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Sleep Spindle Density is Associated with Worry in Children with Generalized Anxiety Disorder and Healthy Controls

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Abstract

Background: Childhood generalized anxiety disorder (GAD), characterized by uncontrollable worry, is associated with long-term psychopathology risk, yet understanding of developmental trajectories is limited. Despite common complaints about sleep, ‘macro’ sleep abnormalities have not been identified. Emerging findings suggest micro-architectural features of sleep, including sleep spindles, differentiate various psychiatric populations. The current study investigated sleep spindle density during non-rapid eye movement (NREM) sleep among youth with GAD and healthy controls, including relationships with anxiety, worry, global functioning, and subjective sleep quality.

Methods: 58 pre-pubertal children, $n=26$ with GAD and $n=32$ matched healthy controls, aged 7–11 years ($M=8.86$, $SD=1.47$), completed diagnostic assessments and a week of actigraphy monitoring prior to a night of polysomnography (PSG) either at home or in a sleep laboratory. NREM spindle activity was detected in frontal and central regions.

Results: Sleep spindle activity did not differ based on diagnostic group or sex. Sleep spindles were unassociated with anxiety and sleep quality but showed a significant positive association with worry in all youth. Among youth with GAD, global functioning was negatively associated with spindle density in frontal regions during NREM stage 3. Spindle density was significantly greater during in-lab compared to at-home PSG.

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Contributors:

Jessica Meers completed statistical analyses and wrote the first draft of the manuscript.

Raffaele Ferri and Oliviero Bruni provided guidance, completed automated spindle analyses, and edited the final manuscript.

Candice Alfano designed the study and wrote the protocol, assisted with statistical analyses, and edited the manuscript.

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Conflicts of Interest:

Jessica Meers, Raffaele Ferri, Oliviero Bruni, and Candice Alfano have no conflicts of interest to report.

Institutional Review Board:

All study procedures were approved by institutional review boards at the University of Houston and Children's National Medical Center.

Limitations: The small sample size and reliance on only one night of PSG necessitate additional studies.

Conclusions: The identified link between spindle activity and worry in pre-pubertal children highlights a need for investigations on transdiagnostic features of child psychopathology rather than specific disorders. Longitudinal studies are needed to explore spindle characteristics and affective risk across development.

Keywords

Generalized anxiety; Sleep spindles; Worry; Children; Development

Introduction

Youth with psychiatric disorders frequently complain of poor sleep (Alfano and Gamble, 2009), especially those with generalized anxiety disorder (GAD). GAD is fundamentally characterized by pervasive, uncontrollable worry across various domains that results in physical complaints and functional impairments (Alfano, 2012; Beidel and Alfano, 2011). A majority of children with GAD also report sleep-related difficulties including prolonged sleep onset and increased daytime sleepiness (Alfano et al., 2010, 2007). Numerous examinations of objective sleep characteristics nonetheless provide little evidence of sleep abnormalities in this population, with the exception of mildly prolonged sleep onset (Alfano, 2018). Researchers have therefore called for investigation into more ‘micro’ aspects of sleep among clinically-anxious youth to better elucidate the nature of perceived poor sleep quality and to potentially identify neurophysiologic markers of pre-pubertal anxiety disorders and long-term outcomes (Alfano et al., 2018; McMakin and Alfano, 2015).

There is increasing evidence that micro-architectural features of sleep underlie differences in cognitive and emotional processing in both healthy and psychiatric populations. For instance, Prehn-Kristensen et al. (2013) investigated sleep-dependent consolidation of emotional memory in children with and without ADHD, finding deficits in emotional memory in the ADHD group correlated negatively with frontal EEG activity (slow oscillations) during sleep (Prehn-Kristensen et al., 2013). In a follow-up study, the same group showed the application of transcranial oscillatory direct current stimulation during slow wave sleep improved sleep-dependent consolidation of declarative memory in the children with ADHD (Prehn-Kristensen et al., 2014). Examinations of more micro aspects of sleep might therefore provide understanding of sleep-based mechanisms to be leveraged in the treatment of child psychopathology.

