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One-week escitalopram intake alters the excitation–inhibition balance in the healthy female brain

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Abstract

Neural health relies on cortical excitation–inhibition balance (EIB). Previous research suggests a link between increased cortical excitation and neuroplasticity induced by selective serotonin reuptake inhibitors (SSRIs). Whether there are modulations of EIB following SSRI-administration in the healthy human brain, however, remains unclear. Thus, in a randomized double-blind study, we administered a clinically relevant dose of 20 mg escitalopram for 7 days (time when steady state is achieved) in 59 healthy women (28 escitalopram, 31 placebo) on oral contraceptives. We acquired resting-state electroencephalography data at baseline, after a single dose, and at steady state. We assessed $1/f$ slope of the power spectrum as a marker of EIB, compared individual trajectories of $1/f$ slope changes contrasting single dose and 1-week drug intake, and tested the relationship of escitalopram plasma levels and cortical excitatory and inhibitory balance shifts. Escitalopram-intake was associated with decreased $1/f$ slope, indicating an EIB shift in favor of excitation. Furthermore, $1/f$ slope at baseline and after a single dose of escitalopram was associated with $1/f$ slope at steady state. Higher plasma escitalopram levels at a single dose were associated with better maintenance of these EIB changes throughout the drug administration week. These findings demonstrate the potential for $1/f$ slope to predict individual cortical responsivity to SSRIs and widen the lens through which we map the human brain by testing an interventional psychopharmacological design in a clearly defined endocrinological state.

KEYWORDS

aperiodic spectral component, cortical plasticity, escitalopram, excitation–inhibition balance, resting-state electroencephalography, sex hormones

Rachel G. Zsido and Eóin N. Molloy contributed equally to this study.

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1 | INTRODUCTION

The balance of excitation and inhibition in neuronal circuits is essential for brain network function and stability (Froemke, 2015; Sohal & Rubenstein, 2019). Failure to maintain this excitation–inhibition balance (EIB) can underlie circuit dysfunction observed in several neuropsychiatric and neurodevelopmental disorders (Selten, van Bokhoven, & Kasri, 2018), as evidenced by studies in patients with autism (Gao & Penzes, 2015), schizophrenia (Gao & Penzes, 2015; Molina et al., 2020), and major depressive disorder (Luscher, Shen, & Sahir, 2011). Conceptual models propose that selective serotonin reuptake inhibitors (SSRIs), a class of antidepressants upregulating serotonergic transmission, act by enhancing synaptic plasticity (Castrén, 2013). Findings from animal studies (Schneider et al., 2019; Vetencourt et al., 2008) suggest that alterations in cortical excitation and inhibition may be a critical factor driving SSRI-induced plasticity. While many of these findings are limited to animal models, some studies have investigated SSRI-induced changes in intrinsic neural architecture (Klaassens et al., 2017) and EIB in human participants (Gerdelat-Mas et al., 2005; Ilic, Korchounov, & Ziemann, 2002). However, most of these studies investigated only a single kinetic state (e.g., a single dose of the drug) or relatively small samples. Thus, it remains unclear how longitudinal SSRI-intake affects EIB and whether a neurophysiological marker of EIB could predict individual cortical responsiveness to SSRIs.

Resting-state electroencephalography (rs-EEG) provides a reliable, noninvasive method for investigating pharmacologically driven alterations in human cortical activity. Power of alpha oscillations could provide insight into EIB alterations due to its functional role in cortical inhibition (Klimesch, Sauseng, & Hanslmayr, 2007). For example, decreases in relative alpha power, thought to reflect enhanced cortical excitability (Klimesch et al., 2007), have been observed in healthy male participants ($n = 12$) following 1 week of litoxetine administration, an SSRI under development (Patat et al., 1994), as well as in depressed patients following 1 week of escitalopram administration (Leuchter et al., 2017). Another exploratory study in healthy male participants (Knott, Howson, Perugini, Ravindran, & Young, 1999; $n = 14$ /group) found that decreased serotonin synthesis via tryptophan depletion was associated with a trend toward increased relative alpha power. A systematic review of the effects of SSRIs in healthy participants reported decreases in power of alpha oscillations following a single administration of low and medium dose SSRIs (Dumont, De Visser, Cohen, & Van Gerven, 2005); alpha power results for high doses, however, were inconclusive (Dumont et al., 2005). Given that (Sohal & Rubenstein, 2019) alpha power is associated with inhibitory processes, (Froemke, 2015) serotonergic manipulation has been shown to modulate alpha power, and (Selten et al., 2018) abnormal alpha power is associated with psychiatric symptoms in clinical populations such as depression (Kemp et al., 2010; Olbrich & Arns, 2013), it is possible that SSRIs may act via decreases in alpha-band activity that reflect a shift in favor of cortical excitation in the human brain.

Beyond the more canonically defined measures such as alpha power, $1/f$ slope of the power spectral density (PSD) is thought to

more directly reflect EIB. Neurophysiological brain signal consists of periodic oscillatory activity and aperiodic activity ($1/f$ slope) of the nonoscillatory PSD background (Donoghue et al., 2020), which have been shown to play functionally distinct roles (Ouyang, Hildebrandt, Schmitz, & Herrmann, 2020). While more conventional approaches have focused on narrowband oscillations or frequency band ratios, there has been an upsurge in neuroscience research in recent years focusing on $1/f$ slope as a unique neurophysiological marker (Donoghue, Dominguez, & Voytek, 2020; Lendner et al., 2020; Molina et al., 2020; Ouyang et al., 2020; Weber, Klein, & Abeln, 2020). Simulation data with local field potentials demonstrate that $1/f$ slope inversely reflects EIB (Gao, Peterson, & Voytek, 2017), a finding that has been validated in *in vivo* animal models in which anesthesia administration led to an increase in $1/f$ slope or steepening of the PSD decay (Gao et al., 2017). A recent interventional rs-EEG study in healthy humans showed that ketamine and anesthesia administration, which respectively tip the balance in favor of cortical excitation (increase in EIB) and inhibition (decrease in EIB), resulted in the expected decrease and increase in $1/f$ slope (Colombo et al., 2019). Since then, several recent studies have shown the reliability of this measure using human scalp EEG activity in both healthy (Donoghue, Dominguez, & Voytek, 2020; Lendner et al., 2020; Weber et al., 2020) and clinical populations (Lendner et al., 2020; Molina et al., 2020).

