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Hormonal Contraceptives and EEG Biomarkers for Antidepressant Treatment Response in Women

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Abstract

Background

Women are disproportionately affected by major depressive disorder (MDD). Widely used hormonal contraceptives are linked to depression and altered brain function, yet their unstudied impact on EEG-biomarkers of antidepressant response may confound efforts to develop biomarkers for women.

Methods

In 60 unmedicated premenopausal women with MDD: non-users (n=25), combined oral contraceptive users (COC, n=19), and progestin-only contraceptive users (POC, n=16), we assess five EEG-biomarkers before eight weeks of 10-20 mg escitalopram: Alpha peak frequency (APF), Vigilance level, Loudness-Dependence of Auditory Evoked Potentials (LDAEP), frontal alpha asymmetry (FAA), and theta activity at the anterior cingulate cortex (tACC). Analyses include age-adjusted ANCOVAs, hierarchical logistic regression, and repeated LASSO-regressions to evaluate the effects of hormonal contraceptives on EEG-biomarkers and treatment response.

Results

No differences between contraceptive groups are found in EEG-biomarkers ($\omega^2<0.03$, $p>0.15$). Adding contraceptive groups improves EEG-based predictions for all biomarkers ($p<0.044$). While hierarchical regressions show no significant EEG-biomarker contraceptive-group interactions, LASSO-regressions select contraceptive status in interaction with APF and tACC in models that best predict treatment outcome. Disregarding EEG, hormonal contraceptive use is associated with treatment response ($p=0.01$). COC-users exhibit lower response rates than non-users (24% vs 71%, OR=0.14 [0.03, 0.65], $p=0.012$). POC-users have a 44% response rate ($p=0.140$).

Conclusions

Although hormonal contraceptive use is not associated with EEG-biomarkers in unmedicated depressed women, they may modulate links between specific EEG-biomarkers and antidepressant response. However, contraceptive use, specifically COC, is associated with worse treatment outcomes and may be critical to developing biomarkers, including EEG-based, to guide treatment in women with MDD.

Plain language summary

Women commonly use hormonal contraceptives, which may alter brain activity in ways that might affect how antidepressants work. We measured brain waves (EEG) in 60 women with depression before they started antidepressant treatment. The women either used combined oral contraceptives, progestin-only contraceptives, or no hormonal contraceptives. We examined five EEG-biomarkers associated with antidepressant treatment response. We found that hormonal contraceptives did not directly alter these brain wave patterns. However, women using combined oral contraceptives responded poorly to treatment compared to non-users, and knowing whether women used hormonal contraceptives helped the brain wave patterns better predict treatment success. These findings suggest that hormonal contraceptive use, particularly combined oral contraceptives, should be considered when developing personalised depression treatments for women.

Introduction

Major depressive disorder (MDD) significantly affects the quality of life and is more frequent in women than men, highlighting the need to explore sex-specific factors in depression.[1] Hormonal contraceptives are widely used among women of reproductive age; for example, 42% of women in Denmark use oral contraceptives (OC).[2] Epidemiological studies suggest a link between initiating hormonal contraceptive use and the onset of depressive episodes, particularly among adolescents.[2–4] Hormonal contraceptives may influence brain structure and function, particularly in areas related to mood regulation, such as the amygdala and prefrontal cortex.[5–8]

Electroencephalography (EEG) studies from the 1970s and 1980s noted that OC use could alter brain activity, particularly by reducing overall alpha power. [9,10] However, more recent work, focusing on alpha peak frequency (APF), suggests that women using OC show similar APF values to naturally cycling women in the early follicular phase, and that APF negatively correlates with estradiol levels.[10] Although findings still remain inconsistent, as other recent work reports no differences in alpha peak frequency between OC users and naturally cycling women.[11] This evolving literature highlights the need to distinguish between alpha power and peak frequency, especially since alpha peak frequency is a promising predictor of antidepressant treatment response.[12]

Moreover, OC use affects emotional processing, as demonstrated by changes in event-related potential components.[13] Estradiol, a key component in combined oral contraceptives (COC), i.e. *the pill*, modulates brain serotonin systems at multiple sites, affecting synthesis, reuptake, and receptor activity.[14] Intriguingly, OC-induced changes in serotonergic neurotransmission have been suggested as a potential mechanism underlying the putative OC-related mood effects and a potential modulating effect of OC on antidepressant treatment in depression.[5,15] The loudness dependence of auditory evoked potentials (LDAEP) is an indirect measure of serotonergic function, with shallower slopes indicating higher serotonergic neurotransmission and steeper slopes reflecting lower serotonergic activity.[16] Estrogen increases LDAEP, suggesting that LDAEP is sensitive to changes in hormonal exposure and thus may reflect hormone-related changes in serotonergic neurotransmission.[17] Indeed, recent research suggests hormonal contraceptive users may exhibit higher LDAEP than non-users.[18] EEG measures, like the LDAEP, may be a promising tool to assess the impact of OC use on antidepressant treatment effects.

Concurrently, EEG has emerged as a promising tool for identifying biomarkers of antidepressant treatment response. In this study, we focus on five EEG biomarkers: APF, frontal alpha asymmetry (FAA), EEG vigilance, theta activity at the anterior cingulate cortex (tACC), and LDAEP, based on their established associations with treatment outcomes [19–21] and their biological relevance to both serotonergic function and sex-specific responses.[22–24] Lower APF has consistently predicted better SSRI outcomes[12,22,25,26]; it also appears sensitive to hormonal fluctuations, as evidenced by its negative correlation with estradiol.[10] LDAEP, a marker of central serotonergic activity [27–30], is modulated by estrogen[17] and has been shown to predict SSRI response, with steeper slopes indicating lower serotonergic tone. [16,20,30,31]. FAA, derived from frontal alpha power, has been linked to better SSRI outcomes in women [22–24]. EEG vigilance, which reflects arousal stability during rest, predicts antidepressant response [32–35] and may capture arousal regulation mechanisms affected by hormonal contraceptives. Lastly, increased theta activity in the ACC has been variably associated with treatment outcomes [22,36–40], possibly due to unaccounted biological factors such as hormonal status. Together, these biomarkers were chosen for their predictive value in MDD and their potential sensitivity to hormonal modulation relevant to contraceptive use.

