C: males). Data were plotted using the average of 9 fronto-central electrodes (F1, Fz, F2, FC1, FCz, FC2, C1, Cz and C2). Arrows indicate increase (↑) or decrease (↓) in the amplitude from baseline. First arrow indicates T1 and second arrow indicates T2.

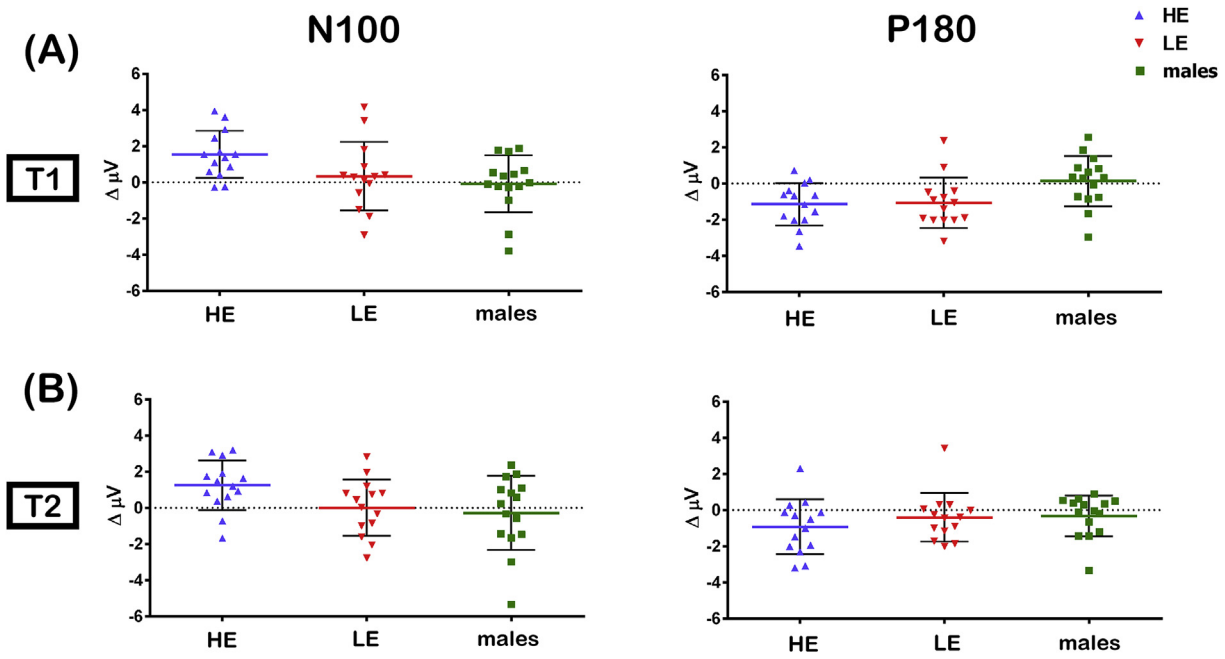

Fig. 4. Between-condition comparison of the variability in rTMS-induced change in TMS-evoked N100 and P180 (HE: High estrogen; LE: Low estrogen; M: males). Data were plotted using the average of 9 fronto-central electrodes (F1, Fz, F2, FC1, FCz, FC2, C1, Cz and C2). Error bars represent standkard deviations.

is possible that HE is a pro-excitatory state which allows for a more neuroplastic response to facilitatory neuromodulation.

Estradiol is known to increase neuronal excitability by the activation of the NMDA receptor [54,55] and to attenuate $GABA_A$- and $GABA_B$-mediated responses [56–58]. Although N45 has been associated with $GABA_A$-mediated inhibition [59,60], while N100 linked to $GABA_B$-mediated inhibition [32,39,41], the mechanisms behind the changes in these peaks remain to be elucidated in the DLPFC. Recently, however, a TMS-EEG study revealed an abnormality in these peaks in patients with major depressive disorder (MDD). Displaying larger amplitudes in the patients compared to healthy participants [61], these peaks may represent a potential biological marker of MDD based in DLPFC physiology. It is possible that estrogen may enhance the attenuating effect of rTMS in these peaks, which could aid in stabilising the abnormality seen in MDD patients. Replication of the current study in a cohort of individuals with MDD will be an interesting next step in exploring this possibility. The reduction in N100 amplitude is also somewhat consistent with a previous study which demonstrated increased N100 amplitude following low-frequency rTMS (1 Hz) over the motor cortex, a paradigm that typically has an opposite effect to HF-rTMS [62]. Furthermore, females during HE showed high consistency in the direction of N100 change following HF-rTMS, whereas females during LE and males exhibited substantial variability in this component (Fig. 3). This pattern of consistency is similar to our previous study using tDCS in the prefrontal cortex [17]. Significant differences in the change in N100 amplitude between females during HE and males indicate that the plastic effect following HF-rTMS was bigger when the estrogen level was high. This finding was corroborated by Bayesian analysis where it was 7.982 times more likely to be bigger in females during HE compared to males. Despite not being significantly different in the cluster-based analysis, the change in N100 was 6.923 times more likely to be bigger in females during HE than that of females during LE, which supports our hypothesis that estrogen plays a role in the magnitude of plastic change following HF-rTMS.