Nevertheless, the effect of SSRIs on $1/f$ slope has yet to be investigated. To clarify the neurophysiological mechanisms underlying serotonergic action in health and identify a potential marker to predict individual cortical responsiveness to SSRIs, we require a longitudinal model of how SSRI-intake affects EIB in a homogenous sample of healthy controls. In this study, we administered a clinically relevant dose of 20 mg escitalopram continuously for 7 consecutive days (Kasper et al., 2009; Kasper, Spadone, Verpillat, & Angst, 2006; Klein et al., 2006, 2007; Rao, 2007). Given known sex differences in neural responses to serotonergic intervention (LeGates, Kvarta, & Thompson, 2019), higher antidepressant prescription rates in women (Abbing-Karahagopian et al., 2014) as well as the clear need to increase female samples in neuroscience research (Beery & Zucker, 2011; Taylor, Pritschet, & Jacobs, 2020; Will et al., 2017), we recruited 59 healthy female participants (28 escitalopram, 31 placebo) who underwent rs-EEG at three time points: before randomization (baseline), after a single dose of administration (single dose), and after 1 week of daily administration (steady state; Rao, 2007). All participants were using oral contraceptives to downregulate ovarian hormone fluctuations to control for potential effects of sex hormones on escitalopram responsiveness (LeGates et al., 2019), brain resting-state connectivity (Lisofsky et al., 2015; Petersen, Kilpatrick, Goharзад, & Cahill, 2014; Pritschet et al., 2020), and resting-state alpha activity specifically (Brötner, Klimesch, Doppelmayr, Zauner, & Kerschbaum, 2014). We estimated $1/f$ slope of the PSD as a measure of EIB. Given our decision to separately investigate oscillatory activity from $1/f$ activity, we calculated power of alpha oscillations independently from aperiodic activity. To compare to previous findings, however, we additionally calculated relative alpha power from the original PSD. We hypothesized that escitalopram administration would be associated with decreases in both $1/f$ slope and power of alpha oscillations.

2 | MATERIALS AND METHODS

2.1 | Participants and eligibility

Participants provided written informed consent after study procedures were explained. Eligible individuals were female, right-handed, 18–35 years old, with a body mass index (BMI) 18.5–25 kg/m², and without any neurological or psychiatric illness as confirmed with a structured clinical interview (Fydrich, Renneberg, Schmitz, & Wittchen, 1997; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). All participants were taking oral contraceptives for ≥ 3 months to downregulate ovarian hormone fluctuations. Exclusion criteria were medication, tobacco or alcohol use, positive drug or pregnancy tests, and abnormal QT times in electrocardiogram readings. Of the 87 participants screened, 70 were enrolled. We included 59 participants in analyses as 6 (4 escitalopram) chose to discontinue and 5 (3 escitalopram) were excluded after data quality assessment. Participants were under medical supervision for the entire experiment. The Ethics Committee of the Faculty of Medicine of Leipzig University (approval # 390/16-ek) approved all procedures.

2.2 | Study design and experimental protocol

These data were acquired as a secondary outcome measure from a randomized, double-blind, parallel study design (ClinicalTrials.gov: NCT03162185, Open Science Framework <https://osf.io/g9usb>), as previously reported (Molloy, Mueller, et al., 2021; Molloy, Zsido, et al., 2021). The present study was designed to test the hypothesis that 1-week SSRI-administration shifts cortical EIB using a novel EEG surrogate marker (Gao et al., 2017), and to investigate whether the acute EIB response to a single dose of escitalopram can predict individual EIB responsivity after 7 days of drug-intake (when plasma levels no longer fluctuate and relative steady-state levels in healthy participants are reached (Rao, 2007)). We administered 20 mg of escitalopram, which reliably blocks 80% of serotonin transporter and achieves steady-state conditions after 1 week of administration (Kasper et al., 2006, 2009; Klein et al., 2006; Klein et al., 2007; Rao, 2007) or an identical placebo capsule (mannitol/aerosol) from sequentially numbered containers at fixed times each day for 7 consecutive days. We recorded a baseline rs-EEG prior to drug administration (baseline). Participants were then randomized to receive either escitalopram or placebo. Randomization employed an independent block randomization with a 1:1 allocation ratio, conducted by the Pharmacy of the University Clinic at Leipzig University. The experimenter and participants were blind to treatment allocation. We recorded another rs-EEG measurement following a single dose (single dose) and after 7 days of administration (when relatively steady-state plasma levels are reached; Figure 1). All rs-EEG measurements took place at approximately the same time of day for participants and 4–5 hr after escitalopram or placebo intake, as previous pharmacokinetic modeling in healthy participants suggests

maximum drug plasma concentration is reached 3–5 hr after 20 mg oral escitalopram intake (Drewes, Thijssen, & Mengel, 2001; Søgaard, Mengel, Rao, & Larsen, 2005). We assessed potential changes in anxiety (State-Trait Anxiety Inventory [STAI-S]; Laux, Glanzmann, Schaffner, & Spielberger, 1981, nonpatient edition), current mood (German version of Profile of Mood States [POMS]; Dalbert, 2002), daytime sleepiness (Epworth Sleepiness Scale [ESS]; Bloch, Schoch, Zhang, & Russi, 1999), and escitalopram side effects (Antidepressant Side-Effect Checklist [ASEC]; Uher et al., 2009). The STAI, POMS, ESS, and ASEC took place at approximately the same time of day for each participant. Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were measured by electrochemiluminescence immunoassay (ECLIA; Cobas; Roche) prior to enrollment to confirm downregulated ovarian hormones. We analyzed plasma escitalopram concentration from single dose and 1-week steady state using a validated high-performance liquid chromatography method (Teichert et al., 2020), with four quality control samples covering the low, medium, and high range of the calibration curve. Deviation of the measured concentrations of the quality control samples was tested for an acceptance interval of $\pm 15\%$.

2.3 | rs-EEG acquisition

We used a 32-channel EASYCAP (Brain Products GmbH, Germany) electrode cap, BrainAmp amplifier, and Brain Vision Recorder (Brain Products GmbH, Germany). Sintered Ag/AgCl point electrodes were mounted using the international 10–20 system, and impedance levels per electrode were maintained at < 10 k Ω (typically < 5 k Ω). The reference (M2) electrode was placed on the right mastoid and an additional electrode (M1) was placed on the left mastoid. Four electrodes were placed to monitor eye movement and one ground electrode was placed on the sternum. Data were recorded using a sampling rate of 1 kHz, a high-pass filter of 0.015 Hz, and a low-pass filter of 250 Hz. Participants sat in an acoustically-shielded room with eyes closed for 11 min, with a 30-s break after 5.5 min.