Despite the growing interest in hormonal contraceptives on brain function and EEG biomarkers as a predictive tool for treatment response, the intersection of these two areas remains largely unexplored. Given the widespread use of hormonal contraceptives and their potential to

modulate brain activity, clarifying how oral contraceptives impact EEG biomarkers is crucial for optimising their clinical utility. By combining our previous observations regarding hormonal contraceptives' effect on treatment response[15] and the use of EEG biomarkers to predict response in MDD[22], we here investigate the effect of hormonal contraceptive use on specific EEG biomarkers in unmedicated women with MDD and whether it affects the prediction of antidepressant treatment response. We aim to identify potential confounding factors in EEG biomarker research and contribute to developing better treatment biomarkers for women. We hypothesised that: 1) hormonal contraceptive use would be associated with differences in pre-treatment EEG biomarkers, 2) contraceptive status would moderate the relationship between EEG biomarkers and treatment response, and 3) incorporating contraceptive status would improve EEG-based prediction of antidepressant treatment outcomes.

In this study, we find that contraceptive use is not associated with differences in EEG biomarkers before medication. However, contraceptives emerge as a strong predictor of antidepressant treatment response and substantially enhance EEG-based models of treatment outcome. LASSO analyses consistently identify interactions between contraceptive use and specific EEG biomarkers, including APF and tACC. Moreover, women using combined oral contraceptives, but not progestin-only contraceptives, show markedly lower treatment response rates compared to non-users. Together, these findings highlight hormonal contraceptive use as a key factor influencing EEG signatures and antidepressant treatment response in women.

Methods

We use data from the NeuroPharm-1 study, an open-label clinical trial investigating biomarkers for antidepressant treatment (clinicaltrial.gov: NCT02869035), which was approved by the National Committee on Health Research Ethics, Denmark (H-15017713). A detailed description of the study protocol is available elsewhere.[22,25]
The current EEG analysis was not part of the original study protocol plan.

Population

We selected premenopausal women aged <45 years (n=60). They were unmedicated and diagnosed with moderate to severe episodes of MDD lasting less than two years by a certified psychiatrist and confirmed by the Mini-International Neuropsychiatric Interview.[41] See supplementary for more information and CONSORT-diagram (Suppl. Figure 1).

Antidepressant treatment

Patients started treatment with escitalopram, individually adjusted to 10-20 mg daily depending on response and side effects. Per standard practice, patients experiencing intolerable side effects or <25% reduction in the 6-item subscale of the HAMD17 from pretreatment to week four were offered to switch to duloxetine (n=7), individually adjusted to 30-120 mg daily. Plasma medication levels at week eight assessed treatment adherence.

Electrophysiological recording and data reduction

Resting-state EEG was recorded in four 3-minute periods, counterbalanced as OCOC or COCO (O: eyes open, C: eyes closed) between participants, followed by a LDAEP-paradigm using a 256-channel HydroCel Sensor Net system. Based on their validation in prior studies that demonstrated robust associations with treatment outcomes.[22,34]

APF was determined by identifying the frequency showing maximum alpha power (8-13 Hz) across frontal, parietal, and occipital electrodes (F3, F4, P3, P4, O1, O2) using spectral analysis with 4-second epochs. FAA calculated the difference in alpha power between right and left frontal electrodes (F4-F3). Vigilance levels were classified using the validated VIGALL algorithm, which automatically categorised each 1-second epoch into arousal stages (0, A1, A2/3, B1, B2/3) based on the spatial-temporal distribution of delta, theta, and alpha activity. Source tACC was computed using eLORETA localisation for the 4.5-7 Hz band, extracting log-transformed, normalised activity from a predefined rostral ACC region. Loudness dependence of auditory evoked potentials (LDAEP) was measured by determining the N1/P2 amplitude slopes at electrode Cz across five acoustic intensities (60-100 dB), recorded during a separate auditory paradigm following the resting-state session. The supplementary materials provide more detailed information on preprocessing and the biomarkers.

Statistical analysis

We compared three contraceptive user *groups*: Non-users (None), women using *combination* oral *contraceptives* (COC), and women using *progestin-only contraceptives* (POC), which included users of progestin-only pills and intrauterine devices (IUDs). We grouped progestin-only pills and hormonal IUDs into a single POC category because: First, both groups use similar progestins (levonorgestrel in 11 and desogestrel in four of the 16 POC users) and lack the estrogen component that distinguishes COCs. Second, despite arguments about local versus systemic exposure, epidemiological evidence demonstrates that both progestin-only pills and IUDs are associated with increased depression risk compared to COC and non-hormonal

methods, suggesting meaningful systemic effects.[2] Third, our primary research question focused on estrogen-containing versus estrogen-free contraceptives, making the COC versus POC distinction most relevant. Finally, the small sample sizes of individual POC subtypes (n=5 oral, n=11 IUD) would severely limit statistical power for separate analyses.

We compared the mean ages of the three user groups using an ANOVA. Despite small and non-significant group differences, age is included as a covariate in all models due to established associations with the EEG measures [42–44].

Contraceptives and EEG biomarkers before treatment

We conducted five one-way ANCOVAs to examine the effects of hormonal contraceptive use on the average value of the EEG biomarkers, controlling for age. The independent variable was the hormonal contraceptive user status: Non-users, COC users, and POC users. The dependent variable was APF, vigilance level, LDAEP, FAA, or tACC. Assumptions of normality and homogeneity of variances were verified using Q-Q plots and Levene's test.

