

RESEARCH ARTICLE

The interplay of resting and inhibitory control-related theta-band activity depends on age

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Abstract

Resting-state neural activity plays an important role for cognitive control processes. Regarding response inhibition processes, an important facet of cognitive control, especially theta-band activity has been the focus of research. Theoretical considerations suggest that the interrelation of resting and task-related theta activity is subject to maturational effects. To investigate whether the relationship between resting theta activity and task-related theta activity during a response inhibition task changes even in young age, we tested $N = 166$ healthy participants between 8 and 30 years of age. We found significant correlations between resting and inhibitory control-related theta activity as well as behavioral inhibition performance. Importantly, these correlations were moderated by age. The moderation analysis revealed that higher resting theta activity was associated with stronger inhibition-related theta activity in individuals above the age of ~ 10.7 years. The EEG beamforming analysis showed that this activity is associated with superior frontal region function (BA6). The correlation between resting and superior frontal response inhibition-related theta activity became stronger with increasing age. A similar pattern was found for response inhibition performance, albeit only evident from the age of ~ 19.5 years. The results suggest that with increasing age, resting theta activity becomes increasingly important for processing the alarm/surprise signals in superior frontal brain regions during inhibitory control. Possible causes for these developmental changes are discussed.

KEYWORDS

age, cognitive control, response inhibition, resting-state activity, theta power

1 | INTRODUCTION

Cognitive control processes, which include inhibition, cognitive flexibility and working memory, are functions we need to master our everyday lives (Diamond, 2013). Concerning the neurophysiological processes underlying inhibitory control, medial frontal theta oscillations play an important role (Cavanagh & Frank, 2014; Dippel, Chmielewski, Mückschel, & Beste, 2016; Huster, Enriquez-Geppert,

Lavallee, Falkenstein, & Herrmann, 2013; Liu, Woltering, & Lewis, 2014; Mückschel, Dippel, & Beste, 2017). The corresponding theoretical approach explains the role of medial frontal cortical theta activity as an “alarm” or “surprise” signal (Cavanagh & Frank, 2014), which increases when cognitive control is needed and enables inhibitory control (Wessel, 2018). Several findings based on Go/Nogo tasks support this concept, since task-related theta power increases during Nogo trials compared to Go trials (Dippel, Mückschel, Ziemssen, &

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Beste, 2017; Nigbur, Ivanova, & Stürmer, 2011; Pscherer, Mückschel, Summerer, Bluschke, & Beste, 2019; Yamanaka & Yamamoto, 2009). Nogo trials require motor inhibition control as evidenced by movement related potentials (Smith, Johnstone, & Barry, 2008), machine learning applied to EEG data showing a role of the primary motor cortex (Vahid, Mückschel, Neuhaus, Stock, & Beste, 2018) and fMRI data (Rubia et al., 2001), but might also elicit other processes, such as effects of low stimulus frequency or of response selection (Braver, Barch, Gray, Molfese, & Snyder, 2001; Mostofsky & Simmonds, 2008). Such an increase in theta activity during Nogo trials has been associated with regions in the supplementary motor area (SMA) and the superior frontal gyrus (Dippel et al., 2017; Mückschel et al., 2017; Pscherer et al., 2019). Interestingly, a recent study revealed that inhibitory control-related theta activity and response inhibition performance are related to resting-state theta activity (Pscherer et al., 2019). This result ties up with mounting literature reporting interrelations between resting-state and cognitive control-related activity (Haag et al., 2015; Mahjoory, Cesnaite, Hohlefeld, Villringer, & Nikulin, 2019; Nakao, Bai, Nashiwa, & Northoff, 2013; Tavor et al., 2016), and with findings showing that specific aspects of inhibitory control can be predicted by resting EEG activity (Schiller, Gianotti, Nash, & Knoch, 2014). These findings are plausible in light of evidence (Tsujimoto, Shimazu, & Isomura, 2006; Tsujimoto, Shimazu, Isomura, & Sasaki, 2010; Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005) showing that structures involved in control-related theta-band activity also produce endogenous theta activity (Cohen, 2014). Since resting theta activity and inhibitory control-related theta activity seem to be closely linked, the question arises to what extent other factors, which are already well-known to impact inhibitory control, affect the interrelation of resting-state theta and inhibition-related theta activity.

One such factor may be age for a number of reasons: Inhibitory control processes are subject to strong age-dependent modulations (Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015) and response inhibition-related increases in theta-band activity have been shown in adults (Dippel et al., 2017; Nigbur et al., 2011; Stock, Popescu, Neuhaus, & Beste, 2016; Vahid et al., 2018) and children (Farbiash & Berger, 2016). Interestingly, the power of such inhibition-related theta activity decreases from childhood to young adulthood (Liu et al., 2014), suggesting age-related effects on oscillatory activity central for inhibitory control (but see Marek et al. (2018) for controversial findings on this). Recent findings from various cognitive control domains including response inhibition show that event-related theta and resting-state theta are correlated (Pscherer et al., 2019; Pscherer et al., 2020). Importantly, especially for task-related theta activity age-related modulations have been shown (Tafuro, Ambrosini, Puccioni, & Vallesi, 2019). Considering response inhibition, developmental effects of inhibitory control-related theta activity (Liu et al., 2014), other theta-depending neurophysiological correlates of response inhibition (Brydges, Anderson, Reid, & Fox, 2013), and an increase in inhibitory control performance from childhood to young adulthood are well established (Bodmer, Mückschel, Roessner, & Beste, 2018; Davidow et al., 2018; Hämmerer, Li, Müller, & Lindenberger, 2010; Huizinga,

Dolan, & van der Molen, 2006; Johnstone et al., 2007; Jonkman, 2006; Luna, Garver, Urban, Lazar, & Sweeney, 2004). If task-related theta is strongly influenced by age (see above), other processes that are highly correlated with task-related theta should also show age effects. Thus, age may moderate the relationship between resting state and response inhibition-related theta-band activity. We hypothesize that age is a modulator of the interrelation of resting theta-band activity and theta-band related inhibitory control processes. The hypothesis that especially the interrelation of resting and task-related theta-band activities may show age-related modulations is also likely from a brain maturational perspective. Biophysical data show that high amplitude/low power oscillations (i.e., theta) are important for information integration from widely distant brain regions (Buzsáki & Draguhn, 2004), an aspect that is affected by brain maturation processes between childhood and early adulthood (Bunge & Wright, 2007; Leyva-Díaz & López-Bendito, 2013; Rubia, 2013; Rubia et al., 2006). In line with that, other data from our group have shown that properties of theta oscillations during inhibitory control are affected by neurobiological parameters determining white matter structure (Beste et al., 2019).

