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# Theta oscillatory dynamics serving cognitive control index psychosocial distress in youth

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#### ABSTRACT

*Background:* Psychosocial distress among youth is a major public health issue characterized by disruptions in cognitive control processing. Using the National Institute of Mental Health's Research Domain Criteria (RDoC) framework, we quantified multidimensional neural oscillatory markers of psychosocial distress serving cognitive control in youth.

*Methods*: The sample consisted of 39 peri-adolescent participants who completed the NIH Toolbox Emotion Battery (NIHTB-EB) and the Eriksen flanker task during magnetoencephalography (MEG). A psychosocial distress index was computed with exploratory factor analysis using assessments from the NIHTB-EB. MEG data were analyzed in the time-frequency domain and peak voxels from oscillatory maps depicting the neural cognitive interference effect were extracted for voxel time series analyses to identify spontaneous and oscillatory aberrations in dynamics serving cognitive control as a function of psychosocial distress. Further, we quantified the relationship between psychosocial distress and dynamic functional connectivity between regions supporting cognitive control.

*Results*: The continuous psychosocial distress index was strongly associated with validated measures of pediatric psychopathology. Theta-band neural cognitive interference was identified in the left dorsolateral prefrontal cortex (dIPFC) and middle cingulate cortex (MCC). Time series analyses of these regions indicated that greater psychosocial distress was associated with elevated spontaneous activity in both the dIPFC and MCC and blunted theta oscillations in the MCC. Finally, we found that stronger phase coherence between the dIPFC and MCC was associated with greater psychosocial distress.

*Conclusions*: Greater psychosocial distress was marked by alterations in spontaneous and oscillatory theta activity serving cognitive control, along with hyperconnectivity between the dIPFC and MCC.

#### 1. Introduction

Psychosocial distress refers to the emotional and psychological suffering experienced by individuals in response to various social and psychological stressors such as isolation, bullying, trauma, major life changes, and chronic stress (Lupien et al., 2009, 2017). Psychosocial

distress is ubiquitous and predisposes individuals to a myriad of mental health disorders, half of which start by 14 years of age (United Nations Office on Drugs and Crime, 2017). Addressing mental health complications among youth has become an increasingly urgent public health issue (Jones et al., 2022; Bitsko et al., 2022). In fact, in 2019, 36.7% of high school students across the United States reported experiencing

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persistent feelings of sadness or hopelessness, and 18.8% reported having seriously considered attempting suicide, compared to 26.1% and 13.8% reported in 2009, respectively (Youth Risk Behavior Survey Data, 2019). Given these soaring prevalence rates, understanding the neurophysiological precursors to psychiatric disorders during this vulnerable stage of neural development is crucial. The National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) framework may prove to be a promising avenue for advancing the field's current understanding of psychosocial distress by integrating cognitive, social, emotional, behavioral, and neurophysiological measures to conceptualize the impacts of stress on mental health in youth (Glenn et al., 2017, 2018; Stewart et al., 2019).

There are many factors that have been associated with greater psychosocial distress in youth including aggression, anxiety, depression, social withdrawal, poor peer relationships, and executive dysfunction (van Heeringen et al., 2014; O'Connor and Nock, 2014). Executive function refers to the partially independent, top-down cognitive processes involved in behavioral and emotional control, cognition, and supports goal-directed behavior (Nigg, 2017). One component of executive function is cognitive control, which supports conflict resolution and aids in detecting salient stimuli through several distributed networks in the brain (e.g., frontoparietal, salience; Dosenbach et al., 2006; Halassa and Kastner, 2017). Identifying aberrations in the neural circuits serving cognitive control in youth is especially crucial to predicting and mitigating psychosocial distress, given its central role in regulating one's thoughts, behaviors, and emotions. Cognitive control has been repeatedly associated with activation of the PFC and its interaction with other brain areas (e.g., reward and motor regions; Merrick et al., 2017). The PFC is central to executing higher-order cognitive processes and goal-directed behavior (Cavanagh and Frank, 2014) and neuroimaging studies have provided evidence of dysfunction in the PFC, anterior cingulate, and other neural regions serving cognitive control in youth with affective disorders such as depression (Zhang et al., 2022).

Given the important role that cognitive control processes play in a wide range of complex emotional, psychological, and cognitive functions, it is critical to understand how deviations in these processes may scale with impaired concentration and decision-making abilities, difficulties in inhibiting inappropriate responses, or challenges in managing negative emotions during stressful situations. Chronic stress, especially during childhood and adolescence, has been shown to perturb the intricate neural networks underlying higher-order cognition by interfering with the modular segregation of the association cortices, which are important for synchronous activity and the integration of information (Numssen et al., 2021; Bzdok et al., 2016; Bzdok et al., 2012). Such stress-induced disruptions are thought to be driven by glucocorticoid stress hormones, which are known to regulate critical periods of synaptic pruning and can drive excessive pruning and an irreversible loss of synapses (Lupien et al., 2009; Gabard-Durnam and McLaughlin, 2020; Sydnor et al., 2021; Liston and Gan, 2011; Liston et al., 2013). Thus, youth experiencing high levels of stress during the acquisition of cognitive control skills early in development and into the maturational fine-tuning during adolescence and early adulthood may be particularly susceptible to disruptions in cognitive control and thereby difficulties in emotional regulation and the potential emergence of psychopathology (Stewart et al., 2017; Merrick et al., 2017; Dube et al., 2001; Gloger et al., 2021).