In a sensitivity analysis to test robustness, we excluded a non-user who was found to be pregnant after the baseline EEG assessment and a COC user who reported spontaneous remission a week before medication was started. In another sensitivity analysis, we excluded five progestin-only pill users, rendering the POC group only progestin-IUD users.

Contraceptives, EEG biomarkers and treatment response

Treatment response (response vs. non-response), defined as a ≥50% reduction in Hamilton Depression Rating Scale, 17-item (HAMD) at week 8 from pretreatment. Three subjects (2 COC users and 1 POC user) dropped out of the study at week seven due to adverse side effects, acute suicidality and hospitalisation, or lost contact (see CONSORT-diagram in supplementary). Their treatment responses were classified as non-response based on their HAMD at week four; i.e., the last observation was carried forward.

To examine whether hormonal contraceptive use moderated the relationship between EEG biomarkers and treatment response, we conducted five hierarchical logistic regression analyses. We compared three nested models for each EEG biomarker: a base model that included age and the EEG biomarker, a model that included contraceptive group status, and a full model that added contraceptive group and its interaction with the EEG biomarker. Model comparisons were evaluated using likelihood ratio tests, changes in the Bayesian Information Criterion (BIC), Nagelkerke's R^2, and the Area Under the Receiver Operating Characteristic Curve (AUC) to

assess discriminative ability and overall classification accuracy.

Model assumptions were evaluated using diagnostic plots, which showed appropriate linear relationships between continuous predictors and predicted outcomes, no systematic patterns in residuals, and squared Pearson residuals predominantly <4, indicating no extreme outliers or influential observations that would compromise model validity. Multicollinearity among continuous predictors was assessed using variance inflation factors, which yielded acceptable values for age (VIF ≤1.2) and all EEG biomarkers (VIF ≤4.1) across all models.

We report model coefficients for predictors in each interaction model (Supplementary Table 2) and the simple EEG-biomarker-only models (Supplementary Table 3). These results contextualise the biomarker-contraceptive interactions within the broader model structure; however, our primary focus was on interaction effects rather than replicating individual biomarker validation. Individual biomarker effects have been reported from the larger mixed-sex cohort from which this subsample is drawn.[22,34]

Post-hoc power analyses for APF, vigilance and tACC were conducted (description in the supplementary materials).

Prediction model specification based on contraceptives and EEG biomarkers

The hierarchical models formally test our a priori hypotheses about biomarker-contraceptive interactions. Given power limitations, we employed LASSO regression to explore optimal prediction models without formal significance testing. Given our sample size limitations, we interpret the LASSO variable selection frequencies as indicators of potential predictive value that require confirmation in larger samples.

For each EEG biomarker, we conducted stratified 5-fold repeated cross-validation with 500 repetitions using Least Absolute Shrinkage and Selection Operator (LASSO) regression analyses to systematically evaluate the predictive contributions and interactions of each EEG biomarker with contraceptive group status. The stratification ensured a balanced representation of contraceptive groups across folds.

For each EEG biomarker, we performed a separate LASSO regression with treatment response as the outcome and contraceptive group, the EEG biomarker, their interactions and age as predictors. Age was included in all models and was not penalised. The optimal regularisation parameter (λ) was determined through cross-validation using the *cv.glmnet* function.

This variable selection approach helps identify which features consistently contribute to prediction across multiple model iterations, providing insight into the stability and reliability of

potential biomarker-contraceptive interactions. Selection frequency was calculated as the proportion of bootstrap samples in which each variable was retained in the model.

Contraceptives and treatment response

We compared treatment responses among the contraceptive-user groups with a chi-squared test. Next, we examined whether the contraceptive group predicted treatment response in a logistic regression with age as a covariate. We also compared the proportions of dropouts and switches from escitalopram to duloxetine between user groups (during weeks four to seven) using Fisher's exact tests and group differences in escitalopram dosage at week eight using the Fisher-Freeman-Halton exact test.

Statistics were done using (JASP, 0.19.3),[45] apart from the LASSO regressions and power analyses that were done in R. 4.4.0.[46] Estimates are presented with [95%-confidence intervals], and results $p<0.05$ were considered statistically significant.

Results

The 60 women in the study were 18-44 years old (Table 1), of whom 19 were COC users and 16 POC users (Supplementary Table 1 provides an overview of the different hormonal contraceptives used). Age was not significantly different between user groups ($F(2,56)=2.32$, $\omega^2=0.04$, $p=0.11$).

Contraceptives and EEG biomarkers before treatment

In five ANCOVAs (Figure 1), we found no significant effect of the contraceptive group on the EEG biomarkers (supplementary material, ω^2□<0.03, p-value>0.15).

One non-user was unexpectedly pregnant based on a urine sample collected after the EEG, and one COC user reported spontaneous remission a week later before medication. Removing them did not change the estimates or conclusion (ω^2□<0.03, p-value>0.16).

The POC group consists of five progestin-only pill users and 11 progestin-only IUDs. Excluding the five progestin-only pill users similarly did not change the estimates or conclusion (ω^2□<0.03, p-value>0.17).

Contraceptives, EEG biomarkers and treatment response

We conducted three hierarchical model comparisons for each biomarker to examine whether hormonal contraceptive use moderated EEG biomarker relationships with treatment response

(Table 2, complete model coefficients in Supplementary Table 2). Adding the contraceptive group to the base EEG models significantly improved model fit across all biomarkers (all $\Delta X^2>6.3$, all $p<0.044$), with improved accuracy (63-72%) and AUC (0.74-0.79) compared to their respective EEG-only base models (accuracy: 56-61%; AUC: 0.64-0.66, Figure 2), but at the cost of increased BIC (Table 2). Adding interaction terms increased model fit (i.e. higher R^2 for all except LDAEP) and complexity (i.e. higher BIC), although without providing significant improvement (all $\Delta X^2<3.9$, all $p>0.140$).

