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Individual dynamics of delta–beta coupling: using a multilevel framework to examine inter- and intraindividual differences in relation to social anxiety and behavioral inhibition

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Background: Variation in EEG-derived delta–beta coupling has recently emerged as a potential neural marker of emotion regulation, providing a novel and noninvasive method for assessing a risk factor for anxiety. However, our understanding of delta–beta coupling has been limited to group-level comparisons, which provide limited information about an individual's neural dynamics. **Methods:** The present study used multilevel modeling to map second-by-second coupling patterns between delta and beta power. Specifically, we examined how inter- and intraindividual delta–beta coupling patterns changed as a function of social anxiety symptoms and temperamental behavioral inhibition (BI). **Results:** We found that stronger inter- and intraindividual delta–beta coupling were both associated with social anxiety. In contrast, the high-BI group showed weaker coupling relative to the non-BI group, a pattern that did not emerge when analyzing continuous scores of BI. **Conclusions:** In characterizing inter- and intraindividual coupling across the sample, we illustrate the utility of examining neural processes across levels of analysis in relation to psychopathology to create multilevel assessments of functioning and risk. **Keywords:** Delta–beta coupling; social anxiety; behavioral inhibition; intraindividual variability.

Introduction

Delta–beta coupling is the correlation between relative power in the delta and beta frequency bands of the electroencephalography (EEG) signal. Empirical and theoretical studies (Knyazev & Slobodskaya, 2003; Wang et al., 2013) suggest that delta–beta coupling reflects crosstalk between subcortical and higher-order cortical networks of the brain, indicative of top-down (i.e., beta) processes regulating or dampening bottom-up (i.e., delta) activity (Engel, Fries, & Singer, 2001). Emerging studies suggest that delta–beta coupling may be useful as a neural marker of emotion regulation.

For example, Miskovic & Schmidt (2009) found that higher testosterone levels in adult men were associated with a de-coupling of the delta–beta correlation, potentially reflecting the hormone's role in fear suppression and behavioral activation (Knyazev & Slobodskaya, 2003). In contrast, van Peer, Roelofs, and Spinhoven (2008) reported enhanced delta–beta coupling after cortisol administration, mapping onto activation of the hypothalamic–pituitary–adrenal axis, a system involved in activating and sustaining fearful states. Together, these findings suggest that delta–beta coupling is associated with the endocrine patterns that these hormones can induce in emotion reactivity, fluctuating with levels of inhibition and disinhibition.

These studies, like most in the literature, examined delta–beta coupling using group-level analyses, in which correlations between delta and beta power are computed for separate groups based on averaged power scores and then compared, often through a Fisher's *Z* analysis. These studies help us understand the basic association of delta–beta coupling with behavior. However, they cannot provide information regarding individual differences in brain dynamics which may provide a closer link to individual affective profiles. Person-level dynamics may move us closer to understanding individualized profiles of risk, leading to more sensitive and efficient early detection and intervention efforts. The current paper examines the utility of employing inter- and intraindividual analyses to capture variation in delta–beta coupling, particularly as a function of anxiety risk in childhood.

Several studies suggest that enhanced or stronger delta–beta coupling is associated with anxiety symptoms (Knyazev, 2011; Miskovic et al., 2011) and intergenerational risk for anxiety (Harrewijn, van der Molen, van Vliet, Houwing-Duistermaat, & Westenberg, 2018). For example, Knyazev (2011) reported that inducing anxious states in a sample of adults led to significant increases in delta–beta coupling. Miskovic et al. (2011) showed that delta–beta coupling significantly decreased after 12 sessions of cognitive behavioral therapy (CBT) in a clinical group of socially anxious adults, suggesting that delta–beta coupling patterns can be responsive to anxiety treatment.

Similarly, temperamental antecedents of anxiety such as behavioral inhibition (BI) have been associated with stronger delta–beta coupling (Poole, Anaya, & Pérez-Edgar, 2020). BI is a temperament profile

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characterized by shy, hypervigilant, and fearful behaviors in novel social situations that typically would not be interpreted as threatening (García Coll, Kagan, & Reznick, 1984). BI is a strong predictor of social anxiety with an up to sevenfold increase in risk (Clauss & Blackford, 2012), and given the overlap of fear-related behaviors, delta–beta coupling may be associated with anxiety and BI temperament in a similar manner. Indeed, researchers have reported stronger delta–beta coupling in behaviorally inhibited individuals with adult (van Peer et al., 2008) and child (Poole et al., 2020) samples. However, specific studies on the link between delta–beta coupling and BI remain scarce.

The literature suggests that stronger delta–beta coupling may reflect inflexible neural patterns of overcontrol and over-regulation, which fit the phenotypic profiles of anxiety and inhibited temperament, often characterized by ruminative, rigid, and hypervigilant cognitive patterns (Liu, Taber-Thomas, Fu, & Pérez-Edgar, 2018). However, most if not all studies supporting this functional interpretation have compared delta–beta coupling across anxiety and temperament using categorical groups, providing no information regarding whether a participant's individual neural patterns of delta–beta coupling actually map onto group-level hyper-regulated or overcontrolled neural dynamics. Thus, the link between a participant's individual delta–beta coupling dynamics and individual anxiety and temperament risk is missing, limiting both experimental and clinical utility.

Conclusions based on group-level designs alone limit our understanding of delta–beta coupling as a neural mechanism of anxiety, because the functional relevance of delta–beta coupling may differ across inter- and intraindividual levels of processing. Indeed, Poole et al. (2020) demonstrated in a recent study that while delta–beta coupling at the group level was always positive, some participants in the sample actually showed negative average coupling scores. This discrepancy across group and individual coupling has clinical significance, since we have yet to show how an individual's own neural pattern of weaker or stronger delta–beta coupling is associated with their individual anxiety risk and symptomatology. Modeling both inter- and intraindividual patterns of delta–beta coupling could answer this question and contribute unique information regarding the stability of individual neural dynamics across measurement models.