Sleep spindles, defined as short bursts of cortical activity in the ~12–15 Hz frequency range, represent a micro feature of sleep increasingly linked with various forms of psychopathology. A hallmark feature of non-REM (NREM) stage 2 sleep (though also found in NREM stage 3), spindles are generated in thalamocortical circuits and serve to aid in the synchronization of information from limbic structures to the cortex (Astori et al., 2013; De Gennaro and Ferrara, 2003). Spindle activity correlates with overnight retention of various types of learning and with intellectual ability, underscoring the role of spindles in brain plasticity and off-line memory consolidation (Fogel and Smith, 2011; Geiger et al., 2011;

Schabus et al., 2006, 2004). Further, while responsiveness to the external environment is generally diminished during sleep, spindles constrain cortical transmission of external stimuli during NREM sleep (a phenomenon called sensory gating (Steriade, 2005; Urakami et al., 2012) reducing vulnerability to sleep disruption (Dang-Vu et al., 2011, 2010).

Patients with schizophrenia show sleep spindles deficits that are in turn associated with impairments in sleep-dependent memory consolidation and cognitive functioning (Manoach and Stickgold, 2019). For example, compared to healthy controls, spindle density was 38% lower in one sample of schizophrenia patients, and coordination between spindles and slow waves predicted memory consolidation in the patient group only (i.e., patients for whom spindles peaked later in the upstate of slow waves showed better memory consolidation; Demanuele et al., 2017). Spindle abnormalities have also been identified in those with bipolar disorder (Ritter et al., 2018), autism spectrum disorders (Limoges et al., 2005) ADHD (Khan and Rechtschaffen, 1978; Poitras et al., 1981) and depression (De Maertelaer et al., 1987; Plante et al., 2013), though findings in the latter two groups are notably mixed.

Examinations of sleep spindle activity in youth with affective disorders are surprisingly rare but most often find decreased spindle activity compared to typically-developing children. For example, 8 to 15-year-old youth with major depressive disorder (MDD) and those at risk for MDD based on family history, showed significantly reduced spindle density compared to youth with no diagnosis, with the lowest rates found in the MDD group (Lopez et al., 2010). Similarly, in a sample of 4 to 18-year olds at high and low risk for MDD, comparatively lower spindle activity was found in the high risk group (Sesso et al., 2017). One earlier study however, found increased spindle frequency, but not density, in pre-pubertal children with MDD compared to healthy controls (Goetz et al., 1983). Further, these differences persisted even among treated youth whose MDD remitted.

In the only published study to include clinically-anxious youth, Wilhelm and colleagues (2017) compared 9 to 17-year-old youth with social anxiety disorder (SAD), characterized by fear of negative evaluation and social avoidance, to healthy controls in terms of spindle activity and relationships with emotional arousal and memory. Widespread reduction in spindle activity was found in the anxious compared to control group, and self-reported social anxiety severity was negatively associated with spindle activity. Interestingly, one week later however, spindle activity was significantly correlated with the consolidation of negative memories in healthy youth only. These collective results suggest alterations in spindle activity may both mirror and perpetuate core symptoms of SAD (i.e., avoidance of social situations limits social learning which reduces opportunity to create adaptive emotional memories) (Wilhelm et al., 2017).

Differences in sleep spindle activity are also evident based on sex, with greater activity found in females as young as five years (Mikoteit et al., 2013). Studies in youth also reveal sex-based differences to interact with emotional functioning. In the study by Lopez and colleagues (2010), healthy control females showed significantly higher spindle density during the second half of the night than control males as well as females with MDD and at-risk males. Spindle generation may therefore partially underlie the increased incidence of internalizing and externalizing problems observed in females and males, respectively.

The objective of the current study was to investigate sleep spindle activity in non-depressed, pre-pubertal youth with a primary GAD diagnosis compared to age-matched healthy controls. Consistent with previous research, we expected children with GAD to exhibit reduced spindle density relative to healthy controls, and that boys with GAD would show the lowest levels of spindle density compared to all other groups (i.e., all boys and girls without GAD). We also examined relationships between spindle density, anxiety symptoms, worry, global functioning, and subjective sleep quality, hypothesizing negative associations between spindles, anxiety and worry, and positive associations with global functioning and sleep quality in all youth.

Method

Participants

The sample included 58 children (52% female), ages 7 to 11 years ($M = 8.86$, $SD = 1.47$) recruited for a study examining sleep in children with a primary diagnosis of GAD and matched healthy controls (Alfano et al., 2013; Patriquin et al., 2014). Two types of children were recruited via community flyers and print advertisements in two major US cities (Houston, TX and Washington, DC): children with elevated worry/anxiety symptoms and children without any mental health problems. Eligibility criteria for all children included English fluency, living with the participating parent or caregiver for a minimum of one year, and enrollment in regular education courses. Children were excluded if they took any medications known to impact sleep or mood/anxiety, were utilizing treatment services for anxiety or sleep problems, had a full-scale IQ < 80 , and had current or lifetime history of a unipolar or bipolar mood disorder, psychotic disorder, pervasive developmental disorder, eating disorder, substance abuse, or suicidal ideation/self-harm behaviors. Children with diagnosed or suspected breathing-related sleep disorders were also excluded.