The baseline amplitude of P180 was significantly different between male and female (HE vs males and LE vs males) (Fig. 1C). Little is known of the mechanisms of this peak. However, the P180 is sensitive to the intensity of TMS pulses in the prefrontal cortex [63] and broadly reflects the reactivity of the stimulated brain region as its amplitude change has been observed following different neuromodulatory paradigms [39,42,43]. We have previously observed a broadly similar pattern of larger P180 amplitude in women than men (i.e. P180 females > males [17]), suggesting the possibility of a link between P180 and gender differences. However, until the origins and functional significance of this peak are better understood it is difficult to speculate on the origins or functional relevance of this observation.

In the current study, the amplitude of the baseline P180 peak was not affected by differences in estrogen during the menstrual cycle in females. Therefore, it is possible that additional variables, or sex itself, may drive these observed gender differences, and assessment of other hormones such as testosterone and progesterone may shed light on the origin of this component. Although both female conditions showed a reduction in P180 amplitude following HF-rTMS, significant differences were only observed in females during high estrogen phase of menstrual cycle (Fig. 2A and B). The differences were more noticeable from Bayesian analysis where females during HE had a higher likelihood (16.468 times) compared to females during LE (4.474 times). Similarly, the change in P180 post-stimulation was only found between females during HE and males. The Bayesian analysis confirmed this finding, where the change in P180 was 4.298 times more likely to be larger in females during HE than males, and 2.375 times more likely to be larger in females during LE than males. Although there may be other confounding factors such as mood swing, body temperature and other hormones, it appears estrogen levels may also play a role in the magnitude of the plastic effects in the prefrontal cortex, as has also been observed following tDCS [17]. In addition, the response rate of rTMS treatment was markedly higher in premenopausal female patients with depression compared to

postmenopausal women [18], indicating the importance of sex hormones on the therapeutic efficacy of rTMS. The absence of rTMS-induced effects in male subjects was unexpected, but not surprising as several studies both in animals and humans have demonstrated better response to rTMS in females in therapeutic [64–66] and non-therapeutic settings [67].

Taken together, our findings indicate that the endogenous estrogen levels can impact the magnitude and consistency of the neuromodulatory effect of prefrontal HF-rTMS in humans. As the prefrontal application of rTMS is an increasingly popular method for alleviating the symptoms of treatment-resistant depression [68–70], it may be useful to tailor rTMS protocols around periods of hormonal flux and potentially use ovarian hormones as an adjunct to rTMS application to investigate the potential increase in therapeutic efficacy.

Limitations

As the study sample was modest in size and limited to relatively young adults, the current results are best considered preliminary and cannot yet be generalised to a population level. Although steps were taken to mask the TMS click sound, it is possible that some multisensory artefacts impacted the TEPs [71]. There is some evidence suggesting that estrogen and progesterone can affect the amplitude of auditory evoked potentials [72,73], although results of gender-based investigations have been inconsistent [74,75]. No significant differences in baseline TEPs between females during LE and HE stages of the menstrual cycle were observed in the current study suggests that any multisensory artefacts present were not affected by estrogen differences. It is currently unclear whether the difference in baseline TEPs between male and female are attributed to differences in sensory-related processing or other factors mentioned in the discussion. While TMS coil localisation followed our established and verified methods [19], it is possible MRI-navigated targeting of DLPFC may improve the accuracy and the consistency of the coil positioning. Furthermore, a more precise selection of neural populations could be achieved using monophasic pulses [76]. The focus of the study was specifically on the effects of estrogen on rTMS after-effects, however, the menstrual cycle involves fluctuations not only in estrogen but also in other hormones. As the relationship between these hormones and cortical reactivity is not well defined, future studies should consider investigating the effect of other hormones on the effect of rTMS. Lastly, it is important to note that rTMS treatment regimens often involve multiple visits and future studies should investigate the effect of estrogen in repeated rTMS sessions.

Conclusion

In conclusion, while preliminary, the current results suggest that the physiological effects of DLPFC rTMS can be augmented by endogenous estrogen. The data also provide evidence that endogenous estrogen levels contribute to inter-individual variability in response to rTMS. More broadly, they attest to the value in investigating the impact of hormonal status on response to non-invasive brain stimulation.

Disclosures and conflict of interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.05.007.

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