Despite moderate to large observed effect sizes for APF, vigilance and tACC (Supplementary Table 2), we had only 23% power for APF interactions and 24% for vigilance interactions. The tACC analysis had better power (77%) due to larger observed effect sizes. The power limitations must be considered when interpreting the hierarchical regression findings (Table 2). Despite the low power, the improved model performance metrics (e.g., $\Delta R^2=0.09$, $\Delta AUC=0.04$ for APF × group) suggest these effects warrant further investigation.

Prediction model specification based on contraceptives and EEG biomarkers

We conducted LASSO regression analyses with repeated cross-validation to examine the potential predictive value of hormonal contraceptive use, EEG biomarkers and their interaction (Table 4). In all LASSO analyses, the contraceptive group is selected (Table 4), confirming the added value of the contraceptive group to the base EEG models (Table 3). Notably, the non-user group was consistently selected across all analyses in 42-95% of iterations, reinforcing its importance as the reference group. The small lambda values (<0.07) indicate mild regularisation was optimal for these models, suggesting that overfitting is not a concern.

The LASSO analyses frequently retained selected interaction terms between APF and COC (selected in 85% of iterations) and between POC and COC (70%), as well as interaction terms between tACC and COC (94%) and between tACC and POC (68%).

There was a limited value of group interactions with vigilance. The interactions with COC and POC were selected only in 53% and 33% of iterations, respectively, along with a main vigilance effect (60%). Figure 3 shows the ROC curves of these models.

In contrast, FAA was selected in <1% of interactions and the interactions with COC and POC only in 39% and 27% of iterations, respectively, consistent with a negligible increase in R^2 (Table 3). Similarly, the LASSO analysis with LDAEP selected only the contraceptive group,

consistent with no increase in R^2 (Table 3). Thus, LDAEP and FAA were outperformed by the contraceptive group.

Contraceptives and treatment response

The treatment response rates were 71% for non-users, 24% for COC, and 44% for POC (Figure 1). There was a significant association between hormonal contraceptive usage and treatment response: $\chi^2(2, N=54) = 8.81$, $p=0.012$. Based on medication plasma concentrations at week eight, one COC user with non-response was deemed treatment non-adherent; removing her from the analysis did not substantially change the result (24%, $p=0.017$). There was no significant group difference in loss to follow-up ($p=0.26$), switching to duloxetine after week four ($p=0.23$), nor in escitalopram dosage ($p=0.15$, Table 1).

A logistic regression of the contraceptive group and age showed an AUC of 0.75 [0.610; 0.88] and an accuracy of 68.5% in predicting treatment response (Table 2 and Figure 2). Compared to the non-users, the COC group had significantly lower odds of treatment response (OR: 0.14 [0.03, 0.65], $p=0.012$, FDR-adjusted p=0.024). The POC group did not differ significantly from the non-users (OR: 0.35 [0.09, 1.42], $p=0.140$). Age was not a significant predictor (OR: 1.05 [0.94, 1.17], $p=0.64$).

In sensitivity analyses, the response rate among progestin IUD users was 55% and did not differ from that of non-users (OR: 0.52 [0.11, 2.41], $p=0.40$).

Discussion

This study examined relationships between hormonal contraceptive use, EEG biomarkers, and antidepressant treatment response in women with MDD. We found that: 1) Contraceptive use was not associated with pre-treatment EEG biomarkers. 2) The contraceptive group emerged as a strong predictor of treatment response and improved all EEG-based models of treatment response. 3) LASSO analyses consistently selected interactions between contraceptive use and specific EEG biomarkers, i.e. APF and tACC. 4) Women using COC, but not POC, showed markedly lower treatment response rates (24%) compared to non-users (71%).

Contrary to expectation, we found no differences in EEG biomarkers between contraceptive groups. However, contraceptive status improved EEG-based treatment prediction, and exploratory analyses suggested potential moderation effects for specific biomarkers, particularly

APF and tACC, though these interactions did not reach statistical significance in confirmatory analyses.

The lack of significant effects of hormonal contraceptive use on EEG biomarkers suggests that these contraceptives may not substantially alter specific aspects of brain electrophysiology during depression. These results are somewhat surprising, given previous findings of hormonal influences on brain function and structure,[47,48] including brain oscillations; preclinical evidence supports that estradiol modulates GABAergic and glutamatergic transmission, which are key determinants of cortical oscillations. [49] Nonetheless, these results align with recent findings in healthy women showing no significant differences in alpha frequency and power between contraceptive users and naturally cycling women.[11] The effects of depression may overshadow any contraceptive hormonal impact on EEG markers, and/or our study may be underpowered to detect subtle effects. There is, e.g. preliminary evidence in healthy women suggesting hormonal contraceptive users may exhibit higher LDAEP than non-users[18], which we did not find in our depressed sample.

While we found no strong evidence of a moderating effect of the contraceptive group on the association between EEG biomarkers and treatment outcome, exploratory LASSO analyses for specifying optimal prediction models consistently selected the contraceptive group in interaction with several EEG biomarkers, indicating that it may potentially contribute valuable information in predicting treatment response, particularly for APF and tACC.

Although sex hormones influence frontal asymmetry [24,50], central serotonergic activity [17], arousal circuitry[51], and we found no or very limited support for a potential interaction of hormonal contraceptive use with FAA, LDAEP or vigilance level. The differential LASSO selection of the contraceptive group, in interaction with the different EEG biomarkers, suggests that these selections are EEG biomarker-specific. If confirmed in an independent sample, such selectivity could have important implications for the clinical use of these biomarkers.

Our models showed improved predictive performance when combining the contraceptive group with EEG biomarkers at the cost of a minimal increase in model complexity. The improved predictive performance by combining the contraceptive group with APF suggests this particular biomarker may be especially relevant for treatment prediction in women. The LASSO analyses frequently selected interactions between contraceptive type and specific EEG biomarkers (i.e. APF and tACC), with COC interactions being selected more often than POC interactions,

possibly due to the estrogen component in COCs. This is supported by recent findings showing that IUD users have similar neural activity to naturally cycling women during emotion regulation tasks, while COC users show reduced frontal regulation-related activity.[52] However, other work indicates hormonal IUD users show increased regulation-related activity compared to both COC users and naturally cycling women [53], highlighting that hormonal IUDs should not be assumed to be neurobiologically inactive. Indeed, we observed that the POC interacted with APF (Supplementary Table 2), and the interaction was frequently selected in LASSO models.