After an initial phone screen, children meeting basic inclusion/exclusion criteria were invited to complete a comprehensive clinical assessment including structured, diagnostic interviews. Anxious children who met criteria for a primary GAD diagnosis (based on DSM-IV criteria) during the initial diagnostic assessment were eligible to participate ($n=26$). Secondary diagnoses in the GAD group included social anxiety disorder ($n=7$), specific phobia ($n=3$), separation anxiety ($n=1$), attention deficit hyperactivity disorder ($n=1$), and oppositional defiant disorder ($n=1$). Children in the healthy control group ($n=32$) completed the same assessment procedures as anxious children and did not meet DSM-IV criteria for any disorder. The overall sample was primarily Caucasian (60%) and relatively affluent, with a median family income of \$100,000(/year). All sample characteristics by group are presented in Table 1.

Measures

Clinical Interview.—Diagnostic criteria were established using the Anxiety Disorders Interview Schedule for DSM-IV – Child Version (ADIS C/P; Silverman & Albano, 1996). The ADIS C/P assesses for a range of anxiety, mood, and externalizing disorders and is considered the gold standard for diagnosing anxiety disorders in children. Separate parent and child interviews were conducted by a PhD level psychologist, post-doctoral fellow, or

trained doctoral level graduate student and reviewed with a licensed clinical psychologist prior to the assignment of a final diagnosis. Clinician severity ratings (range = 0–8) were used to determine severity of each disorder, with ratings of 4 or above signifying clinically-significant impairment. Mean clinician severity ratings for children with GAD ranged from 4–8 ($M = 6.15$, $SD = 1.14$). High test-retest, inter-rater, and concurrent reliability for the ADIC C/P has been well established (Lyneham et al., 2007; Silverman and Albano, 1996; Wood et al., 2002). Reliability for a GAD diagnosis in the current sample was excellent ($\kappa = 1.0$).

Intelligence.—IQ was estimated using the four-subtest form of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999; WASI). Estimates of Verbal IQ (Vocabulary and Similarities) and Performance (Block Design and Matrix Reasoning) were combined to create a Full Scale IQ score (FSIQ).

Global Functioning.—The Children's Global Assessment Scale (CGAS) was used as a global measure of functioning. Clinician-based scores range from 0–100 and scores above 70 are typically considered to be in the normal range (Shaffer et al., 1983). Inter-rater and test-retest reliability as well as concurrent and construct validity have been demonstrated (Bird et al., 1990, 1987; Green et al., 1994).

Subjective Sleep Quality.—To measure subjective sleep quality on the night of PSG monitoring, participants completed a brief questionnaire in the morning regarding their sleep. The question, “*How well did you sleep last night?*” was used as a measure of subjective sleep quality, rated on a scale from 1 to 3 (from *poorly* to *great*).

Anxiety and Worry Severity.—Child anxiety severity was assessed using the *Screen for Child Anxiety Related Disorders* (SCARED; Birmaher et al. 1999). This 41-item scale assesses symptoms of panic, GAD, separation anxiety, social phobia, and school phobia based on DSM classifications. Participants report how true each item has been over the past 3 months. Items are measured on a 3-point Likert scale from 0 (*not true or hardly every true*) to 2 (*very true or often true*). Ratings were summed to create a SCARED total score, with higher scores indicating greater anxiety. The SCARED has been shown to have good internal consistency, and adequately discriminates anxiety from other psychiatric conditions (Birmaher et al., 1999).

Children reported on the severity of their worry via the *Penn State Worry Questionnaire for Children* (PSWQ-C; Chorpita et al., 1997). This 14-item measure assesses for symptoms of generalized worry (e.g., related to school, family, health, future events, etc.) in children and adolescents. Participants responded on a 4-point Likert scale from 0 (*never true*) to 3 (*always true*). Scores are summed to create a total score, with higher scores indicating greater anxiety. The PSWQ-C has been found to have good convergent and discriminant validity as well as good reliability in a clinical sample (Chorpita et al., 1997).