2.4 | rs-EEG preprocessing

Data were preprocessed using EEGLAB toolbox (v14.1) in MATLAB (v9.3). EEG data were band-pass filtered between 1 and 45 Hz (fourth order, forward and backward directions, Butterworth filter) and a notch filter was applied at 50 Hz to ensure artifact removal related to power line noise. Data were down-sampled to 500 Hz. The 30-s break was removed, creating a single 11-min recording. Bad segments from the time series data were marked and rejected by an algorithm with individually adjusted noise thresholds: for low frequencies (1–15 Hz), the threshold was set to 3 SDs above the filtered mean amplitude; for higher frequencies (15–45 Hz), the threshold was 40 μ V. Electrocardiogram, electrooculography, and two frontal channels (Fp1, Fp2)

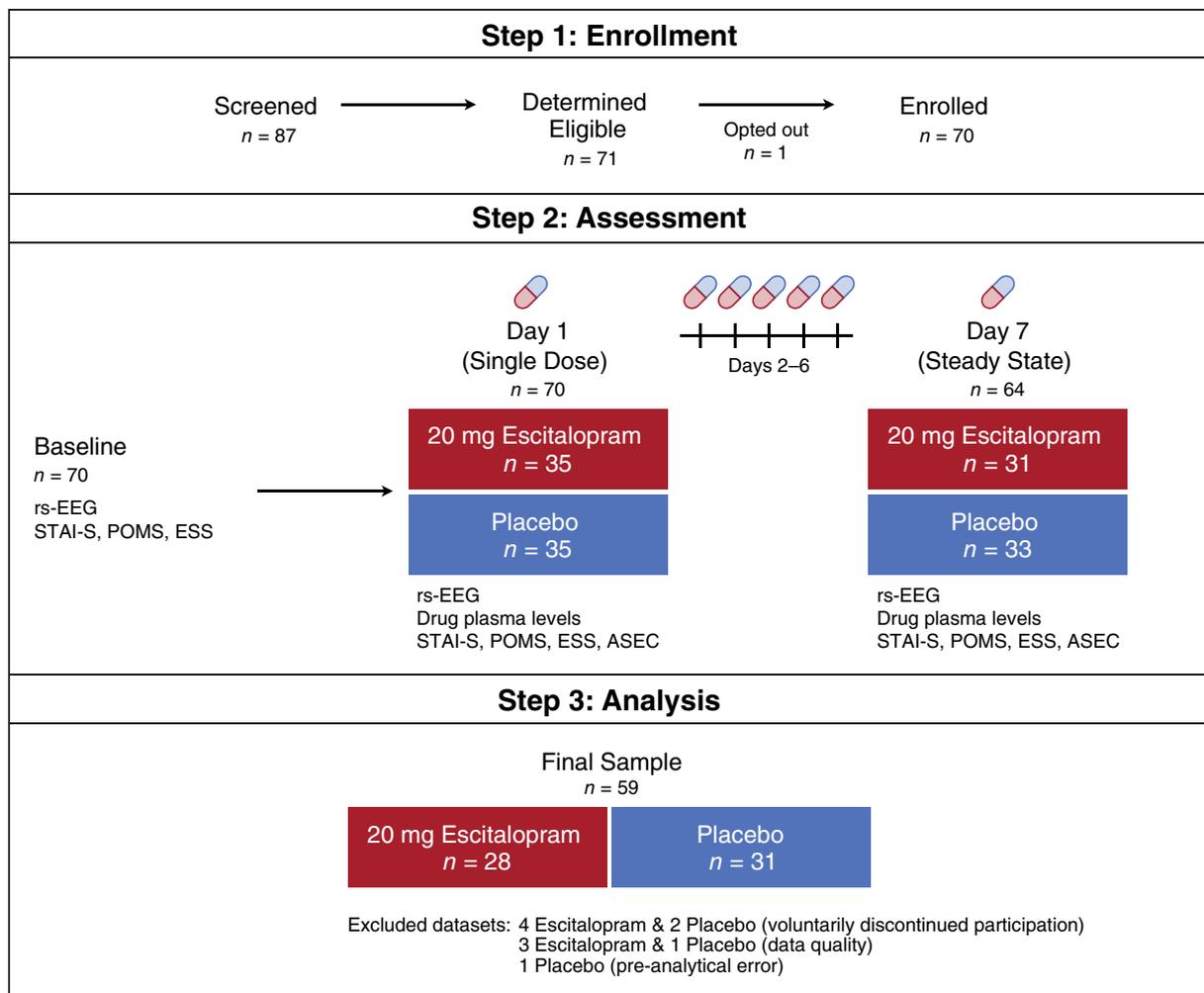


FIGURE 1 Study design and experimental protocol. Step 1 details screening and enrollment numbers. Step 2 depicts study design, with either escitalopram or placebo administered for 7 days following a baseline resting-state electroencephalography (rs-EEG) recording. In total, six participants voluntarily discontinued participation during this phase. Step 3 lists the final sample included in the analyses ($n = 59$). ESS, Epworth Sleepiness Scale; ASEC, Analysis of Antidepressant Side-Effect Checklist; POMS, Profile of Mood States; STAI-S, State-Trait Anxiety Inventory

were removed prior to bad segment estimation due to high amplitudes of eye blinks and heartbeat artifacts. Marked bad segments were applied to the full dataset of 27 scalp electrodes. Flagged bad segments (>60 s) were manually reviewed while broken channels were assessed with visual inspection of the PSD and excluded if necessary. Bad segments were removed prior to re-referencing to ensure noise was not projected to other channels, and so that independent component analysis (ICA) is performed on data that is not contaminated by major noise artifacts spread over all electrodes (Onton & Makeig, 2006). We re-referenced to the common average, where every electrode is referenced against the average of all electrode recording, to avoid prioritizing voltage differences coming from one specific location. ICA weights (Infomax; Bell & Sejnowski, 1995) were then calculated on remaining segments of the time series for each participant that were used to project out ocular, muscular, and cardiac activity components. The second mastoid electrode (M2) was then removed.

2.5 | Rs-EEG data analysis

We estimated $1/f$ offset and slope per channel from the PSD (Welch's PSD with 4-s windows overlapping by 50%) of the preprocessed signal in a frequency range of 1–40 Hz using the FOOOF toolbox (Donoghue, Haller, et al., 2020) in Python (v3.5), a module for parameterizing neural power spectra that quantifies both the periodic and aperiodic activity from the PSD (Donoghue, Haller, et al., 2020). Major oscillatory peaks were excluded when estimating slope of $1/f$ decay. As the FOOOF algorithm operates on log-transformed data, we converted the aperiodic fit back to the original non-log-transformed scale and subtracted it from the non-log-transformed PSD. Individual alpha peak frequency was measured on a detrended PSD by a peak-search in a range between 7 and 13 Hz. A peak was defined as a curve exceeding a threshold of $0.05 \mu V^2/Hz$. If several peaks were found, we considered the largest one. Taking individual alpha peak frequency as an anchor point at which the peak maxima appeared, we defined

the range (no more than ± 3 Hz from maxima of the peak) and used it to estimate alpha power that was defined as a summed area under the non-logged detrended PSD curve. No alpha peak was found in four participants (three escitalopram) in ≥ 10 channels, thus they were excluded from analyses.

2.6 | Statistical analysis

2.6.1 | Monitoring

We assessed potential group differences in age, BMI, and endogenous sex hormonal profiles using independent samples *t* tests in R (v3.5.2; R Core Team, 2013). We assessed potential group differences in total ASEC, POMS, STAI-S, and ESS scores at both single dose and 1-week steady state. Questionnaire results were considered statistically significant at a Bonferroni-corrected threshold of $p < .006$ to account for multiple comparisons. For questionnaires that showed significant group differences, we conducted bivariate correlational analyses to test for potential associations between total questionnaire scores and either escitalopram plasma levels, alpha power, or $1/f$ slope.