Taken together, we hypothesize that age changes (moderates) the relationship between resting theta activity and inhibitory control processes. To test this hypothesis, we examined resting theta activity as well as behavioral performance and event-related theta dynamics during a standard Go/Nogo task in a large cross-sectional sample of children, adolescents, and young adults ($N = 166$ participants between 8 and 30 years of age). For the data analysis, we perform a moderation analysis focusing on age as a moderating factor of the correlation between resting-state theta activity and behavioral performance as well as event-related theta indices of response inhibition. However, also a different perspective (i.e., that resting state-theta activity moderates the relationship between age and inhibitory control on a behavioral and neurophysiological level) is equally valid. This analysis is presented in the supplemental material. Since previous data suggest that theta-band activity during inhibitory control processes is associated with regions in the supplementary motor area (SMA) and the superior frontal gyrus (Dippel et al., 2017; Mückschel et al., 2017; Pscherer et al., 2019), we assume that these regions are associated with theta-related inhibitory control processes in the current study. This is examined applying dynamic imaging of coherent sources (DICS) beamforming analysis (Gross et al., 2001).

2 | MATERIALS AND METHODS

2.1 | A priori power calculations

The study question assumes that age moderates the relationship between resting theta activity (predictor variable) and inhibitory control processes (outcome variables) at the neurophysiological and behavioral level. We used G*Power (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007) to estimate the sample size required to identify small to medium effect sizes

($R^2 \approx .10$, corresponding to $f^2 = \frac{R^2}{1-R^2} \approx .11$). According to G*Power, a sample size of $N = 161$ is required to obtain an R^2 deviation from zero with an effect size of $f^2 = .11$ and with a power of 95% when using a linear multiple regression model with three variables (i.e., predictor variable, moderator variable, the interaction between predictor and moderator variable).

2.2 | Participants

We assessed participants within an age range between 8 and 30 years. After excluding nine data sets with poor data quality and/or extreme outliers in resting theta activity, the final sample consisted of $N = 166$ healthy participants (95 females; age: 18.98 ± 6.50 ; IQ: 109.91 ± 10.80). Participants were classified as outliers if their resting theta value exceeded 1.5 times the interquartile range (IQR) below the 25th percentile or 1.5 times the IQR above the 75th percentile of the resting theta data. The outlier analysis was conducted separately for children (<18 years) and adults (≥ 18 years). For children and adolescents, the absence of psychiatric disorders was evaluated through the parent-version of the ADHD Symptom Checklist (Döpfner, Görtz-Dorten, & Lehmkuhl, 2008) and the CBCL/4-18 (Child Behavior Checklist; (Achenbach, 1991)). For participants over 18 years of age, we used the ASR/18-59 (Adult Self-Report; Achenbach & Rescorla, 2003). No participants reported any previous or current neurological or physical illnesses. The adult participants and the parents of the children/adolescents provided written informed consent before any study procedure was commenced and received financial compensation for participating in the study. The Ethics Commission of the TU Dresden approved this study.

2.3 | Assessment of resting theta activity

The participants' resting theta activity was assessed using the same setup as reported in a previous study (Bluschke, Broschwitz, Kohl, Roessner, & Beste, 2016; Pscherer et al., 2019; Pscherer et al., 2020), based on the same electronic devices and the same data recording system (BrainVision Recorder by Brain Products Inc.) as the setup for assessing the task-related EEG (see Section 2.5). For this purpose, subjects were asked to relax with their eyes open for a 2-min time interval while focusing on a PC screen. Brain electrical activity was continuously recorded from electrode Cz. A reference electrode was placed on the right earlobe, a ground electrode was placed on the forehead. Electrodes above and below the right eye were used to record eye movements. Theta frequency band activity was determined with an online Butterworth filter (sixth order) with a pass band of 4–7 Hz. Strong movement artifacts, as well as blinking artifacts, were removed online since they may affect the estimation of theta activity. For the channel Cz, used for resting theta-band quantification, this bound was set to 100 μV and a minimum activity of 5 μV was required to prevent segment exclusion. For higher frequent artifacts in a frequency range of 25–35 Hz, the bound was defined at

10 μV . It needs to be noted that the software used to record resting theta activity did not store how many segments of the 2-min time interval contained artifacts and were therefore removed online. Yet, the test supervisors were thoroughly instructed to ensure that as little interference as possible occurred (i.e., the signal was checked before recording resting theta activity, participants were instructed to sit still, participants were closely monitored, etc.). We used the mean theta power of the 2-min time interval as an estimate for resting-state theta activity in the statistical analysis.

2.4 | Task

To examine the participants' response inhibition performance, a standard Go/Nogo task (Beste, Baune, Domschke, Falkenstein, & Konrad, 2010) was implemented using the software package "Presentation" (Neurobehavioral Systems). During the task, either the German word for "press" (i.e., "DRÜCK"; Go stimulus) or the German word for "stop" (i.e., "STOPP"; Nogo Stimulus) was presented for 400 ms in white letters on the black background of a 21-in. TFT screen. The inter-trial interval was jittered between 1,600 and 2,100 ms. Participants were instructed to respond as quickly as possible by pressing a button with the right index finger when a Go stimulus occurred. When a Nogo stimulus appeared, participants should refrain from responding. Go trials were coded as hits when a response occurred within 1,200 ms after the stimulus onset. Nogo trials were classified as false alarms when a response occurred within 1,500 ms after the stimulus onset. To increase the probability of premature responses in Nogo trials, 70% of the presented stimuli were Go trials and 30% were Nogo trials (Dippel et al., 2016). Since we expected significantly more variability of the neuronal processes, more movement artifacts and a higher false alarm rate in the children's sub-sample than in the adults' sub-sample (Bodmer et al., 2018; Brydges et al., 2013; Luna et al., 2015), we increased the number of trials among the underage participants by 50%. By doing so, we expected to obtain a similar signal-to-noise ratio in the neurophysiological data and a similar number of usable trials for the analysis of the neurophysiological data across the entire age range. In detail, the experiment consisted of 248 Go trials and 112 Nogo trials for participants aged 8–17 and of 168 Go trials and 72 Nogo trials for participants aged 18 to 30, presented in four blocks with short breaks in between. The task duration for the children's subsample was about 15 min (depending on the length of the breaks between the blocks), the task length for the adults' sample differed only a few minutes. Since fatigue effects are expected after at least an hour (Arnau, Möckel, Rinkenauer, & Wascher, 2017; Guo et al., 2018; Möckel, Beste, & Wascher, 2015; Petruo, Mückschel, & Beste, 2018; Wascher et al., 2014), fatigue effects or age-related differences in fatigue effects are not to be expected in this setting. When comparing Go and Nogo trials, it is important to note that the two trial types differ not only in the presence of the cognitive component of response inhibition, but also in response preparation, selection, and execution processes. For statistical analysis, the mean false alarm rate (given in percent) and the mean reaction time on hits (given in ms) of each participant were computed.