The Eriksen flanker task (Eriksen and Eriksen, 1974) is a classic cognitive control paradigm that probes one's efficiency in ignoring task-irrelevant information (Eriksen and Eriksen, 1974; Eriksen, 1995). In the arrow-based version of the flanker task, participants are presented with a target stimulus that is surrounded by non-target (i.e., "flanker") stimuli and instructed to respond to the centrally presented target and ignore the flanking items, which can either point in the same (i.e., congruent) or opposite direction (i.e., incongruent) as the target stimulus. Studies using the flanker task during electroencephalography (EEG) and magnetoencephalography (MEG) have identified an activated network of regions including the prefrontal cortex (PFC), anterior

cingulate cortex (ACC), and superior parietal lobule, and these studies have shown stronger frontal theta and parieto-occipital alpha oscillations during incongruent trials relative to congruent trials in children and adults (Cavanagh and Frank, 2014; Cavanagh et al., 2009; Cohen and Cavanagh, 2011; Cohen et al., 2014; Gulbinaite et al., 2014; McDermott et al., 2017; Nigbur et al., 2011, 2012; Padrão et al., 2015; Pastötter et al., 2013; Taylor et al., 2021; Lew et al., 2018, 2020; Wiesman and Wilson, 2020b; Embury et al., 2019).

The flanker task has been shown to be a developmentally sensitive measure of interference control, with young children displaying little to no susceptibility to cognitive interference, though the impact of such interference increasingly progresses during late childhood into adolescence and adulthood (McDermott et al., 2007, 2017; Taylor et al., 2021; Gavin et al., 2019; Segalowitz and Davies, 2004; Wiesman et al., 2020). The flanker paradigm has also been implemented in an array of psychiatric populations across the lifespan, though results have been mixed among youth with depression, suicidal thoughts and behaviors, and among those who have been exposed to trauma (van der Meere et al., 2011; Han et al., 2012; Zelazny et al., 2019; Sommerfeldt et al., 2016; Park et al., 2014; Tibu et al., 2016; Loman et al., 2013; Bruce et al., 2013). Further, it remains unclear whether indices of psychosocial distress are a sensitive measure of early disturbances in interference control, and if so, how elevations in psychosocial distress scale with deviations in the spontaneous and neural oscillatory dynamics serving cognitive control among a pre-clinical sample of typically developing youth. Thus, the goal of the present study was to identify neural oscillatory markers of psychosocial distress during late childhood and adolescence using an established cognitive control paradigm and a dynamic functional mapping approach with MEG. First, we mapped the neural flanker interference effect and examined the impact of higher psychosocial distress on the spontaneous and oscillatory dynamics serving cognitive control. Second, we hypothesized that youth experiencing greater psychosocial distress would have elevated spontaneous activity and blunted oscillatory activity in the prefrontal and cingulate cortices and would exhibit hyperconnectivity between these regions relative to those with lower psychosocial distress.

#### 2. Methods

#### 2.1. Participants

A total of 40 youth between the ages of 10- and 16-years-old (Mean = 13.53 years, SD = 1.93; 14 assigned female at birth, 26 assigned male at birth) completed a flanker task during MEG and all elements of the NIH Toolbox Emotion Battery. Participants were recruited from the local community through advertisements, posted flyers, and community events. Flyers were also distributed through local elementary and middle schools. The racial and ethnic distribution of participants was monitored to ensure they reflected the demographics of the surrounding metropolitan area. Exclusionary criteria included any medical illness affecting CNS function, diagnosed neurological or psychiatric disorder, history of head trauma, current substance use, any medication known to affect CNS function, and the standard exclusionary criteria for MEG acquisition (e.g., dental braces, battery operated implants, and/or any type of ferromagnetic implanted material). Parents of participants signed informed consent forms, and the child and adolescent participants signed assent forms before proceeding with the study. All procedures were approved by the local Institutional Review Board and were in accordance with the Declaration of Helsinki.