2.6.2 | Linear mixed-effects modeling

Due to non-normal distribution, alpha power values were log-transformed. To detect possible outliers, we computed a mean over channels per participant at each assessment for $1/f$ slope and alpha power, using a cutoff of ± 3 SDs within each group. No outliers were detected. We analyzed mean rs-EEG $1/f$ slope and alpha power using a random-intercept mixed-effects modeling approach. We applied one model to each metric using the “lmer” function in the “lme4” R package, with group and time as factors and specific outcome as a dependent variable. We compared the contribution of each fixed main effect and interaction term in an omnibus modeling approach using a chi-square log-likelihood ratio test. Model contributions for each level of the fixed effects were determined using marginal R^2 change. Post hoc Wilcoxon rank-sum tests and Wilcoxon signed-rank tests, implemented with the “wilcox.test” function, were conducted on mean whole-brain signal.

2.6.3 | Cluster-based permutation tests

For significant outcomes derived from linear mixed-effects modeling, we performed cluster-based permutation tests to assess spatially specific effects of escitalopram. Given the non-normal distributions of parameters derived from EEG data, we applied nonparametric Wilcoxon rank-sum tests and Wilcoxon signed-rank tests in MATLAB to test between and within-group effects. *Z*-values obtained per electrode were then used in cluster statistics (Maris & Oostenveld, 2007). Significant electrode clusters were defined as ≥ 2 neighboring electrodes significant at $p < .05$. The most robust cluster was validated

with permutation tests ($n = 1,000$). Briefly, the original cluster derived from the data was compared to the clusters formed by randomized partitions (i.e., randomized group information for between-group, day information for within-group) and running the same statistical tests. Next, we calculated the proportion of random significant clusters ($n = 1,000$) that result in a larger statistic than the originally observed one; this is the cluster-level *p*-value, and the observed cluster is significant if $p < .05$.

2.6.4 | Linear regression on residual $1/f$ slope

We tested if $1/f$ slope at one time was associated with $1/f$ slope at a later time in the escitalopram group. We conducted three regressions in R (baseline to single dose, baseline to 1-week steady state, single dose to 1-week steady state). To control for the individual phenotypic trait $1/f$ slope signal and to isolate the change in $1/f$ slope associated with escitalopram, we calculated a whole-brain unstandardized residual for each timepoint using SPSS version 24. Thus, each analysis was targeted toward identifying the association between escitalopram and $1/f$ slope specifically while controlling for the stable nature of the individual trait signal. Results were considered statistically significant at a Bonferroni-corrected threshold of $p < .016$ ($0.05/3$) to account for multiple comparisons.

2.6.5 | Moderation analysis

In the escitalopram group, we tested regression pathways in an exploratory moderation analysis using PROCESS macro (v3.5.3 SPSS; Hayes, 2017), a program using an ordinary least squares-based path analytical framework to test direct/indirect associations. We assessed significance and stability of the interaction of single dose plasma escitalopram levels (moderator) and residual single dose $1/f$ slope (controlled for baseline, independent variable) in association with residual 1-week steady state $1/f$ slope (outcome variable). Variables were mean-centered and we implemented a 95% bias-corrected bootstrap CI (BCCI), excluding 0 and based on 10,000 bootstrap samples to account for a non-normal data distribution in $1/f$ slope.

2.6.6 | Conventional analysis with relative alpha power

We calculated relative alpha power on the non-detrended (conventional) PSD to compare approaches. Relative alpha power was calculated by dividing alpha-band power of individually predefined alpha range (procedure described above) by the total spectral power (3–45 Hz).

Data of this study are available from the corresponding author upon reasonable request. The R and MATLAB code for analyses are publicly available at <https://github.com/EGGLab-2021>.

3 | RESULTS

3.1 | Monitoring

Analyses included 59 participants (28 escitalopram, 31 placebo). We did not observe group differences for any demographic characteristics (Table 1). LH and FSH values were within reference range expected for downregulated endogenous sex hormone profiles (ECLIA, Cobas: Roche). Plasma drug levels of all participants in the escitalopram group at Day 7 achieved expected steady state plasma levels (Mean \pm SD 45.33 \pm 11.26 ng/ml, range 26.6–66.3) based on previously reported therapeutic reference ranges of steady-state plasma concentrations (Ostad Haji, Hiemke, & Pfuhlmann, 2012).

Analysis of STAI-S, POMS, and ESS questionnaires did not show group differences at single dose (STAI-S $t = -1.76$, $p = .083$; POMS $t = 1.73$, $p = .088$; ESS $t = 0.01$, $p = .987$) or 1-week steady state (STAI-S $t = -0.06$, $p = .945$; POMS $t = 1.07$, $p = .287$; ESS $t = 0.23$, $p = .815$). ASEC scores showed a significant group difference at single dose ($t = -3.39$, $p = .002$) but not 1-week steady state ($t = -0.61$,

$p = .551$). However, we did not observe any associations between ASEC scores and plasma escitalopram levels ($R = -.29$, $p = .131$), mean $1/f$ slope ($R = .08$, $p = .660$), or alpha power ($R = .24$, $p = .228$) at single dose in the escitalopram group. Moreover, we did not observe any associations between plasma levels and mean $1/f$ slope ($R = -.21$, $p = .282$) or alpha power ($R = .13$, $p = .503$) at single dose.

3.2 | Analysis of rs-EEG

The intraclass correlation coefficient in the placebo group across the three time-points was 0.923 for $1/f$ slope, 0.990 for power of alpha oscillations, and 0.998 for the conventional analysis of relative alpha power, suggesting excellent test-retest reliability. Analysis of $1/f$ slope yielded an effect of time, of group, and a group \times time interaction (Table 2, Figure 2). We did not observe any significant interaction effect for power of alpha oscillations. Thus, post hoc analyses and cluster-based permutations were only performed for $1/f$ slope.

Demographic	Placebo (M \pm SD)	Escitalopram (M \pm SD)	t-value	p-value
Age (years)	22.48 \pm 3.79	23.71 \pm 2.92	1.387	.171
BMI (kg/m ²)	21.28 \pm 1.69	21.83 \pm 1.64	1.269	.210
FSH (IU/L)	2.10 \pm 2.98	3.16 \pm 3.29	1.297	.200
LH (IU/L)	1.42 \pm 2.02	2.29 \pm 2.90	1.356	.181
OC use (months)	40.47 \pm 42.51	51.04 \pm 39.62	0.97	.337

TABLE 1 Group comparisons for baseline demographic characteristics

Note: Results from independent sample t tests assessing potential group differences for participant age, body mass index (BMI), Follicle-stimulating hormone (FSH) levels, luteinizing hormone (LH) levels, and length of oral contraceptive (OC) use. Mean \pm Standard Deviation (M \pm SD).