2.5 | Task-related EEG recording and analysis

While the participants performed the Go/Nogo task, an EEG was recorded using 60 equidistant Ag/AgCl electrodes mounted in an elastic cap (EasyCap Inc.) and BrainVision Recorder 2.1 (Brain Products Inc.). The reference electrode was positioned at $\theta = 90$, $\phi = 90$, the ground electrode at $\theta = 58$, $\phi = 78$. We kept the electrode impedances below 5 k Ω . During offline data processing with the software package BrainVision Analyzer 2.1 (Brain Products Inc.), the data was down-sampled to 256 Hz. Also, we used an IIR bandpass filter from 0.5 to 20 Hz (slope: 48 dB/oct) and a notch filter of 50 Hz. By manually inspecting the raw data, we removed muscular and technical artifacts. An independent component analysis (ICA, infomax algorithm) was then performed to identify and manually remove recurring artifacts (e.g., eye movements, blinks, muscle, and pulse artifacts). Subsequently, the data were segmented and locked to the onset of the Go and Nogo stimuli. The length of the segments was 4,000 ms (2000 ms before stimulus onset to 2000 ms after stimulus onset) which is a sufficient time window for a reliable analysis of theta frequency oscillations. Only Go trials with a correct response within 1,200 ms after stimulus onset and Nogo trials without a response within 1,500 ms after stimulus onset were included in the data analysis. Trials exceeding an amplitude above 150 μ V or below -150 μ V as well as trials with a maximal value difference of 150 μ V in an interval of 200 ms or with activity below 0.5 μ V in a 100 ms interval were removed from the data by automated artifact rejection. A current source density (CSD) transformation was used to obtain a reference-free representation of the data which facilitates the localization of the electrical activity on the scalp (Nunez & Pilgreen, 1991). We then performed a baseline correction in the time window of -200 ms to stimulus onset and computed time-frequency analyses of the Go trials and Nogo trials of each participant.

2.6 | Time-frequency decomposition and beamforming

The time-frequency (TF) decomposition was computed to analyze the participants' theta activity during the Go/Nogo task. More specifically, we analyzed the participants' total theta power which consists of phase-locked and non-phase-locked aspects of theta power. It can be calculated by applying TF analyses to the single-trial data of each participant for each stimulus type (in our study Go stimuli and Nogo stimuli) before averaging the TF power of all trials. The TF analyses were performed with Morlet wavelets (w):

$$w(t, f) = A \exp(-t^2/2\sigma_t^2) \exp(2i\pi ft)$$

with the parameters t = time, f = frequency, $A = (\sigma_t \sqrt{\pi})^{-1/2}$, σ_t = wavelet duration, and $i = \sqrt{-1}$. A Morlet parameter of $f_0/\sigma_f = 5$ was used, where f_0 represents the central frequency and σ_f defines the Gaussian shape in the frequency domain. The TF decomposition was performed in a frequency range from 1 to 20 Hz in 20 steps.

The wavelet duration can be calculated as $2\sigma_t$ and spectral bandwidth as $2\sigma_f$ for different f_0 . The equation $\sigma_t = 1/(2\pi\sigma_f)$ relates the parameters σ_t and σ_f . We identified maximal total theta power based on the visual inspection of the grand average scalp topographies at electrode FCz in the frequency band of 5 Hz and in a time window between 175 and 375 ms after stimulus onset. The participants' mean total theta power during this time-frequency range for Go trials and Nogo trials was used for statistical analysis. Additionally, nonparametric cluster-based permutation tests were conducted via the FieldTrip toolbox for MATLAB (Oostenveld, Fries, Maris, & Schoffelen, 2011) to test for the increase of total theta power from Go trials to Nogo trials comparing multiple channels while controlling for the family-wise error rate. For this purpose, the mean total theta power was determined in the frequency of 4–6 Hz and the time window of 200–400 ms after the stimulus presentation (for an analysis of the time window from 0 to 750 ms, which is identical to the time window used for the subsequent source reconstruction, please refer to the supplemental material). For the paired sample t -statistics, samples were classified as members of a sample cluster if their t -value exceeded $p = .05$. At least two samples (i.e., two EEG channels) were required to define a cluster. To approximate the reference distribution of the permutation test, the Monte Carlo method was applied based on 1,000 random drawings. If the corresponding p -values were below the critical alpha level of $p < .05$, the clusters were considered significant.

For source estimations of the analyzed activity in the theta frequency band, we applied a dynamic imaging of coherent sources (DICS) beamforming analysis (Gross et al., 2001) to the time-frequency decomposed data to reconstruct the neural sources of the total theta power differences in Nogo trials compared to Go trials. For this purpose, we used the FieldTrip toolbox for MATLAB (Oostenveld et al., 2011). The TF decomposition for the beamforming analysis was computed without prior CSD transformation of the data since both the beamformer and the CSD transformation serve as spatial filters (Kayser & Tenke, 2015; Nunez & Pilgreen, 1991). The TF decomposition was performed on the average-referenced EEG data (Gross et al., 2001) in the frequency range of 4–6 Hz (smoothing window 1.34 Hz) with a time window of 750 ms centered at 375 ms after stimulus onset, employing a multitaper frequency transformation. The time window was set large enough that only significant TF intervals of at least three full cycles were included in the beamforming analysis. The specified TF window overlaps with the previously identified TF window. For source reconstruction, the “standard_bem” forward model (Oostenveld, Stegeman, Praamstra, & van Oosterom, 2003) and the “colin27” MNI brain template (“standard_mri”) were used. Oostenveld et al. (2003) provide mathematical background and details about the construction of the forward model. Only significant effects at the sensor level were included in the analysis. After the EEG data were realigned to the forward model, we computed the leadfield matrix by subdividing the brain volume of the forward model into grids with a resolution of 10 mm. Thereafter, the leadfield matrix was computed for each grid point. To estimate the power of the sources, a common spatial filter based on all conditions with a regularization