#### 2.2. Psychosocial distress index

To index psychosocial distress in the present sample, we conducted an exploratory factor analysis (EFA) using the maximum likelihood extraction method with a varimax rotation to define a latent variable of psychosocial distress using a compilation of metrics that are known to contribute to barriers to mental health and wellbeing (van Heeringen et al., 2014; O'Connor and Nock, 2014). We used fully-corrected T-scores (corrected for age and sex) from 11 fixed form measurements included in the NIH Toolbox Emotion Battery: Anger, Fear, Sadness, Loneliness, Perceived Hostility, Perceived Rejection, Positive Affect, General Life Satisfaction, Emotional Support, Friendship, and Self-Efficacy. Six of the 11 measures including Anger, Fear, Sadness, Loneliness, Perceived Hostility, and Perceived Rejection had moderate-to-high factor loadings ( $\lambda > 0.50$ ) and converged onto one factor that had an eigenvalue of 3.84, which accounted for 64.06% of the variance (Fig. 1). This model was used to define a continuous latent variable for which a psychosocial distress index score was extracted using the regression method per participant, which uses the standardized (i.e., z-scores) observed values for each item included in the final factor and weighted by a regression coefficient (DiStefano et al., 2009). Missing values were excluded using listwise deletion. Modeling was completed using SPSS (Version 25). Higher values were indicative of greater psychosocial distress.

#### 2.3. Eriksen flanker experimental paradigm

Participants completed a 14-min arrow-based flanker task (McDermott et al., 2017; Taylor et al., 2021; Lew et al., 2018; Wiesman and Wilson, 2020b; Embury et al., 2019; Schantell et al., 2022). Briefly, each trial began with a fixation cross presented in the center of the screen for a jittered duration of 1450–1550 ms (Fig. 2A). Then, five centrally-presented arrows were presented for 2500 ms. The center arrow was either congruent (i.e., pointing the same direction as the flanking arrows), or incongruent (i.e., pointing the opposite direction of the flanking arrows). There were 200 pseudorandomized trials, equally split between congruent and incongruent conditions. Participants were instructed to press a button with their right index finger if the center arrow pointed left, or with their right middle finger if the center arrow pointed right. Reaction time and accuracy were collected and used for behavioral analysis.

#### 2.4. MEG data acquisition

MEG recordings were conducted in a one-layer magnetically shielded



**Fig. 1. Modeling of the psychosocial distress index.** The factors contributing to the psychosocial distress index were derived from an exploratory factor analysis (EFA) and included fully-corrected T-scores (i.e., age- and sex-corrected) of the following six measures of the NIH Toolbox Emotional Battery with their corresponding factor loadings: Sadness, Fear, Loneliness, Anger, Perceived Hostility, and Perceived Rejection.

room with active shielding engaged. Neuromagnetic responses were acquired with an Elekta/MEGIN MEG system with 306 magnetic sensors (204 planar gradiometers, 102 magnetometers; Helsinki, Finland) using a bandwidth of 0.1–330 Hz, sampled continuously at 1 kHz. Each MEG dataset was individually corrected for head motion, and noise reduction was applied using the signal space separation method with a temporal extension (tSSS; correlation limit: 0.950; correlation window duration: 6 s; Taulu and Simola, 2006). Only data from the gradiometers were used for further analysis.

#### 2.5. MEG coregistration and structural MRI processing

Prior to MEG recording, four coils were attached to the participant's head and localized with the three fiducial points and scalp surface using a 3-D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). Once the participant was positioned for MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each coil, thus inducing a measurable magnetic field and thereby allowing each coil to be localized in reference to the MEG sensor array throughout the recording session. Since coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system, each participant's MEG data were coregistered with their individual structural T1-weighted MRI data prior to source space analyses using BESA MRI (Version 2.1). Following source analysis (i.e., beamforming), each participant's functional images were also transformed into standardized space using the transform that was previously applied to the structural MRI volume and spatially resampled.

#### 2.6. MEG time-frequency transformation and statistics

Cardiac and ocular artifacts were removed from the data using signal-space projection (SSP), which was accounted for during source reconstruction (Uusitalo and Ilmoniemi, 1997). The resulting artifact-corrected data were then bandpass filtered from 0.5 to 150 Hz, notch filtered at 60 Hz, and divided into 2000 ms epochs (-500 to 1500 ms) with the baseline extending from -450 to -50 ms prior to the onset of the flanker stimulus (i.e., time 0.0 s). Epochs containing artifacts were rejected based on a fixed threshold method that was set per participant and supplemented with visual inspection. Briefly, in MEG, the raw signal amplitude is strongly affected by the distance between the brain and the MEG sensor array, as the magnetic field strength falls off sharply as the distance from the current source (i.e., brain) increases. To account for this source of variance across participants, as well as other sources of variance, we used an individualized threshold based on the signal distribution for both amplitude and gradient to reject artifacts. An average of 168.31 (SD = 11.58) segments were retained for further analyses, and there were no significant differences in the number of segments retained by condition (t = 0.15, p = .880, Congruent: Mean = 84.09, SD = 6.30, Incongruent: Mean = 84.22, SD = 6.17). Finally, psychosocial distress was not significantly correlated with the total number of epochs retained after artifact rejection (r = -0.04, p = .823).