There are important clinical and methodological reasons for examining delta–beta coupling as an intraindividual process. Clinically, we want to model systematic individual differences in neural mechanisms to better understand how such mechanisms unfold and map onto the emergence of clinical disorders. Group-level analyses of delta–beta coupling provide a partial picture of this link because we are unable to map a group-inferred statistic to the potential crosstalk between subcortical and cortical regions for each individual. Thus, no information can be gleaned regarding individual neural dynamics and anxiety. Methodologically, modeling delta–beta coupling at inter- and intraindividual levels will permit more complex analyses and thus expand the scope and the nature of the questions we can ask. For example, an *interindividual* approach can provide us with average delta–beta coupling scores for each individual and allow for between-person comparisons in relation to anxiety symptoms. We can also move beyond average coupling scores and explore quickly changing patterns in the EEG time series by modeling *intraindividual* delta–beta coupling. This approach can shed light on how an individual's neural dynamics deviate from their average neural states, and how variation in these intrinsic patterns of delta–beta coupling is associated with socioemotional profiles.

In the present study, we wished to advance previous work on delta–beta coupling and anxiety by examining coupling at *inter-* and *intraindividual* levels in relation to anxiety symptoms and BI, constructs that are generally highly correlated but have different developmental trajectories and functional outcomes. We also wished to illustrate a multilevel analytic framework that can be easily applied in future studies. We collected delta–beta EEG coupling and parent report of children's anxiety and BI in 177 children between the ages of 9 and 12, oversampled for temperamental BI. Using multilevel modeling, we examined inter- and intraindividual coupling of second-by-second delta and beta power, maximizing our ability to test whether anxiety and BI moderated these coupling patterns. Based on previous findings, we predicted that higher anxiety and higher BI scores would be similarly associated with stronger interindividual delta–beta coupling. Our analyses of intraindividual delta–beta coupling were exploratory, given the lack of studies in the literature using this approach. However, we expected that stronger coupling would likely also be positively associated with anxiety levels and BI.

Method

The present study included data from the baseline visit of a larger project designed to examine the relations between children's temperament, attention, and anxiety. The recruitment, inclusion process, and main findings of the project have been reported elsewhere (Liu et al., 2018). The sample was recruited from areas surrounding Central Pennsylvania, and all study procedures were approved by the Institutional Review Board of The Pennsylvania State University. Written assent and informed consent were obtained from participants and their parents.

Participants

Participants ($N = 706$) were initially screened for BI using the Behavioral Inhibition Questionnaire (BIQ; Bishop, Spence, & McDonald, 2003) and classified as BI if total scores ≥119 or

social novelty subscale scores >60, based on prior literature (Broeren & Muris, 2010). Two hundred and fifty-one children (Mean Age = 10.9 years, *SD* = 0.98, Female = 136) enrolled in the larger study. From the 251 enrolled participants, 30 families dropped out of the study before we could collect any variables of interest. From the remaining participants, 26 parents failed to report on their children's social anxiety and 17 participants did not provide EEG data (4 refused the EEG net, 2 consented to questionnaire data only, and 11 were unable to come back for the EEG visit). During EEG processing, data from 1 participant were excluded due to poor quality.

A final sample of 177 participants was included in our analyses. The study was enriched for BI such that while only 24.5% of the screened sample was high BI, this group represented 44.6% of the final sample (97 girls, M_{age} = 10.87 years, *SD* = 1.03). BI children did not differ from noninhibited (BN) children on gender, age, or ethnicity measures (all *p*'s > .21), but did exhibit more anxiety symptoms (*p*'s < .01). The sample was 82% White, 2% African American, 3% Latino, 2% Biracial, and 11% declined to respond. Analyses showed that missingness of parent reports on children's social anxiety was related to ethnicity ($p = .04$) and missingness of EEG data was related to higher BIQ scores ($p = .001$), suggesting a missing at random (MAR) pattern (Rubin, 1976). Participants included in the analyses did not significantly differ from missing participants in age or gender (*p*'s > .45). Pairwise deletion was used for all analyses. Demographics and zero-order correlations for our behavioral measures are presented in Table 1.

Sample size and number of repeated observations for inter- and intraindividual delta–beta coupling were determined by power analyses. We computed power for intraindividual analyses using effect sizes reported from previous studies where average coupling scores were calculated for each participant, which reflect interindividual differences (Harrewijn, Van der Molen, & Westenberg, 2016, $d = .20$, $N = 56$; Poppelaars, Harrewijn, Westenberg, & van der Molen, 2018, $d = .20$, $N = 52$). Interindividual power analyses suggested that we could detect two main effects and an interaction with a sample size of 54 participants (Power = .80, $\alpha = .05$).

To our knowledge, no study has previously examined delta–beta coupling at intraindividual levels; thus, effect sizes were unknown. In order to compute power, we first simulated repeated observations of delta and beta power, and between-person scores of social anxiety and BI using sample-level parameters reported in previous studies (Muris, van Brakel, Arntz, & Schouten, 2011; van Peer et al., 2008). We then simulated a mixed-effect model with a weak effect size (.10) and found that in order to detect two main effects and one interaction term we would need a sample of 130 participants with a minimum of 10 repeated observations of delta and beta power. Power analyses were computed using the *pwr* and *simr* packages in R (Champely, 2018; Green & MacLeod, 2016).

Measures

Behavioral inhibition. Parents completed the Behavioral Inhibition Questionnaire (BIQ; Bishop et al., 2003); a 30-item instrument designed to measure BI across domains of social and situational novelty. Parents rated their children's behavior using a 7-point Likert scale: 1 ('Hardly Ever') to 7 ('Almost Always'). Bishop et al. (2003) report adequate internal consistency and validity, and the BIQ had good internal consistency (Cronbach's $\alpha = .86$) within our sample.