Model specification	Fixed effects	LRT		Marginal R ²	Conditional R ²
		χ^2 (df)	p-value		
<i>1/f slope (n = 59)</i>					
Intercept	-	-	-	0	.374
Time	Time	117.08 (2)	<.001 ^a	.015	.390
Group	Group + time	4.51 (1)	.03 ^a	.043	.390
Interaction	Group \times time	169.40 (2)	<.001 ^a	.064	.411
<i>α power (n = 59)</i>					
Intercept	-	-	-	0	.687
Time	Time	1.18 (2)	.55	.00	.687
Group	Group + time	3.31 (1)	.06	.037	.687
Interaction	Group \times time	4.53 (2)	.10	.038	.687
<i>Relative α power (n = 59)</i>					
Intercept	-	-	-	0	.680
Time	Time	30.90 (2)	<.001 ^a	.002	.682
Group	Group + time	4.04 (1)	.04	.049	.682
Interaction	Group \times time	55.03 (2)	<.001 ^a	.053	.686

TABLE 2 Linear mixed-effects modeling of $1/f$ slope, detrended α power, and relative α power

Note: Results show omnibus effects of each fixed effect separately, with corresponding p -value and associated effect sizes.

Abbreviations: α = alpha; χ^2 = chi-square; df = degrees of freedom; LRT, likelihood ratio test.

^aSignificant contribution to model.

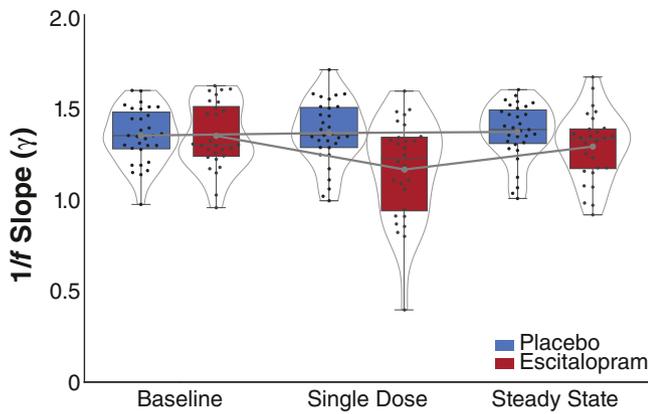


FIGURE 2 Significant changes in $1/f$ slope during 1 week of escitalopram administration. Linear mixed-effects analysis shows that $1/f$ slope, the aperiodic component of the power spectral density, decreases following a single dose of escitalopram. Increases in $1/f$ slope are observed between single dose and 1-week steady state in the escitalopram group. Shown here are the individual data points (black dots) and mean values per group (gray dots). Inner box plot includes median and interquartile ranges, with whiskers extending 1.5 times the interquartile range. Width of the kernel densities reflects proportion of data located there

Post hoc analyses for $1/f$ slope showed a significant group difference at single dose ($W = -237, p = .002$) but not 1-week steady state ($W = 309, p = .058$). Within groups comparisons over time show a significant time effect within the escitalopram group from (i) baseline to single dose ($V = 362, p < .001$), (ii) baseline to 1-week steady state ($V = 292, p = .042$), and (iii) from single dose to 1-week steady state ($V = 50, p < .001$) with decreased $1/f$ slope from baseline to single dose and an increase from single dose to 1-week steady state.

3.3 | Cluster-based permutations in $1/f$ slope

Cluster-based group comparisons of $1/f$ slope did not show differences at baseline. Between-group comparisons at single dose (mean $z_{\text{electrode}} = -2.849, p = .002$) and 1-week steady state (mean $z_{\text{electrode}} = -2.473, p = .026$) show a significant decrease in the escitalopram group compared to placebo (Figure 3a). Within-escitalopram group comparisons showed a significant decrease in $1/f$ slope from baseline to single dose (mean $z_{\text{electrode}} = -3.136, p < .001$) and from baseline to 1-week steady state (mean $z_{\text{electrode}} = -2.693, p = .004$; Figure 3b). Comparisons of single dose to 1-week steady state showed a significant increase in $1/f$ slope (mean $z_{\text{electrode}} = 2.772, p < .001$). Mean power spectra were plotted for the cluster (electrodes F3, FC3, FT7, T7) significant in all contrasts (Figure 3c).

3.4 | Linear regressions on residual $1/f$ slope in escitalopram group

Regression analyses showed that residual baseline $1/f$ slope values were not associated with residual single dose values ($R^2_{\text{adj}} = -.037,$

$p = .849$), residual baseline values were associated with residual 1-week steady state values ($R^2_{\text{adj}} = .235, p = .005$), and residual single dose values were associated with residual 1-week steady state values ($R^2_{\text{adj}} = .462, p < .001$) (Figure 4a).

3.5 | Moderation analysis of residual $1/f$ slope in escitalopram group

For the exploratory moderation analysis, the overall model was significant ($F_{3,24} = 11.16; R^2 = .582; p < .001$; Figure 4b). The interaction of plasma and $1/f$ slope at single dose was significant ($\beta = .40; t_{24} = 2.164; 95\% \text{ BCI} = 0.002-0.071; p = .04$), suggesting that single-dose plasma levels are a moderator of the association between the initial cortical response to escitalopram and the 1-week steady-state response and associated with a maintained decrease in $1/f$ slope during SSRI intake.

3.6 | Analysis of conventional relative alpha power

Relative alpha power analyses yielded an effect of time and a group \times interaction (Table 2). Post hoc analyses showed a group difference at single dose ($t = 2.5, p = .013$) but not 1-week steady state ($t = 1.7, p = .083$).

4 | DISCUSSION

The present study reports changes in the aperiodic component of the PSD, a measure of cortical EIB, during steady-state SSRI plasma levels in healthy female individuals. Our finding that 1 week of escitalopram-intake induces a widespread decrease of $1/f$ slope of the PSD, which represents an increase in EIB (Gao et al., 2017), suggests that escitalopram may tip the balance in favor of cortical excitability. Given that both baseline and single dose $1/f$ slope signals were associated with 1-week steady-state signal, and that escitalopram plasma levels after a single dose strengthened this relationship, we propose that $1/f$ slope could serve as a neurophysiological marker for individual cortical responsivity to SSRIs.