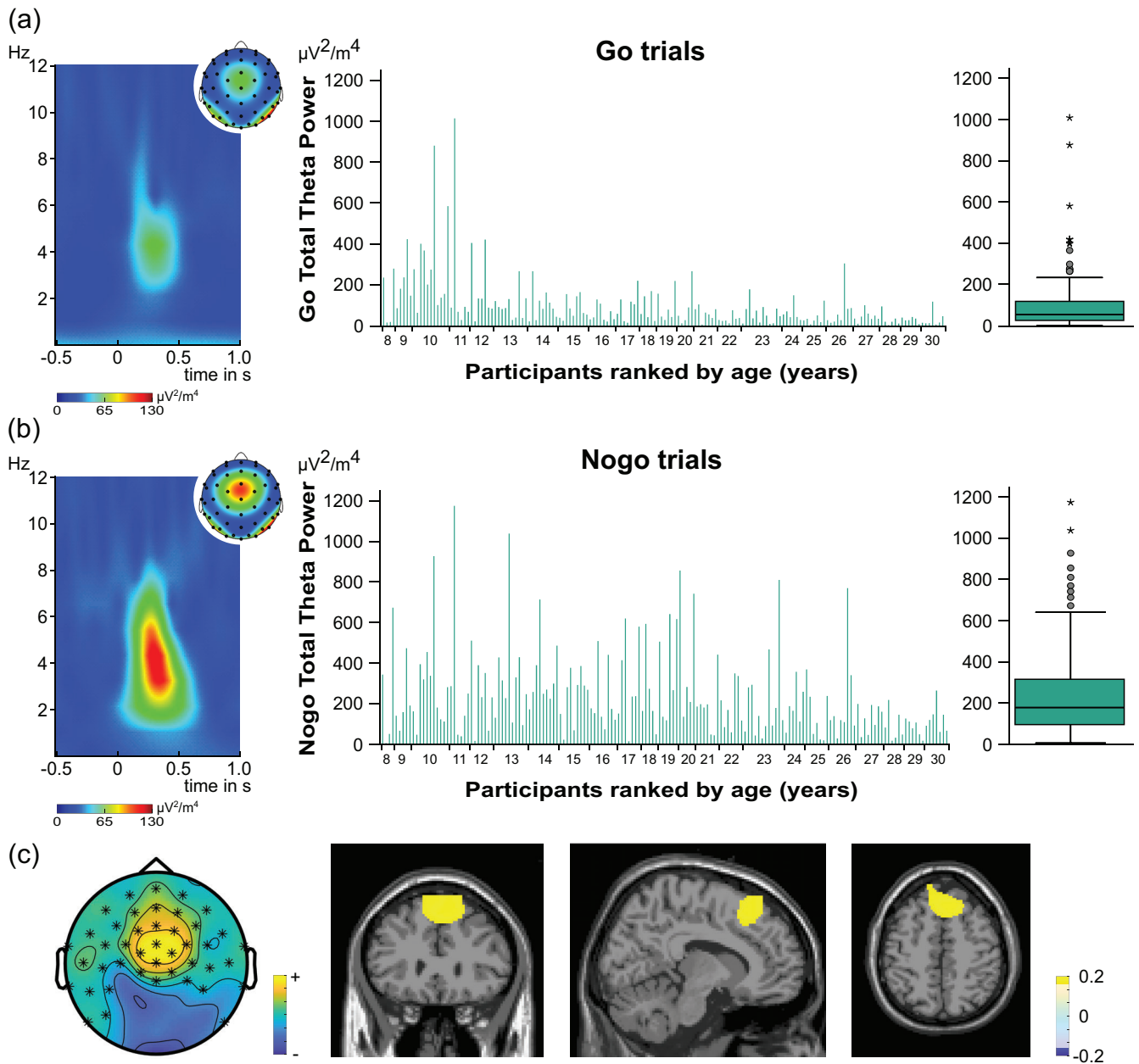


FIGURE 1 Total theta power during Go trials and Nogo trials. The plots in section (a) show the total theta power of the sample during Go trials. The upper left figure is a time–frequency decomposition plot of the overall samples' mean total theta power during the Go trials at electrode FCz including the corresponding scalp topography. The x-axis displays time in seconds (s) relative to the stimulus onset and the y-axis denotes the frequency in Hz. Power is indicated by color. The graph in the upper middle part is a histogram plotting each participant's mean total theta power during Go trials, with participants ranked by age. The upper right plot shows a box plot with the distribution of the sample's total theta power during Go trials. The lower boundary of the box denotes the 25th percentile, the upper boundary of the box indicates the 75th percentile. The black line in the box marks the median. The whiskers above and below the box indicate the lowest and highest data point within 1.5*IQR (interquartile range) below the 25th percentile and above the 75th percentile. Dots and asterisks indicate outliers. The plots in section (b) show the respective data for the sample's total theta power during Nogo trials. Plot (c) displays the results of the cluster-based permutation tests applied on theta-band topography contrasts (left plot). Asterisks indicate significant clusters of electrodes that show activation differences between Go and Nogo trials. The t-values summed at cluster-level are coded by color. The plots aside show the results of the beamforming analysis: total theta power differences between Go and Nogo trials were associated with activation differences in the supplementary motor area (SMA) and the frontal superior lobe in both hemispheres. Only the lower and upper 10% of significant source power differences are shown

filter of 5% was applied separately to each condition (Go trials vs. Nogo trials).

2.7 | Experimental design and statistical analysis

The study uses a cross-sectional design. We analyzed the behavioral and neurophysiological data with SPSS Statistics 25 and MATLAB. For the principal task effects, the mean and standard deviation of the mean are given. Correlations between age and the behavioral outcome variables were analyzed with Pearson's correlation coefficient r (two-tailed). Differences in total theta power between Go and Nogo trials were assessed with a Wilcoxon signed-ranks test. The moderation analyses were computed using the PROCESS macro (version 3.4 for SPSS) by Hayes (Hayes, 2018). The method is based on ordinary least squares regression analysis. For the analyses, the predictor variable *resting theta activity* and the moderator variable *age* were mean-centered. For a moderator analysis using *resting theta activity* as moderator variable, please refer to the supplemental material. Heteroscedasticity-consistent standard errors and covariance matrix estimators were used (HC3; Davidson & MacKinnon, 1993). In the result section, we report unstandardized regression coefficients b . In the case of statistical significant moderation effects, the Johnson-Neyman technique was applied (Bauer & Curran, 2005; Hayes & Matthes, 2009). This method makes it possible to identify those values on the continuum of the moderator variable where the effect of the predictor on the outcome variable changes from statistically nonsignificant to significant ($p = .05$; Hayes, 2018).

3 | RESULTS

3.1 | Principal task effects

The behavioral data showed a mean response accuracy in Go trials of $98 \pm 3\%$ and a mean reaction time (RT) of 396 ± 76 ms for the overall sample. The mean false alarm (FA) rate was $19 \pm 16\%$, and is within the range of false alarm rates obtained using a comparable task in previous studies with a child sample (FA rate = 32%; Bluschke, von der Hagen, Papenhagen, Roessner, & Beste, 2017) and with an adult sample (FA rate = 13%; Beste, Ness, Falkenstein, & Saft, 2011). The mean RT during false alarms was 332 ± 73 ms. The participants' age correlated with these behavioral variables as follows: accuracy in Go trials,

$r = .14$, $p = .065$; RT during hits, $r = -.55$, $p > .001$; Nogo FA rate, $r = -.48$, $p < .001$; RT during false alarms, $r = -.46$, $p < .001$. Figure 1a,b presents the overall total theta power during Go trials (a) and Nogo trials (b). Furthermore, histograms showing the average total theta power of each participant during Go (a) and Nogo (b) trials, ranked by age, and the corresponding box plots are displayed.