Social anxiety. Parents reported on their children's anxiety levels using the SCARED (Muris, Merckelbach, Schmidt, & Mayer, 1998). The SCARED consist of 41 items assessing symptomatology for different anxiety disorders. The SCARED yields different subscales based on DSM-IV criteria for generalized anxiety, panic disorder, social phobia, separation anxiety, and school phobia. Parents rated how frequent their children experienced each symptom using a 3-point scale: 0 – *almost never*, to 1 – *sometimes*, to 2 – *often*. Previous studies have reported good psychometric properties for this measure (Muris et al., 1998), and we also found good internal consistency in our sample (Cronbach's $\alpha = .90$).

EEG. Resting-state EEG activity was recorded using a 128-channel geodesic sensor net (Electrical Geodesics Inc., Eugene, Oregon) during a resting-state, four-minute session of eyes-open and eyes-closed periods. EEG signal was sampled at 1000 Hz rate with channels referenced to Cz. Eye movements were recorded using electrodes placed at approximately 1 cm above and below the eye (vertical) and at the outer canthi of each eye (horizontal). Impedances were kept below 50 kΩ. Data were processed off-line using Brain Vision Analyzer (Brain Products GmbH, Germany). Raw data were rereferenced to the average of the right and left mastoid. A high-pass (0.10 Hz) and low-pass (40 Hz) notch filters were applied. Bad channels were visually identified and manually removed from

Table 1 Sample characteristics

	BI	BN	Sample correlations			
Demographics						
N	79	98				
Gender (M/F)	34/45	46/52				
Age	10.76 (1.01)	10.95 (1.04)				
Delta and beta power						
Frontal delta	1.65 (0.46)	1.51 (0.41)	–			
Central delta	0.81 (0.63)	0.58 (0.47)	.69*	–		
Parietal delta	1.16 (0.66)	0.92 (0.59)	.60*	.72*		
Frontal beta	−1.09 (0.55)	−1.23 (0.50)			–	
Central beta	−1.70 (0.61)	−1.90 (0.49)			.74*	–
Parietal beta	−1.30 (0.63)	−1.51 (0.58)			.69*	.78*
BIQ and anxiety						
BIQ	127.03 (18.74)	73.42 (19.82)	–			
Total anxiety	16.08 (9.66)	7.11 (5.85)	.56*	–		
Social anxiety	6.45 (3.37)	2.00 (2.34)	.67*	.80*	–	
General anxiety	4.86 (3.63)	2.72 (2.96)	.36*	.85*	.55*	–
Separation anxiety	3.10 (3.31)	1.60 (1.88)	.34*	.73*	.38*	.47*

Means and standard deviations (*SD*) based on $N = 177$. Between-regions correlations based on $N = 177$ bivariate coverage. All correlations were significantly different from zero at $p < .001$*.

the data of each participant. After visual inspection, data were corrected for eye blinks and eye movement artifacts using the Gratton, Coles, and Donchin (1983) method. Automatic artifact detection algorithm excluded segments with a voltage step >30 μV/ms, absolute difference >150 μV/ms, amplitude < −100 μV or >100 μV, and low activity <0.5 μV for any electrode. Data were then segmented into 1 s epochs and transformed using a Fast-Fourier Transformation with a Hamming window length of 50% (Phelps, Brooker, & Buss, 2016).

We exported second-by-second EEG power for the delta (1–4 Hz) and beta (12.5–25 Hz) frequency bands. This method yielded up to 240 segments of delta and beta power for individual participants. Based on our power analyses, participants with less than 10 segments were excluded from the intraindividual analyses ($n = 6$), creating the final sample ($N = 171$, $M = 100.38$; $SD = 58.54$, Range = 10–284). The number of cleaned segments was entered as a covariate in our models to control for variation in proportion of available data. Power values across target electrodes (Poole et al., 2020) were averaged to create composites for the Frontal (F3, Fz, F4), Central (C3, Cz, C4), and Parietal (P3, Pz, P4) regions based on the 10–20 System of Electrode Placement.

Data analysis

Full details of the data analysis plan, including analytic formulas, are presented in Appendix S1.

Step 1: We tested whether delta and beta power differed across eyes-open and eyes-closed conditions and tested whether delta–beta coupling changed as a function of time spent in the resting-state task. These data checks allowed us to (a) examine whether our resting-state task produced a stable measure of delta–beta coupling, (b) check internal consistency across eyes-open and eyes-closed conditions, and (c) determine whether these segments could be examined continuously, to mimic previous studies that average across conditions. Separate one-way ANOVAs tested delta and beta power differences across conditions, and a two-level multilevel model (Appendix S1a) examined the extent to which variability in within-person delta–beta coupling could be attributable to time spent in the resting-state EEG task (in seconds).

Step 2: We used multilevel models to characterize inter- and intraindividual delta–beta coupling at Frontal, Central, and Parietal electrodes. In order to decompose inter- and intraindividual variation, we split the time-varying, second-to-second delta and beta power variables into average coupling and individuals' second-by-second deviations from their average coupling (Appendix S1b).

Step 3: We examined whether evident variation could be explained as a function of BI and social anxiety (Appendix S1c). To do so, we used the simple form of the inter- and intraindividual model in combination with between-person variables of BI and social anxiety, separately.

Step 4: We examined whether the association between delta–beta coupling and anxiety symptoms was specific to social anxiety. To do so, we tested the model described in Step 3 in turn with the SCARED subscales of Separation and General Anxiety.

All models were fitted in R using the *lme4* package (Bates, Maechler, Bolker, & Walker, 2015), and statistical significance was set at $\alpha = .05$ and false discovery rate (FDR) correction was used to control for multiple comparisons.