Artifact-free epochs were transformed into the time-frequency domain using complex demodulation (Kovach and Gander, 2016; Papp and Ktonas, 1977), and the resulting spectral power estimations per sensor were averaged across trials to generate time-frequency plots of mean spectral density. These sensor-level data were then normalized with respect to the mean baseline power (i.e., -450 to -50 ms). Time-frequency windows (1 Hz, 50 ms resolution) for subsequent source imaging were identified using a stringent two-stage statistical analysis involving paired-samples *t*-tests against baseline across all participants and both conditions in stage one. Pixels that were significant at the *p* < .005 level were then clustered with spectrally and temporally neighboring pixels that were also above the threshold and a cluster value was derived by summing the *t*-values of all pixels in the cluster. To control for Type 1 error, these clusters were then subjected to nonparametric



**Fig. 2. Experimental paradigm and behavioral results.** (A) An illustration of the classic Eriksen Flanker Arrow paradigm. Each trial had a fixation period lasting on average 1500 ms (variable ISI: 1450–1550 ms) and a stimulus-presentation period lasting 2500 ms, which consisted of one of the four options displayed. (B) Behavioral results from the flanker task. (Left) Reaction time (in ms) is displayed on the *y*-axis by condition. There was a main effect of condition (p < .001), such that participants responded faster for congruent trials relative to incongruent trials. (Right) Further, higher psychosocial distress scores were also associated with slower reaction times across both conditions (p = .002). \*p < .01, \*\*p < .001.

permutation testing in stage two using 10,000 permutations per comparison and a corrected *p*-value of .05 (Proskovec et al., 2018; Wiesman and Wilson, 2020a,b).

#### 2.7. MEG source imaging and statistics

Cortical activity was imaged through an extension of the linearly constrained minimum variance vector beamformer (Gross et al., 2001; Hillebrand et al., 2005; Van Veen et al., 1997), which employs spatial filters in the frequency domain to calculate source power for the entire brain volume. The single images were derived from the cross-spectral densities of all combinations of MEG gradiometers averaged over the time-frequency range of interest, and the solution of the forward problem for each location on a grid specified by input voxel space. This use of the cross-spectral densities is often referred to as the dynamic imaging of coherent sources (DICS) beamformer (Gross et al., 2001). Following convention, we computed noise-normalized, source power per voxel in each participant using active (i.e., task) and passive (i.e., baseline) periods of equal duration and bandwidth (Hillebrand et al., 2005). Such images are typically referred to as pseudo-t maps, with units (i.e., pseudo-t) that reflect noise-normalized power differences (i.e., active vs. passive) per voxel. MEG preprocessing and imaging were completed using BESA version 6.1. Images were derived for all correct trials combined, and separately for congruent and incongruent conditions.

Normalized source power was computed for the selected timefrequency bands per participant at  $4.0 \times 4.0 \times 4.0$  mm resolution. The resulting 3D maps of brain activity were averaged across participants to assess the origin of oscillatory responses identified through the sensor-level analysis across each condition (i.e., congruent and incongruent) both separately and combined. To assess for neural oscillatory interference effects serving cognitive control processing at the whole-brain level, voxel-wise paired samples *t*-tests were conducted using the spectrally specific whole-brain maps by condition (i.e., congruent and incongruent) per participant and time-frequency window. To control for Type 1 error, maps were thresholded at p < .005 to define potentially significant clusters and were subsequently subjected to whole-brain nonparametric cluster-based permutation testing in BESA Statistics (Version 2.1), similar to that performed on the sensor-level spectrograms with at least 10,000 permutations per comparison and a final corrected *p*-value of .05.

#### 2.8. Peak voxel time series

Virtual sensor data were computed from the peak voxel locations of the statistical parametric maps by applying the sensor-weighting matrix derived through the forward computation to the preprocessed signal vector, which yielded two orthogonal time series. Next, these virtual sensor data were decomposed into time-frequency space and vector summed to derive a single temporal envelope of the signal corresponding to the frequency window identified through the MEG sensorlevel statistical analyses. This resulted in absolute and relative (baseline-normalized) power time series for each peak voxel per participant. Absolute power was used to examine relationships between psychosocial distress and spontaneous power during the baseline period (-450 to -50 ms), and relative power was used to assess neural oscillations serving behavioral performance. Cluster-based permutation testing (10,000 permutations) was then used to test for associations with psychosocial distress while accounting for multiple comparisons. Mean power was averaged across the significant time windows and correlated with the psychosocial distress index to evaluate the sensitivity of neural

oscillatory markers of pre-clinical decrements in mental health.

#### 2.9. Functional connectivity analyses

To probe dynamic functional connectivity between the significant cortical regions derived from the neural interference maps identified in our main analyses, phase coherence was computed within the same time-frequency windows derived from our sensor-level statistical analyses. Specifically, we estimated the phase-locking value (PLV; Lachaux et al., 1999) between the active brain regions. The PLV reflects the intertrial variability of the phase relationship between pairs of brain regions as a function of time. Values close to one indicate strong synchronicity (i.e., phase locking) between the two brain regions within the specific time window across trials, whereas values close to zero indicate substantial phase variation between the two signals and, thus, weak synchronicity (connectivity) between the two regions. To investigate the impact of psychosocial distress on the connectivity between critical regions supporting the suppression of cognitive control, we extracted the mean PLV per participant across congruent and incongruent trials separately and together within the time-frequency windows used for beamforming, which were then correlated with the psychosocial distress index, controlling for source power (Arif et al., 2021).