The significant decrease in $1/f$ slope following escitalopram administration is critical given the increasing focus on excitation-inhibition imbalance as a marker for neuropsychiatric disorders (Sohal & Rubenstein, 2019). While $1/f$ slope naturally changes with age in healthy humans (Voytek et al., 2015), an exaggerated disruption of $1/f$ slope could represent noisier, less efficient neural circuits that contribute to plasticity-related deficits. Moreover, recent findings (Demuru & Fraschini, 2020) demonstrated that the aperiodic component of the PSD is a more robust, stable measure of individual variability as compared to conventional power spectral features. Hence, our findings demonstrate that (Sohal & Rubenstein, 2019) escitalopram reliably alters a stable measure of EIB (Froemke, 2015), $1/f$ slope at steady-state levels of escitalopram is associated with baseline and single dose $1/f$ slope, and inter-individual cortical responsivity can

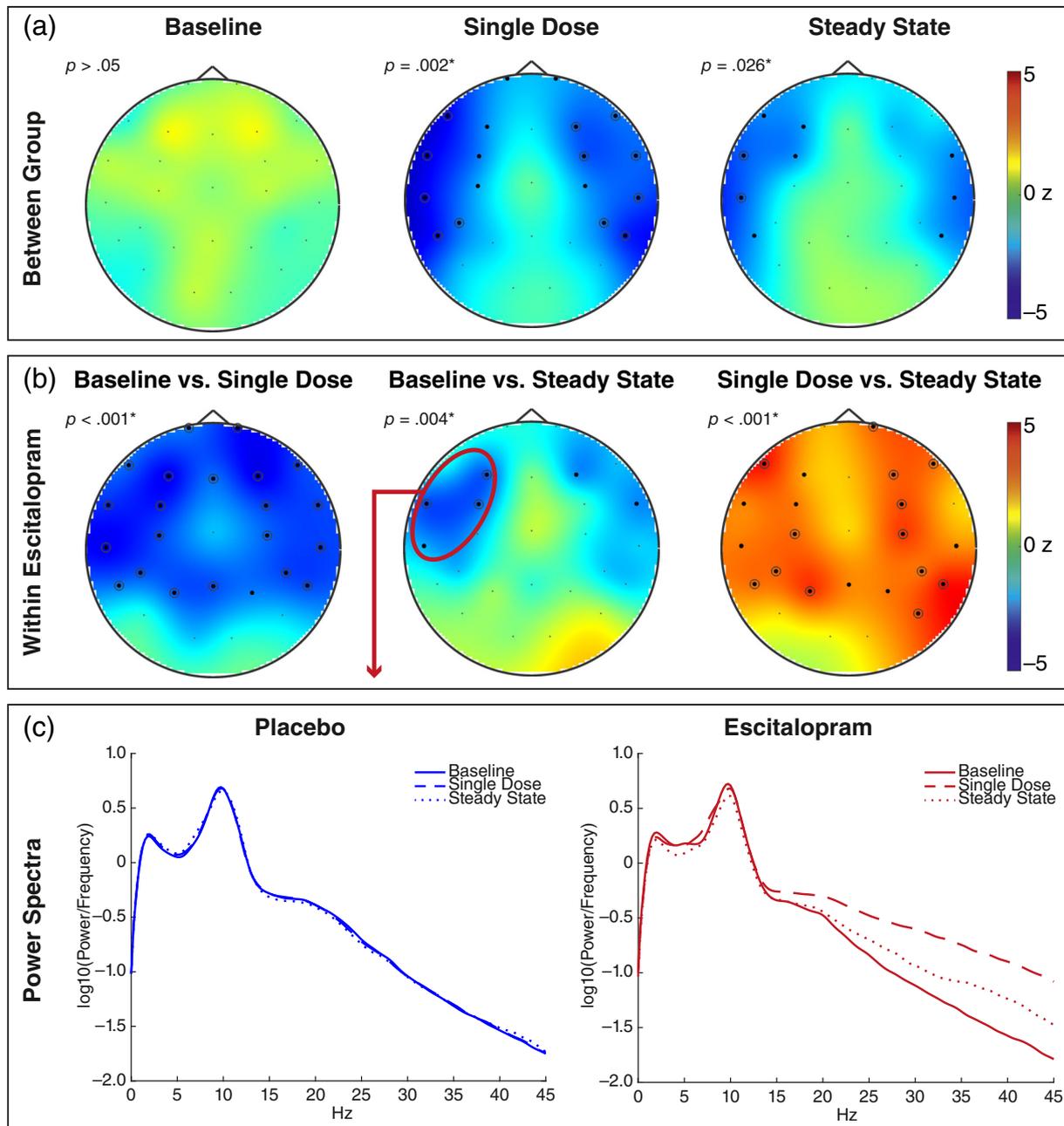


FIGURE 3 Cluster-based permutation tests show decreases in $1/f$ slope following escitalopram-intake at single dose and steady state. Shown are clusters surviving correction for multiple comparisons after computing 1,000 permutations. (a) We observe no group differences at baseline and significant clusters at single dose and 1-week steady state. (b) We observe significant clusters across all three assessments within the escitalopram group. *Significant at $p < .05$, p = cluster statistic, z = effect size, ● = significant electrodes $p < .05$, ● = significant electrodes $p < .01$. (c) Mean power spectra plotted for cluster (electrodes F3, FC3, FT7, T7; indicated in red, Panel b) common to all significant clusters from permutation tests, in order to illustrate shifts in $1/f$ slope over 1 week of escitalopram-intake

influence the strength of this relationship via escitalopram kinetics (Selten et al., 2018). Antidepressants have highly variable response rates in clinical settings (Gaynes et al., 2009), leading to weeks of trial and error (Bschor, Kern, Henssler, & Baethge, 2018). Our preclinical model identifies a neurophysiological indicator of individual human SSRI cortical responsivity and thus establishes a framework to further characterize cortical responses to psychopharmacological intervention at a single-subject level in order to inform future translational research.

Due to the nature of rs-EEG and the fact that we did not directly manipulate EIB, we cannot conclude if an increase in EIB following escitalopram administration is a result of increased excitation or decreased inhibition. Previous research suggests that the reversal of plasticity-related deficits depends on inhibitory transmission (Froemke, 2015; Pinto et al., 2017; Schneider et al., 2019; Vetencourt et al., 2008). A recent review (Schneider et al., 2019) proposes that SSRIs reactivate a plasticity period in the adult human brain by initially decreasing inhibitory tone, thus heightening cortical excitability. After