The neurophysiological data revealed a significantly higher total theta power during Nogo trials ($239.93 \pm 207.50 \mu\text{V}^2/\text{m}^4$) than during Go trials ($101.13 \pm 132.90 \mu\text{V}^2/\text{m}^4$; $Z(N = 166) = -9.92$, $p < .001$). The cluster-based permutation tests substantiated this result by showing that the total theta power in Go trials and Nogo trials differed significantly ($p < .001$). The difference was most distinct at fronto-central electrodes (Figure 1c). Additionally, the cluster-based permutation test was repeated using the larger time window that was used for source reconstruction. Please refer to supplemental Figure S2. As the beamforming analysis revealed, this difference in total theta power between Go and Nogo trials was associated with activation differences in the supplementary motor area (SMA) and the medial superior frontal gyrus (BA6) in both hemispheres (maximum value: 0.24 at coordinates 1.0/2.9/5.0 cm). Figure 1c displays the results of the beamforming analysis.

3.2 | Descriptive statistics of predictor, moderator and dependent variables

The descriptive statistics of the predictor variable *resting theta activity*, the moderator variable *age* and the various behavioral and neurophysiological variables are presented in Table 1.

The scatterplot in Figure 2 shows the relationship between resting theta activity (predictor variable) and age (moderator variable) in detail. With increasing age, resting theta power decreased ($r = -.766$; $p < .01$). For a correlation matrix of all study variables, please see supplemental Figure S3.

3.3 | Moderation analysis of the behavioral data

The moderation analyses showed that age had a moderating effect on the relationship between resting theta activity and the participants' performance in a Go/Nogo task (Table 2).

We found that the false alarm rate increases with increasing resting theta activity ($r = .362$; $p < .01$; Figure 3a) but decreases with

TABLE 1 Descriptive statistics of the study variables

	Resting theta (μV)	Age (years)	FA rate (%)	Go RT (ms)	Nogo total theta ($\mu\text{V}^2/\text{m}^4$)	Go total theta ($\mu\text{V}^2/\text{m}^4$)
Mean	4.22	18.98	19.28	395.74	239.93	101.13
SD	1.21	6.50	16.25	75.73	207.50	132.90
Min	2.19	8.00	0.00	284.85	8.18	4.27
Max	8.16	30.00	76.00	779.53	1,172.27	1,010.19

Abbreviations: FA, false alarm; Max, maximum; Min, minimum; RT, reaction time.

increasing age ($r = -.476$; $p < .01$; Figure 3b). Importantly, the moderation analysis revealed that there was no correlation between the strength of resting theta activity and the false alarm rate in childhood ($p = .890$ for the age of $M - 1SD = 12.49$). Across age, this relationship changed in that a higher level of resting theta activity was associated with a lower false alarm rate ($p = .005$ for the age of $M + 1SD = 25.48$). This moderation effect is shown in Figure 3c. A detailed analysis using the Johnson-Neyman technique revealed that a significant conditional effect existed from the age of 19.5 years on and became stronger with increasing age (age of 19.5: $b = -.03$, $p = .050$; age of 30: $b = -.09$, $p = .003$).

For the reaction times in correct Go trials, the scatterplots in the Figure 4a,b depict that higher resting-state activity was related to longer reaction times ($r = .558$; $p < .01$; Figure 4a) whereas in higher age reaction times became faster ($r = -.545$; $p < .01$; Figure 4b). The results of the moderation analysis showed a positive correlation between resting theta activity and reaction time at a younger age ($p = .003$ for the age of $M - 1SD = 12.49$), but not at (relatively) higher age ($p = .993$ for the age of $M + 1SD = 25.48$). Figure 4c displays this moderation effect. The Johnson-Neyman technique revealed that a higher resting theta level was associated with longer reaction times in hit trials only in children under 16.8 years of age. The younger the participants, the stronger was the significant

conditional effect of age (age of 16.8: $b = 14.86$, $p = .050$; age of 8: $b = 29.98$, $p = .001$).

3.4 | Moderation analysis of the neurophysiological data

The moderation analyses predicting the neurophysiological data revealed a significant moderation effect of age on the relationship between resting theta activity and total theta power during correctly rejected Nogo trials (Table 3).

A higher level of resting theta activity was associated with higher total theta power during Nogo trials ($r = .378$; $p < .01$; Figure 5a). With increasing age total theta power during Nogo trials decreased ($r = -.284$; $p < .01$; Figure 5b).

The moderation analysis showed, that the relationship between resting theta activity and total theta power during correctly rejected Nogo trials was enhanced by age in the sense that the conditional effect became stronger with increasing age ($b = 61.66$, $p = .008$ for the age of $M - 1SD = 12.49$; $b = 163.37$, $p = .001$ for the age of $M + 1SD = 25.48$). Figure 5c presents this moderating effect. The Johnson-Neyman technique showed that the positive correlation between resting theta activity and total theta power during Nogo trials was present from the age of 10.7 years. The equivalent moderation effect of age on the relationship between resting theta power and total theta power during correct Go trials was not significant ($p = .158$).

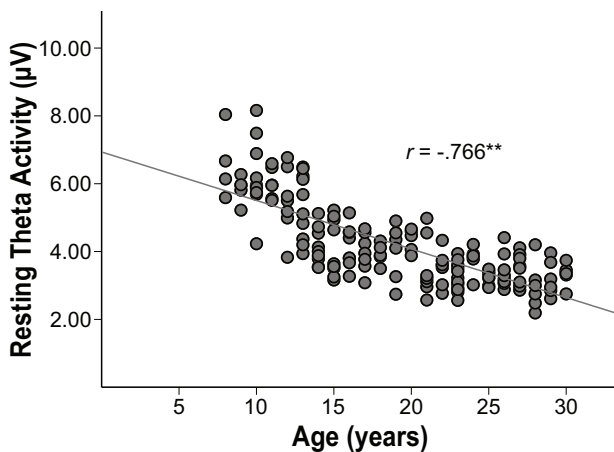


FIGURE 2 Relationship between the participants' age (x-axis) and their resting theta activity, given in μV (y-axis)

4 | DISCUSSION

We investigated how age affects the relationship between resting theta activity and inhibitory control processes. For this purpose, we analyzed resting-state and inhibitory control-related theta data as well as behavioral data of $N = 166$ participants between 8 and 30 years of age utilizing several moderation analyses. As shown by various prior findings (Bodmer et al., 2018; Hämmerer et al., 2010; Huizinga et al., 2006; Johnstone et al., 2007; Jonkman, 2006; Luna et al., 2004), the behavioral data revealed that our participants showed decreasing reaction times and false alarm rates with increasing age. Thus, increasing age is associated with speeded responding and an improved ability