Results

We tested whether relative power differed across eyes-open and eyes-closed conditions and whether delta-beta coupling was influenced by time. There were significant reductions in delta and beta power from eyes-closed to eyes-open but only in posterior regions, in line with previous findings in children of the same age (Barry, Clarke, Johnstone, & Brown,, 2009). Despite this reduction in relative power, the multilevel model showed that delta-beta coupling was not influenced by time across any brain region (all ps > .10), providing empirical support for the EEG eyes-open/eyes-closed task as a stable measure of resting-state coupling.

Inter- and intraindividual delta–beta coupling

We used multilevel models to characterize inter- and intraindividual differences in delta–beta coupling and examine average and time-varying coupling patterns for individuals, which to our knowledge no study has done before. Interindividual coupling captures the average coupling pattern of each person across their EEG time series and allows us to compare these patterns *between* participants. Intraindividual coupling is time-dependent and reflects the coupling pattern that a person shows when delta and beta power deviate from usual states and are higher or lower relative to their own average. Inter- and intraindividual delta–beta coupling were significant across Frontal (Inter: $\gamma_{30} = 0.46$, $p = .001$; Intra: $\gamma_{40} = 0.13$, $p = .001$), Central (Inter: $\gamma_{30} = 0.72$, $p = .001$; Intra: $\gamma_{40} = 0.21$, $p = .001$), and Parietal (Inter: $\gamma_{30} = 0.81$, $p = .001$; Intra: $\gamma_{40} = 0.28$, $p = .001$) regions. These results suggested that across the sample, individuals who on average showed higher delta power also showed higher beta power (positive between-person coupling), and in moments when individuals' delta power was higher than average, their beta power was also higher than average (positive within-person coupling). Figure 1 illustrates predicted frontal delta–beta slopes for each individual in our sample as a function of their average coupling score, characterizing intraindividual variability and the sample-

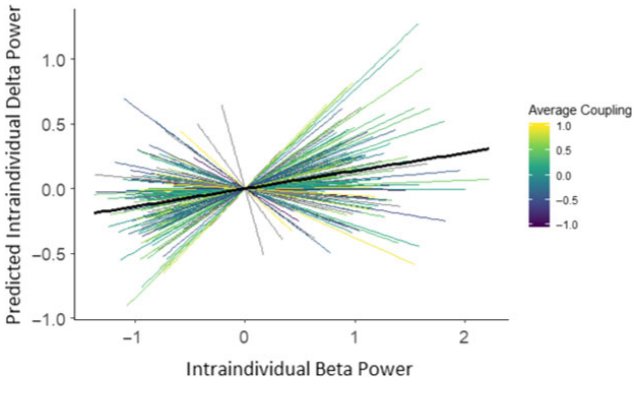

Figure 1 Model-predicted intraindividual delta–beta coupling for each participant as a function of participants' average coupling scores. Black line indicates the sample-level delta–beta coupling [Colour figure can be viewed at wileyonlinelibrary.com]

level coupling (black line). In many participants, intraindividual delta–beta coupling (r_{intra} = -0.16) differed from their own average coupling scores (r_{inter} = 0.39) and from the sample-level coupling (r_N = 0.60).

Delta–beta coupling and social anxiety

The relation between social anxiety scores and intraindividual coupling was only significant at the Frontal region. For every unit increase in social anxiety scores, there was a significant 0.019 increase in within-person delta–beta coupling (*SE* = 0.006, *p* = .001), suggesting that youth with higher social anxiety scores exhibited significantly higher frontal coupling, $\gamma_{40} + \gamma_{80} = 0.136 + 0.019 = 0.155$, compared to within-person delta–beta coupling across the entire sample. Regions of significance analyses (Figure 2) suggest that while within-person coupling between delta and beta power was significant for social anxiety scores >2.72 (most of the sample), the slope or coupling between delta and beta power nonetheless becomes stronger as a function of increasing social anxiety scores.

The extent of between-person coupling also changed as a function of anxiety scores, but only at the Central region. Specifically, a one unit increase in social anxiety scores was associated with a significant 0.034 increase in between-person delta–beta coupling (*SE* = 0.014, *p* = .025), suggesting that children's average delta–beta coupling was significantly greater for participants with higher social anxiety scores, $\gamma_{30} + \gamma_{70} = 0.66 + 0.034 = 0.694$. Simple-slopes analyses (Figure 3) suggested that between-person coupling was stronger in participants with social anxiety scores above 1SD (β = .84) compared to participants with social anxiety scores below 1SD (β = .59, *p* = .02), but these groups were not significantly different from the average group (β = .72, *p* = .16). Probing this interaction with 1SD above and below a clinical cutoff score of 8, as established by the SCARED, found identical results. Full details for these analyses are reported in Table S1.

Delta–beta coupling and behavioral inhibition

Unlike social anxiety, multilevel models of BI showed no significant associations between continuous BIQ scores and inter- and intraindividual delta–beta coupling (all *p*s > .13). Given these unexpected results, we explored the interaction between BIQ and social anxiety scores in these models. BIQ scores did not significantly interact with social anxiety to moderate inter- or intraindividual delta-beta coupling (*p*s > .12). However, our study was underpowered to test these effects. Thus, replications with larger samples are imperative. Previous studies (van Peer et al., 2008) have used categorical high- and low-BI groups, which naturally lend themselves to standard group-level analyses of delta–beta coupling. Thus, we also tested inter- and intraindividual coupling across categorical BI groups to facilitate comparisons between our results and previous studies.