Procedures

Participants completed an in-person comprehensive clinical assessment including structured diagnostic interview, parent and child questionnaires, and abbreviated intelligence testing

using the WASI. Eligible participants were then given a wrist actigraph to wear for one week (in conjunction with completion of a sleep diary) to ensure adequate, regular sleep prior to PSG monitoring. Actigraphy data were scored using the Sadeh algorithm shown to provide reliable estimates of sleep in children (Sadeh et al., 1994). Variables derived included total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency. As described in a previous report, no differences in actigraphy sleep variables were identified between the two groups (Alfano et al., 2015). PSG was conducted on either a Friday or Saturday night so as to minimize disruptions in school and family schedules. Because data collection took place at two different locations, approximately one half of the sample completed PSG monitoring in a sleep laboratory ($n = 32$) whereas the remainder ($n = 26$) were prepared for PSG monitoring at the sleep-lab and then slept at home (unattended). See Table 6 for a summary of sleep characteristics according to sleep location. All participants were given the same bedtime and 8.5 hour sleep opportunity on the PSG night and records were checked for compliance with procedures.

Polysomnography.—Standard, multichannel PSG was conducted for all participants. PSG data were collected by registered polysomnographic sleep technicians (RPSGT) with experience working with a pediatric population. Sleep records were conducted and scored in 30-second epochs per American Academy of Sleep Medicine (AASM) criteria (Iber et al., 2007). All studies were conducted and scored under the supervision of a board-certified sleep physician and technicians were blind to child diagnostic status. Electroencephalogram (EEG; frontal, central, and occipital regions), electrooculogram (EOG), electromyogram (EMG; submental, right/left tibial), electrocardiogram (ECG), nasal pressure, thoracic and abdominal respiratory effort, and oximetry data were collected according to standard procedures. Sleep staging was conducted by trained technicians naïve to diagnostic group status and scored according to AASM guidelines (Iber et al., 2007). Artifacts were visually identified and the entire 30-second epoch containing them removed. All the remaining epochs scored as sleep were analyzed.

Spindle Activity.—Sleep spindle activity was detected via HypnoLab software developed for automatic detection of sleep spindles and other micro-sleep phenomena (SWS Soft, Italy). Left-frontal (F3) and central (C3) electrodes for each epoch of N2 and N3 sleep were used for spindle detection. The program identified spindle events with a frequency of 11–16 Hz, 14 microvolts or higher in amplitude, and 0.5–3 seconds in duration based on standard spindle criteria. All identified spindle events were reviewed visually by the second author (R.F.). Spindle density was defined as the number of sleep spindles per number of N2 and N3 epochs (30 seconds) similar to other studies (Brockmann et al., 2018; Bruni et al., 2009; Lopez et al., 2010). The validity of this approach (i.e., automatic analysis followed by visual confirmation) is well established and shown comparable to visual analysis only (Ferri et al., 1989).

Results

Preliminary Data Analysis

Preliminary analyses were conducted to examine the normality of distributions for the variables of interest. Shapiro-Wilk tests indicated spindle density in central and frontal regions during N2 sleep deviated significantly from normal. These variables were therefore log transformed. Equality of error variances between the two groups was also tested and differences were non-significant.

Independent samples *t*-tests were then conducted to examine potential group differences based on demographic, intellectual, and objective sleep variables based on group. No group differences were found (see Table 1). There were, however, group differences based on PSG type. Children completing in-lab PSG showed significantly shorter total sleep time ($m = 476.52$ minutes) compared to those sleeping at home ($m = 517.73$ minutes; $t(54) = -2.356$, $p = .022$). Similarly, those sleeping in-lab took significantly longer to fall asleep ($m = 40.87$ minutes) compared to those sleeping at home ($m = 24.63$ minutes; $t(54) = 2.125$, $p = .038$).

Next, we conducted a MANOVA to examine possible interaction effects between group and PSG type. The omnibus test was significant (Pillai's Trace = .245, $F(5, 48) = 3.123$, $p = .016$) and follow-up univariate tests indicated children with GAD required longer to initiate sleep ($F(1, 52) = 9.118$, $p = .004$) and had lower sleep efficiency ($F(1, 52) = 7.076$, $p = .01$) when sleeping in the laboratory versus at home. There were no group differences based on diagnostic group or PSG-type in terms of self-reported sleep quality. PSG type was therefore entered as a covariate in all analyses.

Lastly, bivariate correlations were examined to detect associations between intellectual/demographic variables (e.g., overall IQ, age, and race/ethnicity) and outcome variables of interest, but no significant associations were found. See Table 2 for correlation matrix.