TABLE 2 Results of the moderation analyses predicting the false alarm rate and the reaction time in Go trials from the resting theta activity with age as moderator

	False alarm rate				Reaction time in go trials			
	<i>b</i>	<i>SE(b)</i>	<i>t</i>	<i>p</i>	<i>b</i>	<i>SE(b)</i>	<i>t</i>	<i>p</i>
Constant	0.16	0.01	11.79	<.001	385.41	5.95	64.73	<.001
Resting theta	-0.03	0.02	-1.85	.066	11.08	8.24	1.35	.180
Age	-0.02	0.003	-5.42	<.001	-4.30	1.48	-2.91	.004
Resting theta \times age	-0.01	0.002	-2.88	.005	-1.72	0.86	-2.01	.050

Note: $R^2 = .26$ ($p < .001$) and $\Delta R = .04$ for false alarm rate, $R^2 = .36$ ($p = .001$) and $\Delta R = .02$ for reaction time of hits. The predictor and the moderator variable are mean-centered. Heteroscedasticity-consistent standard errors and covariance estimators (HC3) were used. *b*, unstandardized regression coefficient.

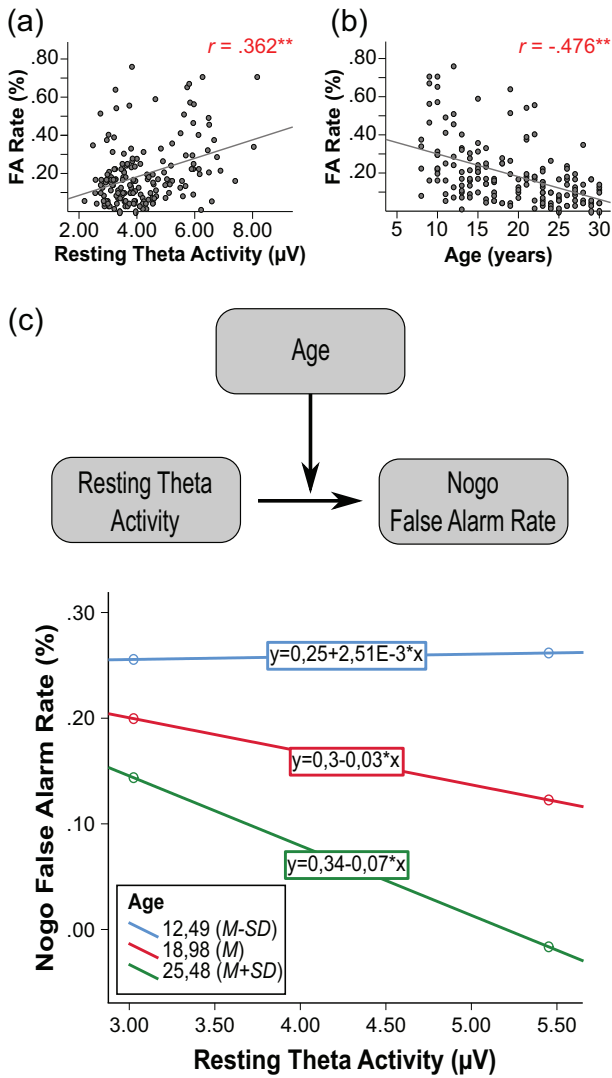


FIGURE 3 (a) Scatter plot showing the relationship between resting theta activity and the false alarm rate. (b) Scatter plot illustrating the relationship between age and the false alarm rate. (c) Moderating effect of age on the relationship between resting theta activity (x-axis) and the false alarm rate during Nogo trials (y-axis). The red fitting line depicts the mean (M) age of the sample, the blue line indicates the age one standard deviation below the mean (M-SD), the green line represents the age one standard deviation above the mean (M + SD)

to inhibit responses. Resting theta activity decreased from childhood to young adulthood, which is consistent with the finding of Gasser et al., (Gasser, Verleger, Bäcker, & Sroka, 1988; sample: children aged 6–17 years), but to our knowledge has not been shown before for an age range including young adults. We found significant correlations between resting-state theta activity and inhibitory control-related theta activity as well as inhibition performance. Importantly, it is shown that these correlations are subject to strong moderating effects by the factor age.

Previous evidence suggests that (inhibition-related) medial frontal theta-band activity may reflect an “alarm” or “surprise” signal that

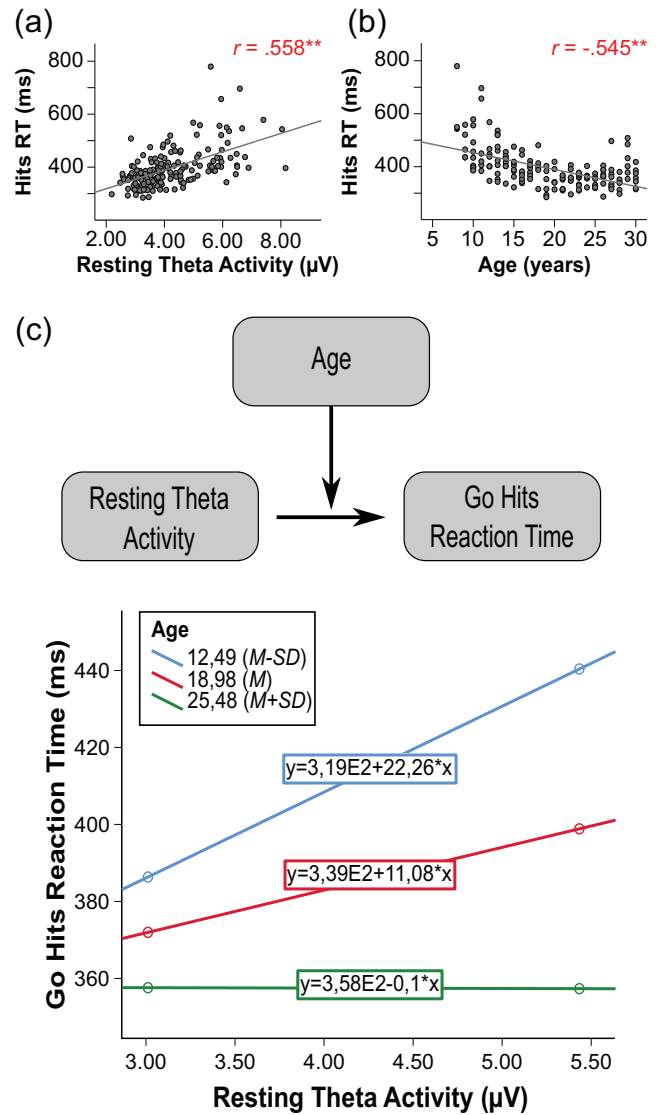


FIGURE 4 (a) Scatter plot showing the relationship between resting theta activity and the reaction time (RT) during hit trials. (b) Scatter plot illustrating the relationship between age and the reaction time (RT) during hit trials. (c) Moderating effect of age on the relationship between resting theta activity (x-axis) and the reaction time during Go hit trials (y-axis). The red fitting line depicts the mean (M) age of the sample, the blue line indicates the age one standard deviation below the mean (M-SD), the green line represents the age one standard deviation above the mean (M + SD)