#### 2.10. Data availability policy

Requests for data can be fulfilled via the corresponding author. Deidentified data have been made available to the public through the Collaborative Informatics and Neuroimaging Suite (COINS; http://coi ns.trendscenter.org) database.

#### 3. Results

#### 3.1. Participant characteristics

Of the 40 participants included for analysis, one participant was excluded during initial preprocessing for excessive muscle artifact during the MEG recording. Thus, the final sample consisted of 39 participants (*Mean* = 13.29 years, SD = 1.58; 14 females; Table 1).

#### 3.2. Psychosocial distress index

Participants had a mean psychosocial distress index score of 0.03 (SD = 0.96; Table 1), and the psychosocial distress index had excellent construct validity (ICC<sub>Consistency</sub> = 0.89 [95% CI: 0.79–0.94], ICC<sub>Absolute</sub>

#### Table 1

Participant characteristics and indices of psychopathology.

	Full Sample ( $n = 39$ )
Sex (% Female)	35.9%
Age (years)	13.92 (10.61–16.99)
Socioeconomic Status <sup>a</sup>	48.61 (17.50-64.67)
Psychosocial Distress Index	0.03 (-1.53-2.25)
Mood and Feelings Questionnaire Score	21.44 (5–26);
Trauma History Profile, number of events	1.84 (0–7)
Anxiety <sup>b</sup>	5.44 (1–15);
Depression <sup>b</sup>	4.00 (0-16)
Anger <sup>b</sup>	5.26 (0-16)
Posttraumatic Stress <sup>b</sup>	7.21 (0-19)
Dissociation <sup>b</sup>	6.31 (0-20)
Dissociation – Overt <sup>b</sup>	4.38 (0-15)
Dissociation – Fantasy <sup>b</sup>	2.08 (0-6)

*Notes.* Means and ranges are displayed for the full sample. Higher scores on the psychosocial distress index, Trauma History Profile, and Trauma Symptom Checklist for Children (TSCC) are indicative of greater symptomatology, while lower scores on the Mood and Feelings Questionnaire indicate greater mood symptomatology.

<sup>a</sup> Barratt Simplified Measure of Social Status.

<sup>b</sup> Trauma Symptom Checklist for Children (TSCC).

= 0.89 [95% CI: 0.79–0.94]) and good-to-excellent construct reliability as a measure of internal consistency ( $\omega$  = 0.88 [95% CI: 0.75–0.94]; Supplementary Table 1). This index was significantly associated with previously validated measures of child and adolescent psychopathology, including subscales of the Child Behavior Checklist (CBCL), Trauma Symptom Checklist for Children (TSCC), and Mood and Feelings Questionnaire (MFQ; Supplementary Table 2). Additionally, the item from the CBCL, "Talks about hurting self" was significantly associated with a higher psychosocial distress score (F = 6.17, p = .018), and the item, "Deliberately harms self" revealed a trend (F = 3.72, p = .062). See Fig. 1 for the psychosocial distress index factor loadings and Supplementary Table 3 for a breakdown of fully-corrected T-scores for each measure included in the factor analysis.

#### 3.3. Eriksen flanker task performance

Participants achieved a mean accuracy of 98.10% correct (SD = 3.78%) on congruent trials, and 96.90% correct (SD = 4.68%) on incongruent trials. A paired-samples *t*-test revealed that average reaction times for congruent (*Mean* = 633.54 ms, SD = 92.77) and incongruent trials (*Mean* = 666.00 ms, SD = 96.15) significantly differed, t = 6.99, p < .001. Thus, we observed the classic flanker effect whereby participants were slower during incongruent relative to congruent trials (*Mean* = 32.46 ms, SD = 28.99; Fig. 2B, left). Further, higher psychosocial distress was significantly associated with slower reaction times across both conditions (r = 0.43, p = .007; Fig. 2B, right).

#### 3.4. Neural oscillatory responses

Sensor-level analyses collapsed across congruent and incongruent conditions revealed two distinct time-frequency windows in all participants. Specifically, significant increases in power relative to the baseline period were observed in the early theta (3–6 Hz) band between 100 and 450 ms (p < .05, corrected; Fig. 3). In addition, decreases in power relative to the baseline period were observed in the alpha/beta (9–18 Hz) band from 200 to 600 ms (p < .05, corrected; Supplemental Fig. 1). These windows were imaged separately for each condition (i.e., congruent and incongruent) per participant. Paired samples *t*-tests comparing incongruent and congruent maps voxel-by-voxel were then conducted for each time-frequency window of interest to identify regions exhibiting significant neural flanker interference effects.

There were significant increases in cortical theta activity during incongruent trials relative to congruent trials (p < .001, corrected; Fig. 3, bottom right). Specifically, there was stronger oscillatory theta power within the left mid-cingulate cortex (MCC) and in the left dorsolateral prefrontal cortex (dlPFC) during incongruent relative to congruent trials. There was also stronger (i.e., more negative) alpha/beta power in the left cerebellum during incongruent relative to congruent trials (Supplemental Fig. 1, bottom right).