These analyses suggested that intraindividual, but not interindividual, coupling systematically changed as a function of BI group at the Central region, although this interaction did not survive FDR correction. This effect indicated that for children in the BN group, increases in delta power in relation to each person's mean were associated with increases in beta power (γ_{40} = 0.27, *p* = .001). In contrast, for BI children, increases in delta power in relation to their mean were not as clearly matched by increases in beta power$\gamma_{40} + \gamma_{70} = 0.27 + (-0.09) = 0.18$ and were thus relatively more uncoupled or asynchronous compared to the BN group. Raw second-

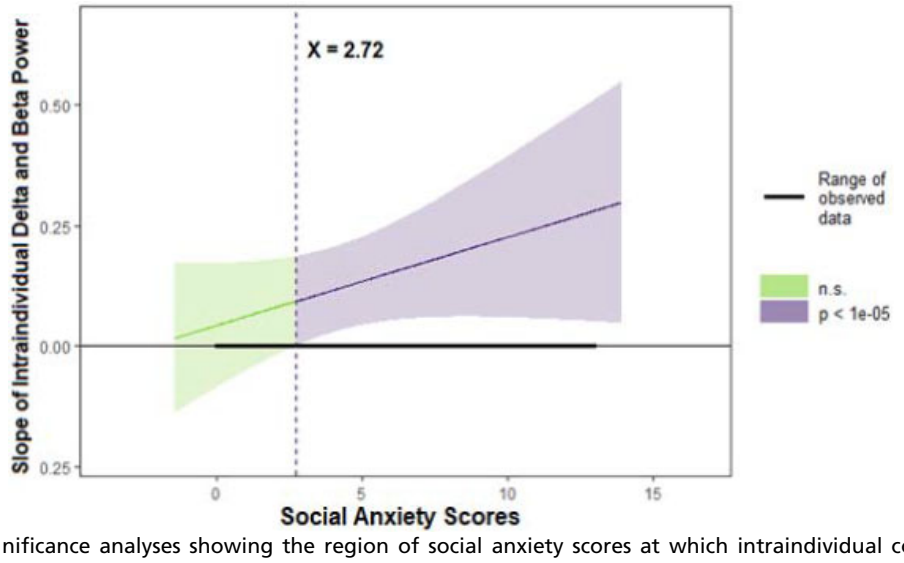

Figure 2 Regions of significance analyses showing the region of social anxiety scores at which intraindividual coupling is significant (purple) versus non-significant (green) [Colour figure can be viewed at wileyonlinelibrary.com]

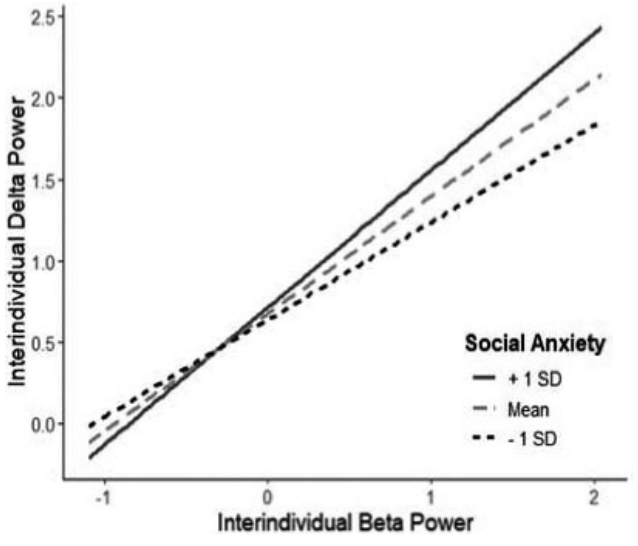

Figure 3 Simple-slope analyses showing differences in the slope of interindividual delta–beta coupling for high (+1*SD*, SCARED = 7.67), average (SCARED = 3.98), and low (SCARED = 0.27) social anxiety participants

by-second power data for a BI and a BN participant are shown in Figure 4 to illustrate individual differences in intraindividual coupling. Full details for the multilevel models are presented in Table S2.

Specificity of delta–beta coupling

Additional multilevel models tested whether inter- and intraindividual delta–beta coupling also changed as a function of separation and general anxiety scores derived from the SCARED. Results indicated that the extent of within- and between-person coupling did not systematically change across any brain region as a function of these other anxiety subscales (all *p*s > .18), suggesting specificity of delta–beta coupling to social anxiety.

Discussion

Previous studies suggest that stronger resting-state delta–beta coupling reflects neural patterns of over-control, and that groups of anxious and behaviorally inhibited individuals are more likely to show this neural signature. In the present study, we sought to examine whether children's anxiety levels and temperamental behavioral inhibition scores moderated their individual delta–beta coupling patterns in order to further understand the functional significance of this neural correlate at inter- and intraindividual levels. We characterized individuals' delta–beta coupling dynamics for the first time and show that intraindividual coupling patterns vary across participants and may also differ from an individual's own average coupling. We found that inter- and intraindividual coupling were significantly stronger in children with more social anxiety symptoms. However, we found no association between continuous BIQ scores and delta–beta coupling. When BI was split into categorical groups based on extreme cutoff scores, we found a significant effect only at