increases when cognitive control is required (Cavanagh & Frank, 2014; Wessel, 2018). The theta-related alarm signal may trigger adjustments in cognitive control (Cavanagh & Frank, 2014) and may help to shift the behavioral strategy to refrain from premature responding (Dippel et al., 2016; Dippel et al., 2017) and support inhibitory control (Wessel, 2018; Wessel et al., 2016). It has been suggested that medial frontal theta activity is also central for several instances of cognitive control (Cavanagh & Frank, 2014; Cavanagh, Zambrano-Vazquez, & Allen, 2012; Womelsdorf, Vinck, Leung, & Everling, 2010) because cognitive control requires the organization of neural processes across distant brain regions (Miller & Cohen, 2001). Biophysical

TABLE 3 Results of the moderation analysis predicting the total theta power during Nogo trials from the resting theta activity with age as moderator

	Nogo total theta power			
	<i>b</i>	<i>SE(b)</i>	<i>t</i>	<i>p</i>
Constant	286.90	24.92	11.51	<.001
Resting theta	112.52	27.69	4.06	<.001
Age	4.89	4.00	1.22	.223
Resting theta × age	7.83	2.98	2.63	.009

Note: $R^2 = .19$ ($p < .001$) and $\Delta R = .05$. The predictor and the moderator variable are mean-centered. Heteroscedasticity-consistent standard errors and covariance estimators (HC3) were used. *b*, unstandardized regression coefficient.

data suggests that particularly slow oscillatory activity is important for communication within large brain networks (Buzsáki & Draguhn, 2004). The current data show that a higher resting-state theta-band activity is related to a stronger inhibitory-control theta-band power and might thus be related to a stronger alarm/surprise signal processing. This is the case above the age of ~ 10.7 years, as suggested by the Johnson–Neyman technique applied in the moderation analysis (Bauer & Curran, 2005; Hayes & Matthes, 2009). Also, this effect becomes stronger with increasing age (i.e., in early adulthood). The strong moderating effect of age on the correlation between resting-state and inhibition-related theta oscillations suggests that resting-state theta-band activity and alarm/surprise-signal-related inhibitory control processes are isolated entities at younger ages and only become related with increasing age. It seems that during adolescence, resting-state activity becomes increasingly important for the generation of strong alarm/surprise signals needed for successful response inhibition in Nogo trials. For successful inhibition, increased power in theta-band activity is necessary to reliably encode an alarm/surprise signal and these increases must occur quickly to allow in-time response inhibition (Dippel et al., 2016; Huster et al., 2013; Liu et al., 2014; Mückschel et al., 2017). It is possible that an increased resting-state theta activity may increase the volatility to code alarm/surprise-signals which are needed to trigger inhibitory control (Pscherer et al., 2019). The stronger resting-state theta activity is, the better it might be used for the generation of alarm/surprise signal-related processes necessary for behavioral inhibition. It has to be acknowledged that the theoretical framework of theta activity acting as alarm/surprise signal when cognitive control is required is not the only possible explanation for these findings. Increased theta activity has also been linked to increased working memory load (Hsieh, Ekstrom, & Ranganath, 2011; Itthipuripat, Wessel, & Aron, 2013). Furthermore, the Go/Nogo task does not allow to disentangle whether the increased theta activity during Nogo trials is related to the alarm/surprise signal or to inhibitory control per se. However, recent findings on a different aspect of cognitive control (i.e., conflict monitoring) have shown that resting theta activity is specifically related to stimulus-related, but not to response-related processes (Pscherer et al., 2020), which supports the concept that

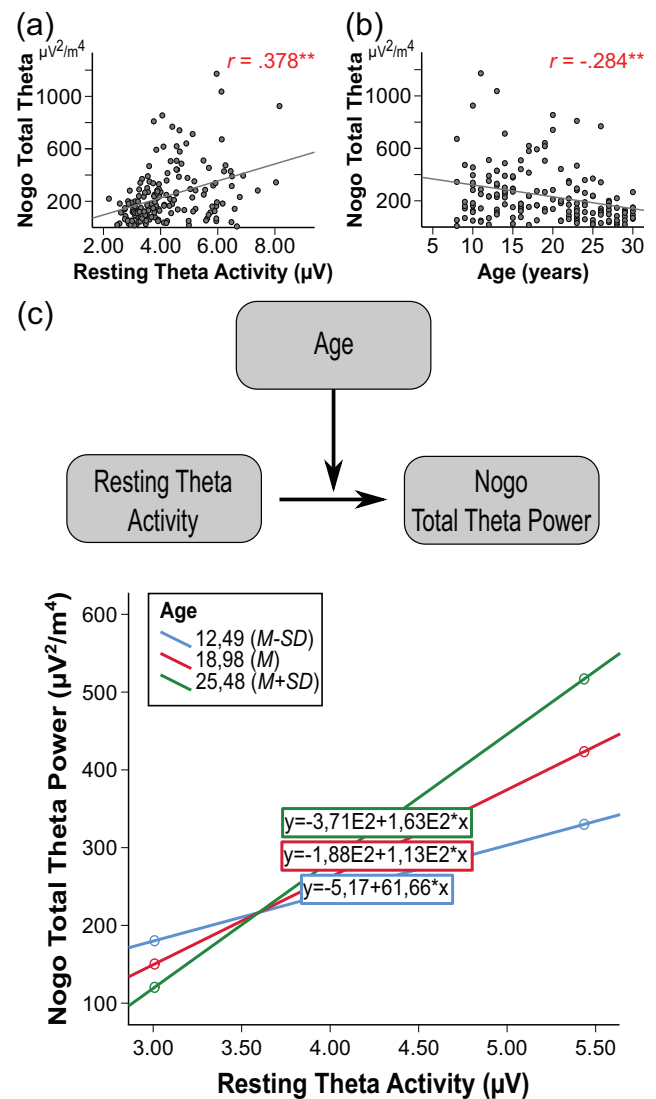


FIGURE 5 (a) Scatter plot showing the relationship between resting theta activity and the total theta power during correctly rejected Nogo trials. (b) Scatter plot illustrating the relationship between age and the total theta power during correctly rejected Nogo trials. (c) Moderating effect of age on the relationship between resting theta activity (x-axis) and the total theta power during correctly rejected Nogo trials (y-axis). The red fitting line depicts the mean (*M*) age of the sample, the blue line indicates the age one standard deviation below the mean (*M*-*SD*), the green line represents the age one standard deviation above the mean (*M* + *SD*)

theta activity acts as alarm/surprise signal or facilitates the processing of such signals.