This finding has practical implications for clinical applications, as APF is a promising biomarker for various treatments, including SSRI[54–56], TMS[57,58], and ADHD medication treatment[59]. The addition of contraceptive groups to vigilance models warrants attention, as vigilance regulation has been shown to predict responses to not only SSRIs and SNRIs in MDD[19,34], but also the antidepressant effects of ketamine.[22,60,61] Theta activity in the frontal cortex and the ACC has been studied in relation to the treatment effects of several antidepressants, TMS and psychotherapy, with mixed results [36]. Early literature has reported associations between elevated resting-state theta activity in rostral ACC and favourable antidepressant treatment responses[39,40,62]. In contrast, more recent, larger studies (e.g., iSPOT-D) have reported higher resting-state ACC theta in non-responders relative to remitters[22,36], suggesting that the directionality of this biomarker may not be robust across cohorts. Such inconsistencies may reflect the inherently low signal quality and state dependence of resting tACC theta [63], as well as unmodeled hormonal influences. Our results are therefore consistent with the view that resting-state tACC theta is a weak and potentially unstable predictor, whose apparent associations with treatment response might depend on participant characteristics such as hormonal status or vigilance.

While EEG biomarkers have shown promise in predicting treatment response,[64] our findings indicate that (combined oral) contraceptive user status in women may constitute an important variable that impacts the predictive utility of EEG biomarkers.

We speculate that failure to account for hormonal contraceptive use may partially explain the inconsistent replication of EEG biomarkers across studies[20], as this variable is rarely accounted for. Combining EEG biomarkers with readily available clinical information like hormonal contraceptive use - might provide a more comprehensive approach to treatment prediction, though this requires validation in larger studies. Nonetheless, these findings also raise questions about the broader effects of hormonal contraceptives on treatment outcomes.

A key finding from our study was that the hormonal contraceptive group serves as an independent predictor of treatment response. That COC users had lower treatment response rates (24%) than non-users (71%) contrasts with previous research, including STAR*D, which reported a trend towards better citalopram remission rates in 226 hormonal contraceptive users compared to 670 non-users; though this did not persist after controlling for confounders.[65] Similarly, an analysis of 17 double-blind, placebo-controlled clinical trials with 1698 women found no difference in treatment response to fluoxetine between oral contraceptive (OC) users and non-users.[66] A previous analysis of our dataset identified a trend toward poorer remission in OC users compared to non-users. [15] While our current study draws from the same clinical trial[25], this analysis differs in participant selection (EEG versus positron emission tomography), with 90% participant overlap.

A key methodological difference from previous work is our separation of hormonal contraceptive types. Earlier studies, such as STAR*D grouped all contraceptive users despite the distinct pharmacological profiles of combined (COC) versus progestin-only methods (POC). These differences could affect SSRI metabolism through differential effects on cytochrome P450 enzymes.[67,68] Our previous analysis partially addressed this by separating oral contraceptives from intrauterine delivery.[15] Nonetheless, as all hormonal contraceptives, regardless of the administration route, ultimately may influence the brain via the bloodstream, that approach still groups combined oral estrogen and progestin with progestin-only contraceptives.

Several mechanisms may explain the lower treatment response in COC users versus non-users. Preclinical studies show conflicting results: estradiol enhances antidepressant effects in some rodent models [69,70], while estrogen-progesterone combinations can block acute antidepressant effects in others[71]. The differential responses between COC and POC users might reflect variations in timing, dosage, and specific hormone combinations. The open question of whether modifying contraceptive regimens could improve SSRI outcomes is complicated by individual differences in hormonal sensitivity - recent evidence shows that even pill-tolerators experience mood worsening during pill pauses[72]. This neurobiological variability in response to hormonal fluctuations may be detectable through future EEG biomarker research.

Several limitations warrant consideration. The sample size limited our power to detect subtle effects of hormonal contraceptives on EEG biomarkers and their potential contribution as predictors of treatment response. We could not account for contraceptive use duration, specific formulations or pill-pause. Validation is needed in more extensive and diverse cohorts such as

the ongoing BrainDrugs-Depression study[73], which also enables taking into account additional clinical and lifestyle variables, and different generations and types of COC and POC, which contain diverse estrogens and progestins with varying androgenic and anti-androgenic properties, as well as different brain [74] and metabolic effects [67,68].

While our cohort substantially overlaps with a previous analysis examining contraceptive effects on treatment response, the studies differ in imaging requirements; the overlap is complete for non-users but only 76% for COC users, which may contribute to the similar observed directions but non-significant earlier finding.[15] Women's contraceptive choices may reflect underlying hormonal sensitivities that independently influence depression outcomes. For instance, women who select progestin-only contraceptives due to previous adverse reactions to combined oral contraceptives might represent a distinct neurobiological subgroup. While a limitation, this potential ‘confounding by indication’ could reveal clinically relevant patient subgroups with different treatment response patterns. Future research would benefit from larger sample sizes and a more granular approach to categorising hormonal contraceptives, incl. specific hormonal components, doses, and regimes.

Conclusion

While hormonal contraceptive use was not associated with EEG biomarkers, integrating contraceptive status with EEG biomarkers enhanced predictive accuracy, suggesting that this readily available clinical information could improve treatment outcome predictions. Our findings also demonstrate that women using combined oral contraceptives showed markedly lower SSRI treatment response rates (24%) compared to non-users (71%). These results indicate that accounting for hormonal contraceptive use may be crucial for developing reliable biomarkers for treatment response, which may guide the future development of personalised depression treatment in women.