### 3.5. Relationships between psychosocial distress and spontaneous and oscillatory activity

Next, we extracted voxel times series data from the significant neural interference peaks. As described in the methods, we computed the temporal envelope of the signal and then estimated spontaneous power during the baseline period (i.e., -450 to -50 ms). Pearson correlations with psychosocial distress were then conducted on these spontaneous power indices, which revealed that greater psychosocial distress was associated with stronger (i.e., less optimal) spontaneous theta power in the left dIPFC (r = 0.43, p = .006, corrected; Fig. 4A and B) and in the left MCC (r = 0.42, p = .008, corrected; Fig. 5A and B). In contrast, psychosocial distress and stimulus induced (relative) oscillatory theta power in the left dIPFC were not significantly associated (Fig. 4C and D), though there was a strong relationship in the left MCC, such that higher psychosocial distress was associated with weaker (i.e., less optimal)



**Fig. 3.** Neural theta responses to the flanker interference task. (Top): Grand-averaged time-frequency spectrogram of a representative MEG sensor exhibiting the significant oscillatory theta (3–6 Hz, 100–450 ms) response. The spectrogram displays frequency (Hz) on the *y*-axis and time (ms) on the *x*-axis. Signal power data are expressed as a percent difference from the baseline period, with color legends shown to the right. (Bottom): Grand-averaged beamformer images (pseudo-*t*) across all participants for the theta time-frequency component for congruent and incongruent conditions separately, and the results of the paired-samples *t*-test showing regions with significant theta interference activity (i.e., stronger in the incongruent condition; p < .05, corrected). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 4. Psychosocial distress is associated with elevated spontaneous theta activity in the left dorsolateral prefrontal cortex.** Neural theta interference effects were observed in the left dorsolateral prefrontal cortices (dlPFC; p < .001, corrected). (A and B) Peak voxel time series were extracted from the dlPFC to estimate spontaneous theta power (nAm<sup>2</sup>) during the baseline period, which revealed that greater psychosocial distress was associated with elevated spontaneous theta activity (p = .006, corrected). However, psychosocial distress was not significantly associated with alterations in oscillatory theta activity across the active period in the dlPFC (C and D; p = .124). Note that a more stringent threshold was used on the functional 3D map (far right) to highlight the peak cluster in the theta flanker interference map. Data from participants in top and bottom quartiles of psychosocial distress were averaged together to visually depict differences in the spontaneous and oscillatory time series data. \*\*p = .006.



Fig. 5. Psychosocial distress is associated with elevated spontaneous and blunted oscillatory theta activity in the left middle cingulate cortex. Theta band neural interference effects were observed in the left middle cingulate cortex (MCC; p < .001, corrected). (A and B) Peak voxel time series were extracted from the MCC to estimate spontaneous theta power (nAm<sup>2</sup>) during the baseline period, which revealed that greater psychosocial distress was associated with elevated spontaneous theta activity (p = .008, corrected). Additionally, greater psychosocial distress was significantly associated with blunted oscillatory theta activity across the active period in the MCC (C and D; p = .002, corrected). Data from participants in top and bottom quartiles of psychosocial distress were averaged together to visually depict differences in the spontaneous and oscillatory time series data. \*\*p < .01.

oscillatory theta power during the active period (i.e., 200–650 ms; r = -0.48, p = .002, corrected; Fig. 5C and D). Of note, we did not find any significant relationships in spontaneous or oscillatory alpha/beta power in the left cerebellum with psychosocial distress (see Supplemental Fig. 1).

#### distress were evaluated using phase coherence between peak voxels in the left dlPFC and left MCC. Briefly, we averaged the PLV during the active period between the left dlPFC and left MCC per condition. We then looked at the continuous association between psychosocial distress and PLV and found that higher psychosocial distress was associated with greater PLV in the theta band between the left dlPFC and left MCC across both congruent and incongruent conditions, controlling for source power (r = 0.40, p = .017; Fig. 6).

#### 3.6. Dynamic functional connectivity

Alterations in functional connectivity as a function of psychosocial



Fig. 6. Psychosocial distress was associated with hyperconnectivity between the left dorsolateral prefrontal cortex and middle cingulate cortex. Theta phase coherence (i.e., phase locking) was computed as a measure of dynamic functional connectivity between the left dorsolateral prefrontal cortex (dIPFC) and middle cingulate cortex (MCC). Controlling for source power, higher psychosocial distress was associated with stronger theta phase coherence (i.e., hyper-connectivity) between the left dIPFC and left MCC (p = .017). \*p < .05.