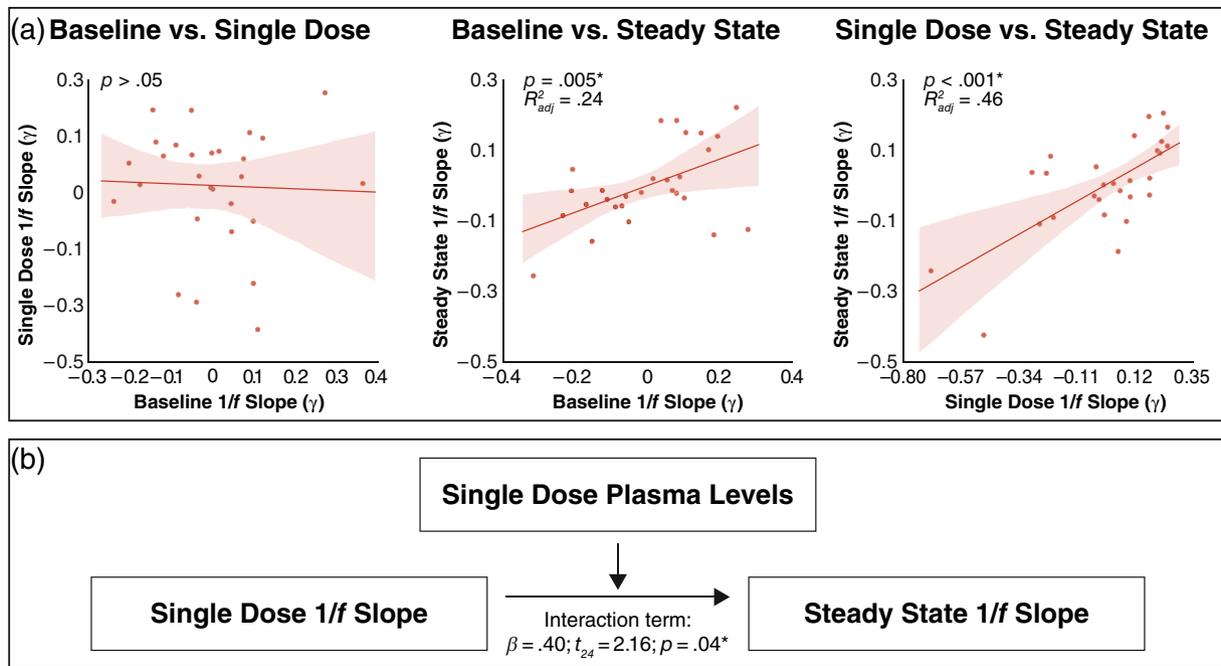


FIGURE 4 $1/f$ slope at baseline and after a single dose of escitalopram predicts $1/f$ slope after 1 week of drug-intake. (a) Linear regression analyses of residuals (controlling for trait EEG signal) show that baseline $1/f$ slope predicts 1-week steady-state response, and single dose $1/f$ slope predicts 1-week steady-state response. Shaded area represents 95% confidence interval. *Significant at $p < .016$ to account for multiple testing. (b) Moderation analysis shows that single dose plasma levels moderate the association between initial residual single dose-response and maintained residual response at 1-week steady state. *Significant at $p < .05$

multiple days of SSRI administration, a subsequent increase in inhibitory tone then re-establishes the balance, allowing for consolidation of these synaptic changes. We observe a similar pattern, with a widespread decrease in $1/f$ slope after a single dose of escitalopram, signifying an increasingly excitable state, followed by a slope increase from single dose to the 1-week steady-state assessment, with a spatially confined region of decreased $1/f$ slope.

Unlike the previously mentioned studies that used SSRIs such as fluoxetine (Pinto et al., 2017; Vetencourt et al., 2008), paroxetine (Gerdelat-Mas et al., 2005), and sertraline (Ilic et al., 2002), however, we administered the faster-acting SSRI escitalopram (Kasper et al., 2006). Escitalopram has the highest degree of selectivity for binding to the serotonin transporter, thereby leading more quickly to increased extracellular serotonin levels (Kasper et al., 2009; Klein et al., 2007). This increase activates various postsynaptic receptors that lead to complex interactions between the serotonergic, the inhibitory γ -aminobutyric acid (GABA)-ergic, and the excitatory glutamatergic systems (Pehrson & Sanchez, 2014). For example, escitalopram inhibits 5HT₃ receptor currents in vitro (Park & Sung, 2019), suggesting that escitalopram can enhance glutamate transmission by reducing GABA-mediated inhibition (Pehrson & Sanchez, 2014). Further support for escitalopram-induced increases in excitatory transmission comes from rodent models that have shown escitalopram enhances glutamate receptor subunit expression (Ryan et al., 2009) and N-methyl-D-aspartate (NMDA)-mediated currents in rats (Schilström et al., 2011), as well as hippocampal long-term potentiation (Bhagya, Srikumar, Raju, & Rao, 2011). Thus, escitalopram may

alter EIB through initially increasing excitatory transmission or decreasing inhibitory transmission. Future integration of quantitative neurochemical imaging, such as magnetic resonance spectroscopy to estimate the main excitatory and inhibitory neurotransmitters, would provide a more direct assessment that would be essential for understanding these dynamic changes in excitatory–inhibitory transmission across time, as we observe a relative increase followed by a decrease in EIB across the drug administration week. This subsequent decrease in EIB we find from single dose to 1-week steady state is consistent with the view of functional serotonergic homeostasis underlying the adaptability of a healthy human adult brain (Carhart-Harris & Nutt, 2017).

We also observe $1/f$ slope signal asymmetry at the 1-week steady-state assessment, with a spatially confined region of significance in the left prefrontal hemisphere (Figure 3b). This finding is of interest in the context of previous studies (Arnone et al., 2018), which have also reported asymmetric findings in intrinsic brain activity following SSRI administration. Given the hypothesis that SSRIs stimulate neuroplasticity (Castrén, 2013), a possible explanation for this observation is that frontal regions have been identified as a central hub in several cognitive, mood regulation, and memory processes (Kumar et al., 2017; Ray & Zald, 2012); and are thus essential to neuroplastic processes. For example, the left dorsolateral prefrontal cortex has been used as the target for transcranial magnetic stimulation (TMS) and neuromodulation in healthy controls (Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011), as well as the most efficacious and responsive target for the FDA-approved TMS-treatment for

treatment-resistant depression (Cantone et al., 2017). The specificity to the left hemisphere may also be attributable to an inherent asymmetry in the serotonergic system. While SSRIs block reuptake of serotonin by occupying the serotonin transporter, inhibitory 5HT_{1A} auto-receptor activation limits initial serotonin firing and release in cortical projection areas (Artigas, Romero, de Montigny, & Blier, 1996). Regional variation in this auto-inhibitory feedback mechanism, possibly due to an individual's 5HT_{1A} auto-receptor density (Carhart-Harris & Nutt, 2017), distribution of 5HT_{1A} auto-receptors in the dorsal raphe nucleus versus whole brain hetero-receptors (Hahn et al., 2010), or differences in hemispheric distribution of serotonin transporter or receptor density (Fink et al., 2009; Madalena, Lopes, Almeida, Sousa, & Leite-Almeida, 2020), may serve as a trait-like signal that influences serotonin release and individual cortical responsiveness to prolonged escitalopram (Garcia-Garcia, Newman-Tancredi, & Leonardo, 2014; Richardson-Jones et al., 2010). In addition, we cannot exclude functional changes in the serotonergic system in response to escitalopram, such as shifts in receptor affinity. Such shifts have been shown to occur at the transcriptional level in a rodent model following sustained fluoxetine-administration (Le Poul et al., 2000) and could also contribute to the regional specificity of SSRI-effects. We acknowledge, however, the observational nature of this finding and future studies with direct quantification of inter-regional differences in the serotonergic system are required to discuss this interpretation in more detail.