Data availability

Source data for Figures 1-3 are available in Supplementary Data 1.
The analysed data is further available by application, which is reviewed by the Cimbi Database group at NRU. The application form and more detailed information are available at https://nru.dk/index.php/allcategories/category/224-cimbi. Upon approval, the Database Manager extracts the requested data. A database inventory is published in NeuroImage [75].

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Author contributions

Conceptualisation: KRJ, VGF, MBJ, CTI; **Formal Analysis:** KRJ, AKJ, SVL, CTI; **Investigation:** KRJ, AKJ, SVL, VGF, MBJ, CTI; **Original Draft:** KRJ, AKJ, MBJ; **Visualisation:** KRJ, AKJ, **Review & Editing:** KRJ, AKJ, SVL, MTA, VGF, MBJ, CTI; **Supervision:** KRJ, VGF, MBJ, CTI; **Administration:** KRJ, VGF, MBJ; **Funding:** KRJ, VGF, MBJ, CTI

Competing interest

CTI is a shareholder of DeepPsy AG. KRJ has given talks sponsored by H. Lundbeck; all honoraria were donated to StrongMinds.org, a non-profit providing free, evidence-based mental health care to under-resourced populations. MBJ has given talks sponsored by H. Lundbeck and Boehringer Ingelheim. VGF has served as a consultant to SAGE Therapeutics and has given lectures at seminars sponsored by Lundbeck A/S, Janssen-Cilag A/S, Gedeon-Richter A/S, and Ferring Pharmaceuticals. The other authors have nothing to disclose.

Tables and Figures

Table 1. Clinical demographics and EEG biomarkers

Alpha Peak Frequency (APF), vigilance level, loudness dependence of auditory evoked potentials (LDAEP), frontal alpha asymmetry (FAA), and theta current source density at ACC (tACC). [1]Two combined oral contraceptive users (COC) and one progestin-only contraceptive user (POC) were lost to follow-up at treatment week seven. Based on their week four HAMD and their reason for dropping out (e.g. acute suicidality), they were coded as treatment non-responders. Mean (standard deviation).

Pretreatment	**NON**	**COC**	**POC**	**All women**
n	25	19	16	60
Age	28.0 (7.2)	24.5 (4.4)	25.0 (5.5)	26.1 (6.1)
HAMD	23.1 (3.8)	22.2 (3.0)	24.3 (3.4)	23.1 (3.5)
Recurrent depression	56%	63%	63%	60%
APF (Hz)	9.98 (1.33)	9.87 (1.38)	10.00 (1.32)	9.95 (1.32)
FAA (a.u.)	-0.04 (0.21)	0.004 (0.23)	0.01 (0.24)	-0.01 (0.22)
Vigilance level (a.u.)	4.41 (0.93)	4.48 (0.92)	3.89 (0.75)	4.2 (0.89)
tACC (a.u.)	-2.69 (0.50)	-2.47 (0.38)	-2.47 (0.38)	-2.56 (0.44)
LDAEP (μV/10dB)	2.53 (1.43)	2.35 (1.51)	2.14 (1.12)	2.37 (1.37)
Week 8	**NON**	**COC**	**POC**	**All women**
n[1]	21	17	16	54
Age	28.0 (6.5)	24.0 (3.9)	25.1 (5.5)	25.9 (5.7)
Escitalopram dose, mg	16.3 (3.2)	17.7 (3.9)	15.0 (4.8)	16.3 (3.9)
Switched to Duloxetine	5%	12%	25%	13%
HAMD[1]	9.0 (5.3)	15.3 (7.3)	13.2 (4.4)	12.1 (6.3)
%-HAMD change[1]	60 (23)	32 (28)	44 (22)	47 (27)
Treatment response[1]	71%	24%	44%	48%

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Table 2. Hierarchical Model Comparisons of Treatment Response

Group, i.e. non-users (NON), combined oral contraceptive users (COC), and progestin-only contraceptive users (POC). Alpha peak frequency (APF), vigilance level, loudness dependence of auditory evoked potentials (LDAEP), frontal alpha asymmetry (FAA), and theta current source density at ACC (tACC). Bayesian Information Criterion (BIC), Area Under the Receiver Operating Characteristic Curve (AUC) with 95% Confidence Interval (CI), and Nagelkerke R^2.
[1]All models include age. Complete model coefficients for interaction models in Supplementary Table 2.

Model[1]	Accuracy	AUC [95% CI]	BIC	R^2	χ^2 test	*p*
APF	56%	0.65 [0.50; 0.80]	83.6	0.07		
APF + group	63%	0.75 [0.61; 0.88]	84.2	0.17	7.4	0.025
APF × group	69%	0.79 [0.67; 0.91]	88.3	0.26	3.9	0.140
FAA	59%	0.64 [0.49; 0.79]	83.7	0.07		
FAA + group	69%	0.75 [0.62; 0.88]	84.8	0.16	6.9	0.032
FAA × group	69%	0.76 [0.63; 0.89]	90.9	0.20	1.9	0.384
Vigilance	59%	0.64 [0.49; 0.79]	83.2	0.08		
Vigilance + group	69%	0.75 [0.62; 0.89]	84.4	0.16	6.8	0.034
Vigilance × group	72%	0.76 [0.63; 0.89]	90.9	0.19	1.5	0.478
tACC	61%	0.66 [0.51; 0.80]	82.7	0.10		
tACC + group	67%	0.75 [0.61; 0.88]	84.4	0.15	6.3	0.044
tACC × group	72%	0.76 [0.62; 0.89]	89.4	0.22	3.0	0.222
LDAEP	56%	0.64 [0.50; 0.79]	84.0	0.07		
LDAEP + group	69%	0.73 [0.60; 0.87]	84.8	0.17	7.2	0.028
LDAEP × group	70%	0.74 [0.60; 0.87]	92.7	0.17	0.1	0.969
Group	69%	0.74 [0.61; 0.88]	80.9	0.22	9.2	0.020
Age-only	56%	0.63 [0.48; 0.78]	80.0	0.07	2.7	0.099