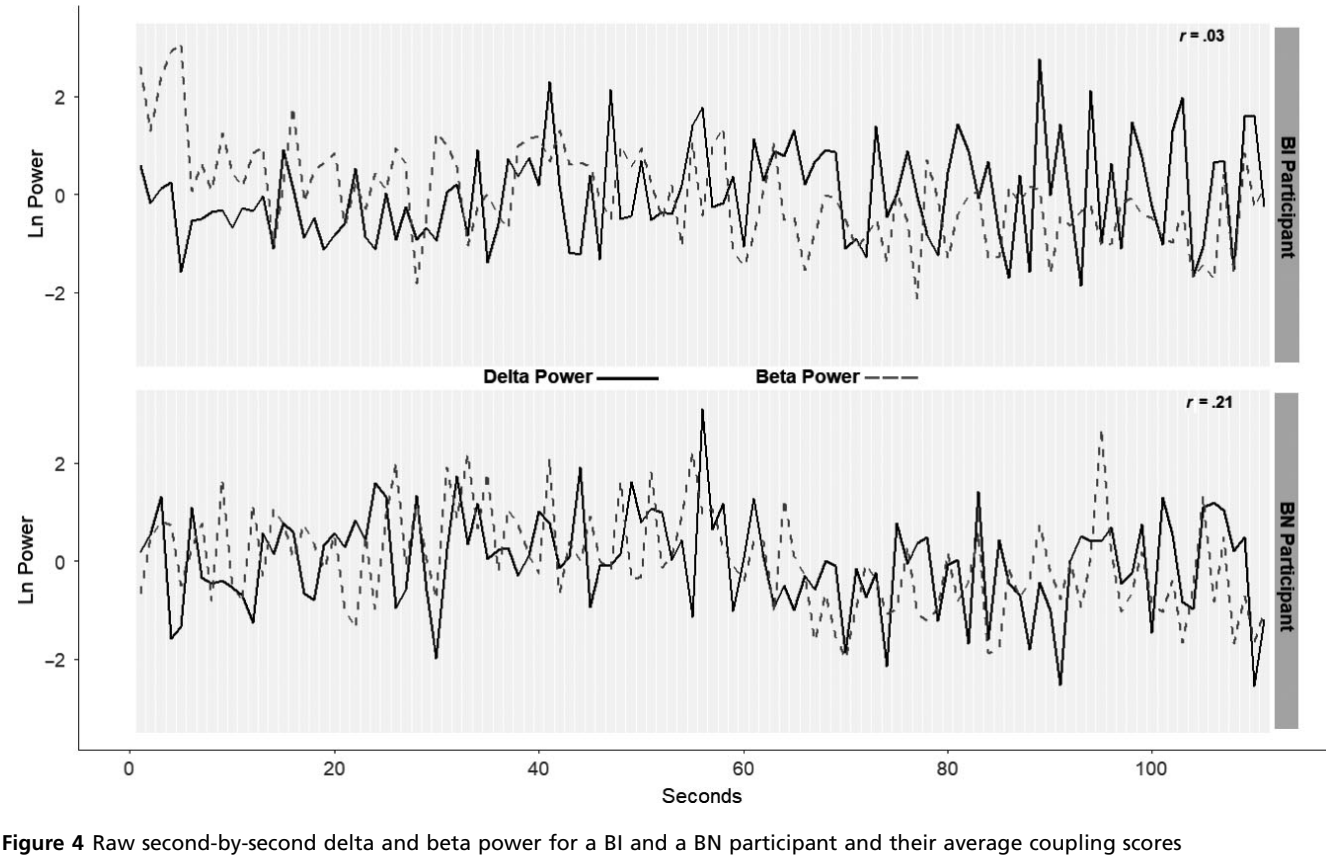

Figure 4 Raw second-by-second delta and beta power for a BI and a BN participant and their average coupling scores

intraindividual levels, indicating that intraindividual delta–beta coupling was weaker in the BI group compared to the BN group.

The moderating effect of social anxiety on inter- and intraindividual delta–beta coupling converges with previous studies that have reported enhanced coupling for high anxiety groups (Knyazev, 2011; Miskovic et al., 2011). Social anxiety symptoms have been linked to hyperactivation of limbic regions usually involved in threat-perception and fear responses (Miskovic & Schmidt, 2012). Our intraindividual findings showed that in children with higher social anxiety, increases or decreases in delta power were more likely to be met by equally strong increases and decreases in beta power, maintaining relatively rigid patterns of strong coupling. Under the functional interpretation that delta–beta coupling reflects top-down control of limbic regions, our findings suggest that these children may sustain neural patterns of overcontrol even as subcortical activation decreases.

By comparing inter- and intraindividual coupling, our results contribute to the existing literature in showing that children with higher social anxiety display delta–beta coupling that is, on average, stronger than their low anxiety peers. In addition, our results suggest that resting-state delta–beta coupling can capture rapid changing neural dynamics. We show that children with higher levels of social anxiety are also more likely to sustain stronger coupling patterns even when delta and beta power deviate from usual levels, potentially reflecting inflexibility of this neural system. It is possible that experiencing repeated anxious and fearful states, and thus hyperactivation of limbic regions, overtrigger control mechanisms that over time lower the threshold at which delta and beta power become highly synchronized. It is also possible that early distortions in the timing and rate of cortical–subcortical connections lead to extremely synchronized patterns in these neural systems, which may then lead to anxious and overcontrol behavioral states. Longitudinal studies of delta–beta coupling early in development are crucial to disentangling these developmental trajectories and further understanding this neural process as a potential mechanism of social anxiety.

It is worth noting that social anxiety moderated intraindividual delta–beta coupling specifically at the Frontal region and interindividual coupling at the Central region. Previous studies have failed to find a significant effect of anxiety on interindividual coupling at Frontal sites (Harrewijn et al., 2016; Miskovic et al., 2010), while most group-level studies of delta–beta coupling and anxiety do report significant differences in Frontal regions (Knyazev, 2011). It is possible that unmeasured intraindividual dynamics in delta–beta coupling are driving the pattern in these previous studies, and that interindividual and group-level differences in delta–beta coupling may only emerge at Central regions once we account for intraindividual variability. Alternatively, Knyazev et al. (2019a) recently showed that personality traits of introversion and neuroticism, which are associated with anxiety risk, were related to enhanced slow-fast (S-F) cross-frequency coupling specifically sourced to the medial prefrontal cortex (mPFC). Therefore, it is also possible that intraindividual delta-beta coupling at Frontal regions may more clossely capture the dynamic cross-talk between cortical and subcortical regions for this risk population.