Finally, we also report a significant relationship between neural responses to single dose administration and the neural responses to 1-week escitalopram administration (Figure 4a), suggesting that initial early neural responses to escitalopram may be informative for a steady-state response in health. Given, however, that peripheral plasma escitalopram levels may be, to some degree, dissociated from brain kinetics (Klein et al., 2007; Meyer et al., 2004), we conducted our analysis viewing single dose plasma escitalopram levels as an early indicator of a peripheral bodily response to an SSRI. We therefore investigated whether these early peripheral pharmacokinetics (as reflected by plasma escitalopram levels following the first dose) interact with concurrent early neural responses to the drug (cortical EIB signal $1/f$ slope following the first dose) to predict the neural response to escitalopram after 1 week of intake (cortical EIB signal $1/f$ slope during relatively stable plasma levels). Our results show that single dose $1/f$ slope values and single dose plasma levels moderate the 1-week steady state $1/f$ slope response. This finding suggests that early peripheral kinetics and the associated neural kinetics jointly influence the steady state neural response to escitalopram. While these finding advocates for the utility of $1/f$ slope as a metric of early pharmacologic sensitivity in both brain and body, we acknowledge that this explanation remains speculative and requires testing in specifically designed studies with larger and more diverse samples and in clinical populations, such as patients with depression or anxiety disorders.

Against our a priori hypotheses, we did not find group differences in power of alpha oscillations following SSRI intake. Unlike previous

studies (Dumont et al., 2005; Kemp et al., 1999, 2010; Olbrich & Arns, 2013), however, we assessed alpha activity from the detrended PSD to avoid potential confounding effects of the broadband $1/f$ component. When we assessed relative alpha power without controlling for this component, we observed the hypothesized decrease in alpha power. These findings emphasize the importance of separately inspecting periodic oscillatory activity and aperiodic $1/f$ activity when testing narrowband oscillations such as alpha power, which have been shown to play functionally distinct roles (Ouyang et al., 2020). Our findings go beyond these previous studies, however, by extending this approach to a preclinical human model of SSRI-induced alterations in EIB.

One limitation of the study is that we investigated resting-state cortical EIB changes in a healthy population. We cannot infer how these changes would manifest in a clinical population, or how they would impact potential clinical outcome. However, changes in cortical excitability, similar to our observed effect, have been linked to changes in mood, attention, and cognitive performance in both healthy (Ouyang et al., 2020) and patient populations (Ostlund, Alperin, Drew, & Karalunas, 2021). Thus, while our findings do provide a model of escitalopram-induced changes in cortical EIB, future studies or existing datasets (Trivedi et al., 2016) should investigate whether SSRI-induced EIB changes early in treatment could predict outcomes in clinical settings. Second, replication studies are required to determine the generalizability of these findings to male participants, mid- and late-life populations, and naturally cycling female participants. Our sample of age-matched female participants using oral contraceptives was explicitly defined, however, to avoid potential confounding effects of sex and ovarian hormonal fluctuations on escitalopram responsiveness (LeGates et al., 2019), resting-state connectivity (Lisofsky et al., 2015; Petersen et al., 2014; Pritschet et al., 2020), and resting-state alpha activity specifically (Brötznner et al., 2014), as well as of age on $1/f$ slope (Voytek et al., 2015). This is also an important demographic (Taylor et al., 2020), as oral contraceptive use is increasing, women of reproductive age are the main population of oral contraceptive users (Daniels & Abma, 2020; United Nations, 2015), and oral contraceptive use has been associated with subsequent use of antidepressants (Skovlund, Mørch, Kessing, & Lidegaard, 2016). Third, we acknowledge that there are certain limitations to this model, such as the assumption of desynchronized cortical states, and that there are alternative methodologies for noninvasive investigation of EIB (Bruining et al., 2020; Trakoshis et al., 2020). We also acknowledge that changes in $1/f$ slope could have been driven by other physiological factors, such as mutual excitation among pyramidal cells (Freeman, 2006) or arousal (Lendner et al., 2020). While we cannot directly investigate the former, we can cautiously address the latter, as we observed neither group nor time differences in the daytime sleepiness scale. Finally, we cannot speculate on potential dose-dependent effects or effects of other SSRIs, given our fixed 20 mg dose of escitalopram. This dose was chosen, however, as 20 mg reliably blocks 80% of the serotonin transporter (Kasper et al., 2006, 2009; Klein et al., 2006, 2007; Rao, 2007).

5 | CONCLUSIONS

By combining a novel measure to assess cortical EIB with a rigorously controlled interventional study design in health, our results suggest dynamic changes in EIB following 1 week of escitalopram-intake. Moreover, our findings demonstrate the potential for $1/f$ slope as a neurophysiological marker for predicting individual cortical responsiveness to SSRIs. Interventional studies in health are an important component in the decision-making process of whether to proceed to more comprehensive clinical trials in heterogeneous patient populations. Given the continuously rising rates of affective disorders and number of prescribed antidepressants (Iacobucci, 2019), which are more often prescribed to women (Abbing-Karahagopian et al., 2014), alongside the current underrepresentation of female samples in neuroscience (Beery & Zucker, 2011; Taylor et al., 2020; Will et al., 2017), establishing these findings in healthy female participants provides a timely framework to test the effects of a frequently prescribed SSRI on human cortical excitability. On a broader scale, this study highlights a population which is rarely considered in human neuroimaging research. Intentionally reporting findings observed in healthy women taking oral contraceptives, as one way to consider sex and hormone state, lays the groundwork for a more comprehensive understanding of the human brain.

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[Correction added on 25 January 2022, after first online publication: Projekt Deal funding statement has been added.]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Funding sources played no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or the decision to submit the manuscript for publication. *Principal investigator*: Julia Sacher; *Conception and design of the study and manuscript*: Rachel G. Zsido, Eóin N. Molloy, Elena Cesnaite, Vadim V. Nikulin, and Julia Sacher; *Data acquisition*: Rachel G. Zsido, Eóin N. Molloy, Gergana Zheleva, Ulrike Scharrer, Nathalie Beinhözl, and Fabian A. Piecha; *Data analysis*: Rachel G. Zsido, Eóin N. Molloy, Elena Cesnaite, Gergana Zheleva, and Ralf Regenthal; *Data interpretation*: Rachel G. Zsido, Eóin N. Molloy, Elena Cesnaite, Vadim V. Nikulin, and Julia Sacher; *Figure creation*: Rachel G. Zsido and Eóin N. Molloy;

Drafting manuscript: Rachel G. Zsido and Eóin N. Molloy; *Critical revision*: All co-authors.

ETHICS STATEMENT

The Ethics Committee of the Faculty of Medicine of Leipzig University (approval # 390/16-ek) approved all procedures.

CONSENT STATEMENT FOR PARTICIPATION

All participants provided written informed consent after study procedures were explained.

DATA AVAILABILITY STATEMENT

Data of this study are available from corresponding author upon reasonable request. The R and MATLAB code for analyses are publicly available at https://github.com/EGGLab-2021/ZsidoMolloy2021_SSRi-EIB_R and https://github.com/EGGLab-2021/ZsidoMolloy2021_SSRi-EIB_Matlab.

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