Table 3. Repeated LASSO regression variable selection

Repeated five-fold LASSO regression models of EEG biomarkers interacting with the hormonal contraceptive group, i.e. non-users (NON), combined oral contraceptive users (COC), and progestin-only contraceptive users (POC). Alpha peak frequency (APF), vigilance level, loudness dependence of auditory evoked potentials (LDAEP), frontal alpha asymmetry (FAA), and theta current source density at ACC (tACC). The probability of model variable selection from 500 repeats is presented with the mean (SD) of Lambda (λ), which controls the amount of regularisation applied to the model, with higher values indicating stronger regularisation to prevent overfitting. The low λ values suggest that mild regularisation provided optimal model fit.
[1]Age was included in all models without penalisation.

Biomarker	Optimal model[1]	Model variable selection probabilities[1]	λ (SD)
APF	Group × APF	95% NON, 85% APF:COC, 78% APF, 70% APF:POC, 63% POC, 45% COC	0.018 (0.033)
FAA	Group	81% NON, 79% COC, 39% FAA:COC, 27% FAA:POC, <1% FAA	0.070 (0.041)
Vigilance	Group + Vigilance	88% NON, 60% Vigilance, 53% Vigilance:COC, 42% COC, 33% Vigilance:POC, 12% POC	0.042 (0.042)
tACC	Group × tACC	94% tACC:COC, 87% tACC, 68% tACC:POC, 42% NON, 20% POC, 7% COC	0.021 (0.033)
LDAEP	Group	93% NON, 93% COC	0.053 (0.026)

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Figure 1: Hormonal contraceptive use and EEG biomarkers

Raincloud plots of alpha peak frequency (APF, Hz), vigilance level, loudness dependence of auditory evoked potentials (LDAEP, μV/10 dB), frontal alpha asymmetry (FAA), and theta current source density at ACC (tACC) in the three hormonal contraceptive use groups, i.e. non-users (NON), combined oral contraceptive users (COC), and progestin-only contraceptive users (POC), with subjects colour-coded by age. We found no significant effect of the contraceptive group on the EEG biomarkers in ANCOVAs with age as a covariate (ω^2<0.03, *p*-value>0.15). Figure data available in Supplementary Data 1.

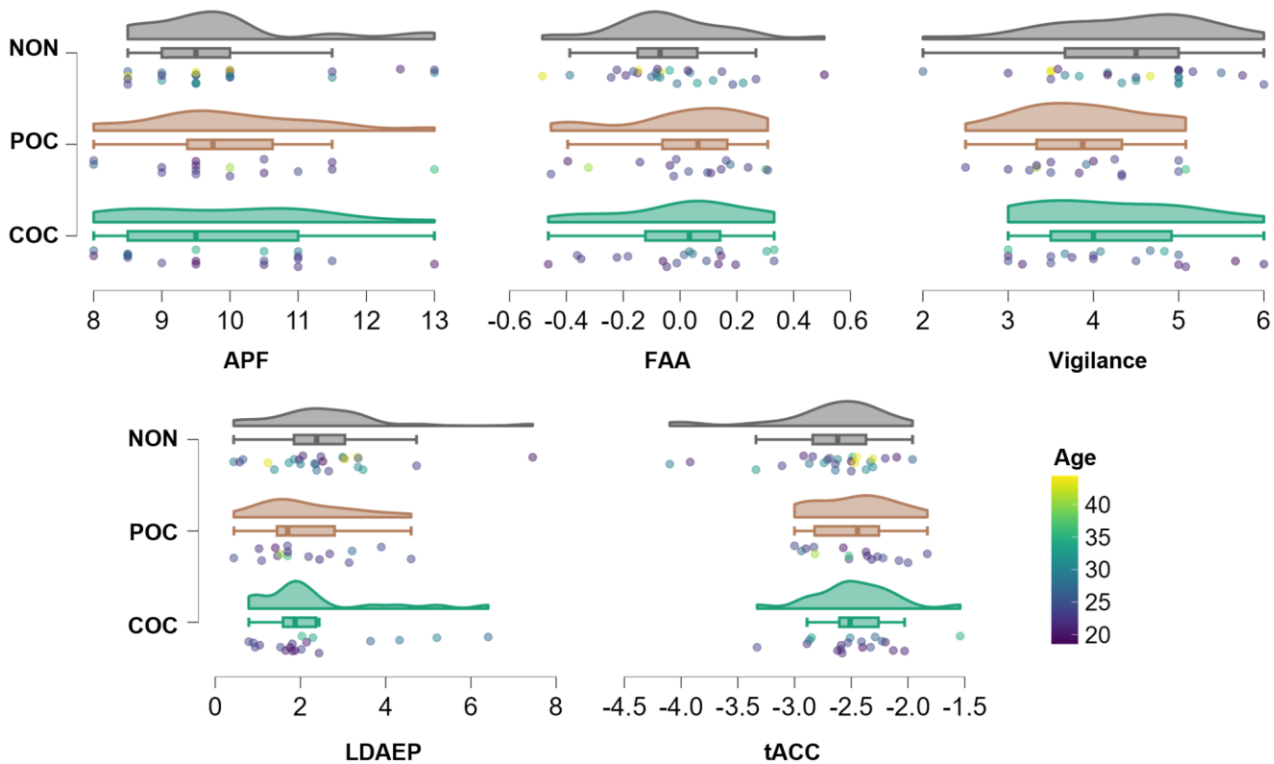

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Figure 2: Hormonal contraceptive use, treatment effect, and response

Distribution of reduction in depression severity and treatment response (a ≥50% reduction from pretreatment) for the hormonal contraceptive user groups: none-users (NON), combined oral contraceptive users (COC), and progestin-only contraceptive users (POC) at week eight. Figure data available in Supplementary Data 1.