#### 4. Discussion

#### 4.1. Key findings

The present study investigated the relationship between psychosocial distress and the neural oscillatory dynamics serving cognitive control in youth. Our key findings were that the neural flanker interference effect was reflected by stronger theta oscillations in the left dlPFC and left MCC. Moreover, we found that greater psychosocial distress was associated with abnormally elevated spontaneous theta activity in both the dlPFC and MCC, and theta oscillations in the MCC were significantly blunted with greater psychosocial distress. Finally, we found that those with greater psychosocial distress exhibited hyperconnectivity between the dlPFC and the MCC. Behaviorally, the participants performed well and showed the classic flanker effect in which they responded faster during congruent trials relative to incongruent trials (McDermott et al., 2017; Taylor et al., 2021; Lew et al., 2018; Wiesman and Wilson, 2020b; Embury et al., 2019). Reaction times overall were sensitive to pre-clinical alterations in mental health as greater psychosocial distress was associated with slower response times.

#### 4.2. Neural flanker effect

We observed stronger theta oscillations in the dlPFC and MCC during incongruent relative to congruent trials, which coincides with previous findings in adult and pediatric populations (Miller and Cohen, 2001; McDermott et al., 2017; Taylor et al., 2021; Lew et al., 2018, 2020; Embury et al., 2019; Schantell et al., 2022; Driver and Frackowiak, 2001; Jiang et al., 2017; Mazaheri et al., 2014; Saenz et al., 2002; Ochsner and Gross, 2005; Ochsner et al., 2009). The dlPFC has been frequently implicated in higher-order cognitive processes (Amso and Scerif, 2015; Couperus, 2011; Pozuelos et al., 2014), and the MCC has been linked to performance monitoring and conflict signaling (McDermott et al., 2017; Botvinick et al., 2004; Danckert et al., 2000). Theta rhythms in these regions have been shown to be essential for top-down modulation of cognitive control processes (Miller and Cohen, 2001; Cavanagh and Frank, 2014; Ochsner and Gross, 2005; Ochsner et al., 2009; Petersen and Posner, 2012; Rihs et al., 2007; Newman et al., 2015; Milham and Banich, 2005; Sammer et al., 2007), and increases in theta power are crucial for resolving cognitive conflict and errors in contexts of uncertainty (Cavanagh and Frank, 2014; Nigbur et al., 2011; Cohen and Donner, 2013; Hanslmayr et al., 2008; Trujillo and Allen, 2007; Cavanagh and Shackman, 2015). In particular, theta oscillations in the MCC are thought to be transiently active through reactive control mechanisms, whereas theta oscillations in the dlPFC are believed to support the maintenance of information trial-by-trial (Jiang et al., 2015). A collection of studies have shown that dysfunction in conflict monitoring is associated with a multitude of psychiatric and neurodegenerative disorders including depression (Georgiadi et al., 2011), anxiety (Cavanagh and Shackman, 2015; Aarts and Pourtois, 2010; Cavanagh et al., 2017; Weinberg et al., 2010; Inzlicht et al., 2015), attention-deficit/hyperactivity disorder (Van De Voorde et al., 2010), obsessive compulsive disorder (Endrass et al., 2008; Min et al., 2011; Abramovitch et al., 2021), substance use disorders (Hampson et al., 2011), schizophrenia (Perez et al., 2012), and dementia (Bettcher et al., 2008).

### 4.3. Impact of psychosocial distress on spontaneous and oscillatory activity

One of our key findings was that greater psychosocial distress was associated with sharply elevated spontaneous theta activity in the dlPFC and MCC, and that stimulus-induced oscillatory theta activity in the MCC was blunted (i.e., less optimal) as a function of greater psychosocial distress. These findings are consistent with an extensive body of work demonstrating reduced activity in the MCC in those with major

depression (Wang et al., 2008a, 2008b; Fales et al., 2008; Pizzagalli, 2011). Further, previous studies have extensively linked elevations in spontaneous activity with neuropathology, as stronger spontaneous activity has been reported in mood disorders (Zhang et al., 2022; Tian et al., 2021), aging populations (Heinrichs et al., 2016; Spooner et al., 2019), neuroHIV (Lew et al., 2018; Schantell et al., 2022; Wiesman et al., 2018; Casagrande et al., 2021), and among those with cognitive impairment (Lew et al., 2018; Wiesman et al., 2018). Intriguingly, elevated spontaneous cortical activity has also been shown to directly modulate stimulus induced oscillatory power, possibly by way of intracortical inhibition (Heinrichs et al., 2016; Schmidt et al., 2010; Rossiter et al., 2014; Wilson et al., 2014). Higher-order cognitive processes rely on synaptic activity in the PFC (Goldman-Rakic, 1995, 1996), which receives excitatory input from a multitude of sources including intrinsic, association, and callosal pyramidal axons, along with thalamocortical afferents (Paspalas, 2005). Executive dysfunction is thought to arise from dysregulated dopaminergic signaling resulting from an excitatory/inhibitory (E/I) imbalance due to a reduction in GABAergic inhibitory inputs in the PFC, thus leading to diminished synchrony of pyramidal cell firing between neurons in the hippocampus and PFC and alterations in dynamic functional connectivity (Paspalas, 2005; Skosnik and Cortes-Briones, 2016), which has been implicated in many psychiatric disorders (Uhlhaas and Singer, 2006, 2012).