Differences across regions may also reflect underlying patterns of brain development. While group-level studies of adults primarily find significant effects at Frontal regions only, studies of infants and toddlers have reported significant effects across all regions (Brooker, Phelps, Davidson, & Goldsmith, 2016; Phelps et al., 2016). In fact, a recent longitudinal study showed that S-F coupling increased or decreased between 7 and 10 years, depending on scalp areas, and that social anxiety and introversion were associated with less stable trajectories (Knyazev et al., 2019b). Despite these exciting findings, regional differences in delta–beta coupling remain poorly understood, and future research is needed to link region specificity to the clinical and functional relevance of this neural process in the development of social anxiety.

We also showed that only social anxiety, and not general or separation anxiety, was associated with inter- and intraindividual delta–beta coupling. These results suggest that delta–beta coupling may capture overcontrol neural patterns that are closely tied to social-related fears. However, this specificity was only assessed through subscales from a single anxiety questionnaire. Further replication with task-based paradigms is needed to replicate this finding and understand what aspects of social anxiety drive the specificity.

The lack of association between BIQ scores and delta–beta coupling, as well as the significantly weaker coupling in the BI group, were unexpected findings. In a recent study, Poole et al. (2020) found that higher BIQ scores were associated with stronger interindividual delta–beta coupling in a sample of 5- to 7-year-old children. Another study formed groups on the basis of the BIS/BAS questionnaire among adults and found stronger coupling for the high-BI group (van Peer et al., 2008). Several aspects in our study differ from previous studies, including the participants' ages and the fact that children were oversampled for BI. More importantly, our study employed mixed-effects models, where the moderating role of continuous BIQ and categorical BI was only considered after accounting for intraindividual coupling, which no study has employed before. Thus, our null results suggest that the relation between BIQ scores and interindividual coupling may depend on coupling patterns at intraindividual levels.

Our intraindividual results indicated that when children in the BI group deviated from their average coupling state, they tended to show more uncoupled patterns of activity relative to the BN group. It is feasible that BI individuals may display weaker intraindividual delta–beta coupling even when showing stronger coupling at interindividual levels. Although we only found evidence for the former, our characterization of inter- and intraindividual coupling across the sample does suggest that these differences may exist. Furthermore, these results are in line with neurocognitive developmental models of BI (Henderson, Pine, & Fox, 2015), which suggest that risk trajectories in BI children emerge because neural systems underlying automatic and controlled processes fail to integrate, preventing them from operating in flexible, context-dependent ways to achieve optimal self-regulation. It is possible that the uncoupled patterns we found in the BI group may also be indicative of this lack of integration across neural systems of regulation.

The following limitations should be acknowledged. First, our study only included a cross-sectional sample, and thus, we could not capture directional effects between delta–beta coupling, social anxiety, and temperament risk. Studies with repeated measures of delta–beta coupling are needed to test its role as a developmental mechanism in social anxiety. Second, our analyses did not account for pubertal status. However, two major studies (Miskovic & Schmidt, 2009; van Peer et al., 2008) that helped establish the functional significance of delta-beta coupling showed that it is associated with decreased testosterone and increased cortisol levels. Thus, accounting for pubertal status could change the present associations with BI and social anxiety in significant ways. Third, delta–beta coupling was measured at rest, and thus, we cannot directly link intraindividual coupling to emotion regulation or coping with anxious states. Future studies should examine changes in inter- and intraindividual delta–beta coupling during active emotion regulation tasks. A fourth limitation is that our sample was primarily white, and larger groups of diverse participants would have been needed in order to probe generalizability. Finally, beyond the scope of our initial examination of intraindividual delta–beta coupling, we were underpowered to test interactions incorporating both BI and social anxiety, or the role of inter- and intraindividual coupling as a moderating factor in the relation between BI and anxiety. Longitudinal studies of delta–beta coupling will be more suitable to test these questions. We urge future studies to continue to tease apart inter- and intraindividual coupling in tandem with task-dependent and repeated measures designs in order to understand how delta–beta coupling develops over time. Additionally, including puberty measures in future studies will shed light on the interplay between hormonal functioning and inter- and intraindividual coupling in the regulation of social fears.

Supporting information

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

Appendix S1. Data analysis plan.
Table S1. Multilevel models of inter- and intraindividual delta-beta coupling as a function of social anxiety symptoms.
Table S2. Multilevel models of inter- and intraindividual delta-beta coupling across behaviorally inhibited and non-inhibited groups.

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Key points

- Delta–beta coupling is associated with patterns of overcontrol or over-regulation.
- This is the first study to explore inter- and intraindividual delta–beta coupling in relation to childhood risk for anxiety.
- Our main findings suggest that inter- and intraindividual delta–beta coupling are associated specifically with social anxiety and temperamental behavioral inhibition.
- These analytic approaches may help institute more personalized uses of biomarkers of risk for early identification and intervention of anxiety disorders.

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References

Barry, R.J., Clarke, A.R., Johnstone, S.J., & Brown, C.R. (2009). EEG differences in children between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology*, *120*(10), 1806–1811. https://doi.org/10.1016/j.clinph.2009.08.006

Bates, D., Maechler, M., Bolker, B., Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*(1), 1-48. https://doi.org/10.18637/jss.v067.i01

Bishop, G., Spence, S.H., & McDonald, C. (2003). Can parents and teachers provide a reliable and valid report of behavioral inhibition? *Child Development*, *74*, 1899–1917.

Broeren, S., & Muris, P. (2010). A psychometric evaluation of the behavioral inhibition questionnaire in a non-clinical sample of Dutch children and adolescents. *Child Psychiatry & Human Development*, *41*, 214–229.

Brooker, R.J., Phelps, R.A., Davidson, R.J., & Goldsmith, H.H. (2016). Context differences in delta beta coupling are associated with neuroendocrine reactivity in infants. *Developmental Psychobiology*, *58*, 406–418.