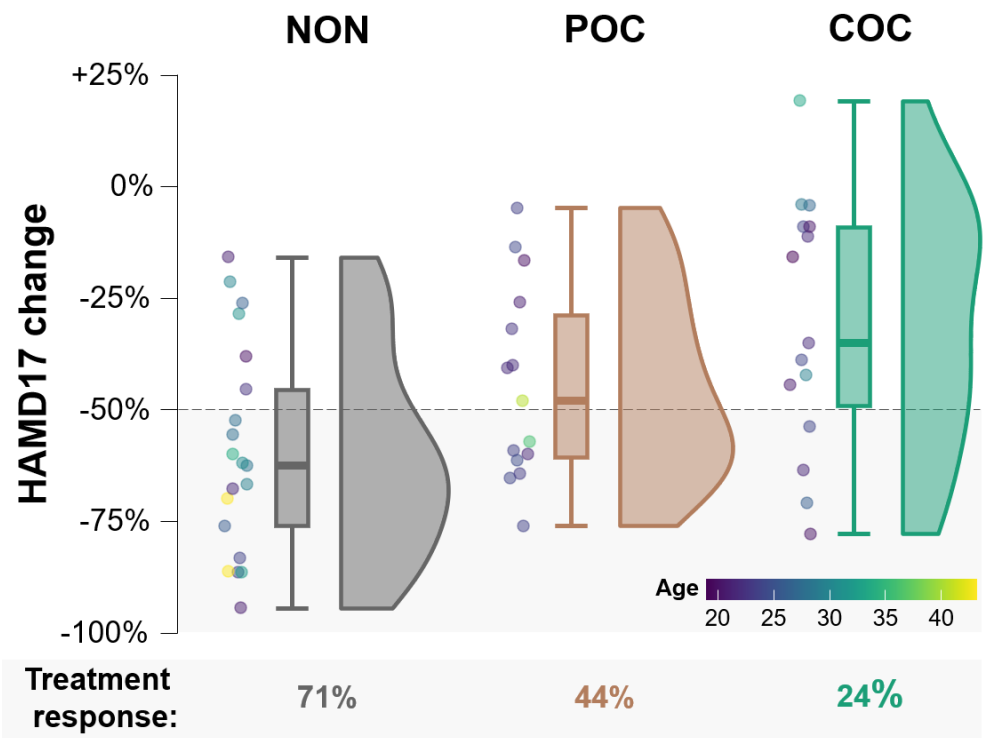

Figure 3: Hormonal contraceptive use and treatment response

Receiver operating characteristic curves (ROC) with Area Under the Receiver Operating Characteristic Curve (AUC) for logistic regression models of treatment response (a ≥50% reduction from pretreatment) with alpha peak frequency (APF), vigilance level, theta current source density at ACC (tACC), hormonal contraceptive user groups, and combined with an interaction. All models include age. Figure data available in Supplementary Data 1.

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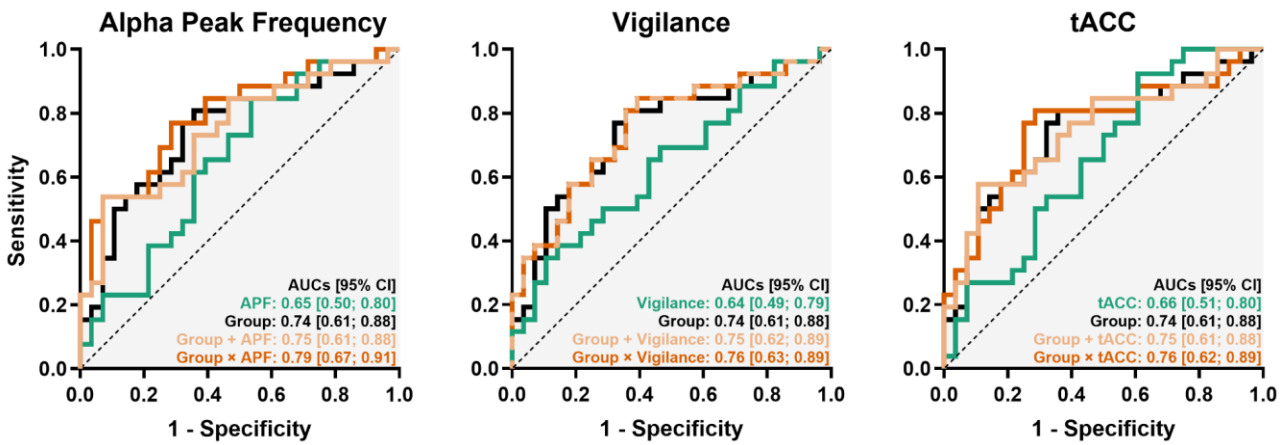
Alpha Peak Frequency
Sensitivity
1 - Specificity
AUCs [95% CI]
APF: 0.65 [0.50; 0.80]
Group: 0.74 [0.61; 0.88]
Group + APF: 0.75 [0.61; 0.88]
Group × APF: 0.79 [0.67; 0.91]
Vigilance
1 - Specificity
AUCs [95% CI]
Vigilance: 0.64 [0.49; 0.79]
Group: 0.74 [0.61; 0.88]
Group + Vigilance: 0.75 [0.62; 0.89]
Group × Vigilance: 0.76 [0.63; 0.89]
tACC
1 - Specificity
AUCs [95% CI]
tACC: 0.66 [0.51; 0.80]
Group: 0.74 [0.61; 0.88]
Group + tACC: 0.75 [0.61; 0.88]
Group × tACC: 0.76 [0.62; 0.89]

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ED Summary:

Jensen et al. examine whether hormonal contraceptives affect EEG-biomarkers associated with antidepressant treatment response in women with depression. Use of combined oral contraceptives shows poorer treatment response to antidepressants compared to non-contraceptive use, indicating a potential interaction with EEG-biomarkers.

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