Corroborating the findings at the neurophysiological level, moderating effects of age were obtained when examining the interrelation of resting-state theta-band activity and response inhibition at the behavioral level. The data suggest that at younger ages there is no relationship between resting theta activity and false alarm rates during Nogo trials. This relationship changes with age in that higher levels of resting theta activity are increasingly associated with a lower false alarm rate. The moderating effect of age becomes stronger when the

participants are older. Yet, it has to be noted that the moderating effect of age on behavioral parameters of response inhibition performance was weaker and occurred later compared to the neurophysiological data (i.e., at an age of ~ 19.5 years). This suggests that there are additional, currently unknown factors important to consider when it comes to response inhibition. Such factors could be that inhibition might not be an independent construct, but “a mixture of energization, task-setting, and monitoring”, as discussed by Friedman and Miyake (2017) and Vallesi (2020). For Go trials, an opposite pattern of moderating effects of age was obtained. Resting-state theta activity only seems important for the speed of a response in younger ages. This mirror-reversed pattern seems plausible considering findings suggesting a close interrelation of processes underlying response execution and inhibition (Dippel et al., 2016; Helton, 2009; Young, Sutherland, & McCoy, 2018). Yet, most important are the current findings in response inhibition.

A possible reason for the observed age-dependent relationship between resting-state theta activity and inhibitory control at the neurophysiological and behavioral level may relate to biophysical properties of theta oscillations and their role in coordinating information processing in a network. Here it is particularly relevant that high-amplitude/low-frequency oscillation regimes are important for the integration of information across distant brain regions (Buzsáki & Draguhn, 2004). On these grounds, it has been argued that medial frontal theta-band activity is important for cognitive control (Cavanagh & Frank, 2014). In line with other studies (Dippel et al., 2017; Mückschel et al., 2017; Pscherer et al., 2019), our beamforming analysis showed that particularly the medial parts of the SMA (BA6) are associated with theta-related response inhibition processes. Interestingly, evidence from clinical studies has shown that patients with lesions in the BA6 showed increased false alarm rates in a Go Nogo task, supporting the importance of this brain region for inhibition processes (Picton et al., 2007). A limitation of our result is that individual brain scans could not be recorded. Since the brain constantly evolves between childhood and late adolescence (Simmonds, Hallquist, Asato, & Luna, 2014) and since gender differences in brain size and structure are reported in children (Wilke, Holland, Altay, & Gaser, 2008), there is no appropriate template for a study that captures childhood, adolescence and early adulthood. Therefore, a standard adult brain template was used for the beamforming analysis. Since the obtained sources of theta-band activity are well in line with the literature (Dippel et al., 2017; Mückschel et al., 2017; Pscherer et al., 2019), we assume that these sources are reliable. The SMA and adjacent regions are important hubs and show considerable structural long-range connections with posterior and frontal brain regions (Hagmann et al., 2008; van den Heuvel & Sporns, 2013). Critically, these long-distance connections continue to develop into young adulthood (Simmonds et al., 2014). The same is the case for fronto-striatal and fronto-parietal connections and cortices (Rubia et al., 2006). These play an important role in response inhibition processes (Bari & Robbins, 2013) and have been implicated in the coding of alarm/surprise signals (Dippel et al., 2016; Geng & Vossel, 2013; Giller & Beste, 2019; Giller, Zhang, Roessner, & Beste, 2019; Wessel

et al., 2016). Thus, a possible theoretical framework for the finding that the relationship between resting-state and task-related theta activity becomes stronger with increasing age might relate to the completion of structural brain maturation processes and the concomitant changes in long-range network dynamics that are important for coding alarm/surprise signals. Since theta activity is important to enable long-range integration of information (Buzsáki & Draguhn, 2004) relevant for the generation of alarm/surprise signals (Cavanagh & Frank, 2014), it might be possible that the interplay of resting-state and inhibitory control-related theta activity, as well as behavioral inhibition is an emergent property of (structural) brain maturation. As brain maturation progresses, the relationship between resting-state and inhibition related theta might become increasingly important, probably to allow high volatility in the coding of “alarm” or “surprise” signals.

Our findings on theta-band modulations are important regarding alterations of cognitive functions in various disorders, which have their roots in childhood and adolescence. For example, increased resting state theta power has been observed in children and adults with attention-deficit/hyperactivity disorder (ADHD), and also in adults with schizophrenia, obsessive-compulsive disorder, and depression (Kiiski et al., 2020; Newson & Thiagarajan, 2019). The onset of these disorders is mostly during adolescence (Giedd, Keshavan, & Paus, 2008). Individuals with anxiety show higher theta response to events that require cognitive control (Cavanagh & Shackman, 2015). Therefore, our findings that only after a certain age (~ 19 years) high resting theta power is beneficial for inhibitory control is even more important since increased levels of theta before that age may confer some susceptibility to develop psychiatric disorders. It will be of major importance for future research to disentangle why the role of high theta-band activity changes across age; i.e., confers detrimental effects in younger age as evidenced by findings in psychiatric disorders, and is on the other hand beneficial for cognitive control in healthy adults. The decrease of resting theta power in the course of adolescence may be crucial for an optimal development of cognitive control functions. Future studies shall further examine the role of structural brain maturation for the effects observed in the current study. This shall ideally also include other instances of cognitive control functions in longitudinal studies to overcome this study's limitation of a cross-sectional analysis. Furthermore, future studies should investigate interrelations of resting-state and task-related activity using a complete electrode setup for the assessment of resting state activity. By this means, interrelated dynamics between diverse frequency bands in long and short-distant regions could be taken into account to provide more details about the interplay between various frequency bands. Nevertheless, the obtained results appear robust and valid since the observed effects sizes in all moderation analyses were larger than those assumed for the estimation of the required sample size.

In summary, we show that above the age of ~ 10.7 years higher resting-state theta-band activity is related to stronger inhibitory control-related theta-band power in superior frontal regions (BA6). The effect of age becomes stronger with increasing age (i.e., in early adulthood). A similar pattern of effects is found for response inhibition

performance, but the importance of resting theta activity for inhibition performance is only evident from the age of ~19.5 years onwards. It seems that during adolescence, resting-state theta activity becomes increasingly important for the generation of alarm/surprise signals which are needed for successful response inhibition. A possible reason for the observed effects might relate to biophysical properties of theta oscillations according to which high amplitude/low power oscillations are important for information integration from large-distant brain regions, an aspect that is strongly affected by brain maturation processes between childhood and early adulthood. The study shows that age is an important parameter in efforts to understand the interplay between resting-state and cognitive control-related neurophysiological processes.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

All participants provided written informed consent and received a financial reimbursement for their study participation. The ethics committee of the TU Dresden approved this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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