Champely, S. (2018). pwr: Basic Functions for Power Analysis. R package version 1.2-2. Available from: https://CRAN.R-project.org/package=pwr

Clauss, J.A., & Blackford, J.U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A Meta-Analytic Study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*, 1066–1075.e1.

Engel, A.K., Fries, P., & Singer, W. (2001). Dynamic predictions: Oscillations and synchrony in top–down processing. *Nature Reviews Neuroscience*, *2*, 704–716.

García Coll, C., Kagan, J., & Reznick, J.S. (1984). Behavioral inhibition in young children. *Child Development*, *55*, 1005–1019.

Gratton, G., Coles, M.G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*, *55*, 468–484.

Green, P., & MacLeod, C.J. (2016). simr: an R package for power analysis of generalised linear mixed models by simulation. *Methods in Ecology and Evolution*, *7*, 493–498.

Harrewijn, A., van der Molen, M.J., van Vliet, I.M., Houwing-Duistermaat, J.J., & Westenberg, P.M. (2018). Delta-beta correlation as a candidate endophenotype of social anxiety: a two-generation family study. *Journal of Affective Disorders*, *227*, 398–405.

Harrewijn, A., Van der Molen, M.J.W., & Westenberg, P.M. (2016). Putative EEG measures of social anxiety: Comparing frontal alpha asymmetry and delta–beta cross-frequency correlation. *Cognitive, Affective, & Behavioral Neuroscience*, *16*, 1086–1098.

Henderson, H.A., Pine, D.S., & Fox, N.A. (2015). Behavioral inhibition and developmental risk: a dual-processing perspective. *Neuropsychopharmacology*, *40*, 207–224.

Knyazev, G.G. (2011). Cross-frequency coupling of brain oscillations: An impact of state anxiety. *International Journal of Psychophysiology*, *80*, 236–245.

Knyazev, G.G., Savostyanov, A.N., Bocharov, A.V., & Aftanas, L.I. (2019a). EEG cross-frequency correlations as a marker of predisposition to affective disorders. *Heliyon*, *5*(11). https://doi.org/10.1016/j.heliyon.2019.e02942

Knyazev, G.G., Savostyanov, A.N., Bocharov, A.V., Tamozhnikov, S.S., Kozlova, E.A., Leto, I.V., & Slobodskaya, H.R. (2019b). Cross-frequency coupling in developmental perspective. *Frontiers in Human Neuroscience*, *13*, 158. https://doi.org/10.3389/fnhum.2019.00158

Knyazev, G.G., & Slobodskaya, H.R. (2003). Personality trait of behavioral inhibition is associated with oscillatory systems reciprocal relationships. *International Journal of Psychophysiology*, *48*, 247–261.

Liu, P., Taber-Thomas, B.C., Fu, X., & Pérez-Edgar, K. (2018). Biobehavioral markers of attention bias modification in temperamental risk for anxiety: A randomized control trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, *57*, 103–110.

Miskovic, V., Ashbaugh, A.R., Santesso, D.L., McCabe, R.E., Antony, M.M., & Schmidt, L.A. (2010). Frontal brain oscillations and social anxiety: A cross-frequency spectral analysis during baseline and speech anticipation. *Biological Psychology*, *83*, 125–132.

Miskovic, V., Moscovitch, D.A., Santesso, D.L., McCabe, R.E., Antony, M.M., & Schmidt, L.A. (2011). Changes in EEG cross-frequency coupling during cognitive behavioral therapy for social anxiety disorder. *Psychological Science*, *22*, 507–516.

Miskovic, V., & Schmidt, L.A. (2009). Frontal brain oscillatory coupling among men who vary in salivary testosterone levels. *Neuroscience Letters*, *464*, 239–242.

Miskovic, V., & Schmidt, L.A. (2012). Social fearfulness in the human brain. *Neuroscience & Biobehavioral Reviews*, *36*, 459–478.

Muris, P., van Brakel, A.M., Arntz, A., & Schouten, E. (2011). Behavioral inhibition as a risk factor for the development of childhood anxiety disorders: A longitudinal study. *Journal of Child and Family Studies*, *20*(2), 157–170.

Muris, P., Merckelbach, H., Schmidt, H., & Mayer, B. (1998). The revised version of the Screen for Child Anxiety Related Emotional Disorders (SCARED-R): Factor structure in normal children. *Personality and Individual Differences*, *26*, 99–112.

Phelps, R.A., Brooker, R.J., & Buss, K.A. (2016). Toddlers' dysregulated fear predicts delta–beta coupling during preschool. *Developmental Cognitive Neuroscience*, *17*, 28–34.

Poole, K.L., Anaya, B., & Pérez-Edgar, K.E. (2020). Behavioral inhibition and EEG delta-beta correlation in early childhood: Comparing a between-subjects and within-subjects approach. *Biological Psychology*, *149*, 107785.

Poppelaars, E.S., Harrewijn, A., Westenberg, P.M., & van der Molen, M.J. (2018). Frontal delta-beta cross-frequency coupling in high and low social anxiety: An index of stress regulation? *Cognitive, Affective, & Behavioral Neuroscience*, *18*, 764–777.

Rubin, D.B. (1976). Inference and missing data. *Biometrika*, *63*, 581–592.

van Peer, J.M., Roelofs, K., & Spinhoven, P. (2008). Cortisol administration enhances the coupling of midfrontal delta and beta oscillations. *International Journal of Psychophysiology*, *67*, 144–150.

Wang, Y., Zhang, X., Huang, J., Zhu, M., Guan, Q., & Liu, C. (2013). Associations between EEG beta power abnormality and diagnosis in cognitive impairment post cerebral infarcts. *Journal of Molecular Neuroscience*, *49*, 632–638.

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