## 4.4. Psychosocial distress and dlPFC-MCC dynamic functional connectivity

Finally, in quantifying the degree of phase locking between the dlPFC and MCC as a function of psychosocial distress, we found that greater psychosocial distress was associated with hyperconnectivity between the dIPFC and MCC, which has been described extensively in the literature across many psychiatric disorders in which emotional dysregulation is stereotypic (Zhang et al., 2022; Sheline et al., 2010; Rogers et al., 2004; Davidson et al., 2002; Fitzgerald et al., 2006; Siegle et al., 2007; Vasic et al., 2009; Schlösser et al., 2008; Wang et al., 2016, 2020; Ye et al., 2012; Lei et al., 2019). Hyperconnectivity between these regions may result in higher clinical symptomatology such as rumination, difficulty inhibiting negative self-introspection, and emotion dysregulation (Pizzagalli, 2011; Comte et al., 2015), which is consistent with the present results. Theta activity in the MCC is believed to signal the need to rapidly tailor goal-directed behavior to facilitate information transfer to other regions by phase locking rhythmic activity, thus creating temporal windows that establish phase synchrony across task-relevant networks for efficient information transmission (Cavanagh and Frank, 2014; McLoughlin et al., 2022; Cavanagh et al., 2012; Wang, 2010; Fries, 2005; Wang et al., 2005; Womelsdorf et al., 2010; Varela et al., 2001). Specifically, theta phase coherence between the dlPFC and MCC has been shown to be crucial for optimal cognitive control processing by supporting on-line adaptations of task-related behavior, and stress-related perturbations to this dynamic loop may result in cognitive inflexibility and a failure to adequately recruit neural resources for successful top-down cognitive control processing (Cavanagh and Frank, 2014; Cavanagh et al., 2009; Ridderinkhof et al., 2004; Reinhart, 2017).

#### 5. Conclusions

We identified theta flanker interference-related neural oscillations in the dIPFC and MCC serving cognitive control. Subsequent analyses examining the relationship between psychosocial distress and spontaneous and oscillatory theta activity in these regions revealed greater disturbances in neural oscillatory dynamics with greater psychosocial distress, pointing to potential E/I imbalances during a developmentally critical period for establishing cortical oscillatory patterns. Stronger dynamic functional connectivity between the dIPFC and MCC was also linked to greater psychosocial distress, which may suggest a disturbance in the complex systems serving cognitive control. Together, these neural indices may be sensitive measures of pre-clinical alterations in mental health functioning pointing to psychosocial distress among youth. Future studies should investigate targeted pharmacological and neuromodulatory techniques designed to modulate stress-related impairments in the theta dynamics underlying vulnerabilities in proactive and reactive control, which are common among several psychiatric disorders (McLoughlin et al., 2022; Fox et al., 2021; Birk et al., 2018). For example, neuromodulatory methods such as transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation (TMS) may be applied to aid in decoupling the hyperactive connectivity between the MCC and dlPFC (Fox et al., 2012; Liston et al., 2014; Noda et al., 2017; Takeuchi and Berényi, 2020). In terms of pharmacological interventions, drugs such as ketamine have been shown to be effective in reducing delta/theta activity and increasing gamma activity, and such alterations in neural rhythms scaled with marked improvements in mood symptomatology (Berman et al., 2000; Hong et al., 2010).

Finally, though this study implemented a highly novel approach to investigating pre-clinical alterations in the oscillatory theta dynamics underlying decrements in cognitive control, there are some factors we were unable to assess that should be explored in future studies. In particular, future work should employ intensive longitudinal designs to better elucidate the putative role of stress on the interplay between complex dynamical systems, including neural oscillations and inflammatory responses to map the precise causal mechanisms potentiating the emergence of psychopathology in youth, thus capturing the full dynamic range of these patterns to provide a better understanding of the contributions of certain symptoms, their duration, and their chronicity that confer clinically meaningful deviations. Such dimensional approaches to quantifying the oscillatory dynamics serving cognitive control across a spectrum of psychosocial distress can inform and potentially guide evidence-based interventions that may effectively prevent and ameliorate suffering associated with stress-related psychopathology.

#### CRediT authorship contribution statement

Mikki Schantell: Methodology, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. Brittany K. Taylor: Methodology, Formal analysis, Data curation, Writing - review & editing. Amirsalar Mansouri: Formal analysis, Writing - review & editing, Visualization. Yasra Arif: Formal analysis, Writing - review & editing. Anna T. Coutant: Investigation, Data curation, Project administration. Danielle L. Rice: Investigation, Data curation, Project administration. Yu-Ping Wang: Conceptualization, Funding acquisition. Vince D. Calhoun: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition. Julia M. Stephen: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition. Tony W. Wilson: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition.

#### Declaration of competing interest

The authors report no biomedical financial interests or potential conflicts of interest.

#### Data availability

Data will be made available upon request.

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#### Appendix A. Supplementary data

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