Sleep Spindles Density $\times$ Group $\times$ Sex

A two-way MANCOVA revealed no overall effect of diagnostic group ($F(4,50) = 2.18$, $p = .084$, $\eta^2 = .149$) or sex ($F(4,50) = 1.09$, $p = .372$, $\eta^2 = .080$) on N2 or N3 spindle density in either frontal or central regions. No interaction effects between group and sex were detected ($F(4,50) = .10$, $p = .982$, $\eta^2 = .008$). Spindle characteristics are included in Table 3.

Associations with Anxiety, Worry, and Global Functioning

A series of hierarchical regression models were conducted to examine relationships with anxiety and worry. In separate models, total SCARED and PSWQ-C scores were entered as predictors and spindle density as dependent variables. PSG type was entered on the first step of all models. SCARED scores did not predict spindle density in the full sample and entering diagnostic group did not improve model fit parameters. In the second model, worry severity (total PSWQ-C scores) significantly predicted spindle density in the full sample, such that youth with greater worry severity showed significantly greater N2 and N3 spindle activity at both frontal and central regions. Adding diagnostic group to the model did not improve fit. Lastly, among youth diagnosed with GAD, clinician rated global functioning

(CGAS) scores were negatively associated with spindle density in frontal regions during N3 sleep (see Table 4).

Associations with Sleep Quality

To examine relationships between spindle density and sleep quality, a series of hierarchical regression models were conducted with spindle density as predictors and sleep quality entered as the dependent variable. PSG type was again entered on the first step in each model. Among the full sample, N2 and N3 spindle density in any region did not significantly predict self-reported sleep quality on the PSG night. The addition of diagnostic group to the model did not improve model fit.

Spindle Density based on PSG type

Based on the uniqueness of our sample, we also examined potential differences in spindle variables based on PSG type (in-lab vs. ambulatory). During N2 and N3, mean spindle density was significantly greater during in-lab compared to at-home PSG. Specifically, spindle density differed significantly in the central region during N2 sleep ($t(56) = 3.70, p = .001$) and marginal differences were found in the frontal region during N2 sleep ($t(56) = 1.96, p = .055$) and central region during N3 sleep ($t(56) = 1.90, p = .06$).

Discussion

Sleep spindles are micro-architectural characteristics of sleep that play an important role in learning, memory, and general cognitive ability (Bódizs et al., 2005; Fogel et al., 2007; Rasch and Born, 2013). They are also increasingly linked with emotional health, and decreased spindle activity has been reported in several clinical samples of youth, including those with depression (Lopez et al., 2010) and SAD (Wilhelm et al., 2017). In the current study we examined sleep spindle activity in youth with GAD, a highly common affective diagnosis in youth, compared to healthy controls. Contrary to our primary hypothesis, we did not detect significant spindle differences between the groups. In fact, overall spindle activity was generally higher in the GAD group and although this result did not reach statistical significance, the observed effect size was large (size $\eta^2 = .15$). We also expected to find differences based on sex based on results of prior studies (Huupponen et al., 2002; Mikoteit et al., 2013); however, no sex-based differences or group $\times$ sex interactions in sleep spindle activity were found.

Our findings notably contrast results of other studies among youth with affective disorders. Two potential explanations are offered in this regard. First, the specific childhood disorder examined in our study must be considered. GAD shares overlapping features and high rates of comorbidity with both MDD and SAD, but is also uniquely characterized by excessive worry. Pathological worry is a verbal mentation process fueled by excessive apprehension and distress related to future potentially threatening events (Barlow, 2002; Borkovec et al., 1998; Vasey and Borkovec, 1992). Individuals who experience pathological worry exhibit attentional bias toward threatening information at the expense of neutral information, which serves to perpetuate and enhance the worry process itself (Hayes and Hirsch, 2007; Mathews, 1990; Mathews et al., 1995). Interestingly, while attentional biases continually

engage working memory, studies have generally failed to find evidence of memory bias or deficits in those with GAD (see Coles and Heimberg, 2002) such as is commonly found in other anxiety disorders including SAD (Alfano and Beidel, 2011). Thus, even in the presence of global affective disturbances, excessive worry may serve to increase spindle generation in youth with GAD.

Findings related to anxiety and worry severity provide support for this thesis. Specifically, spindle activity showed no association with a broadband measure of anxiety severity but was positively associated with worry in all children. In general, worry is a separate construct from anxiety in that the former has been associated with problem-focused coping strategies and information seeking, while the latter is associated with poor problem solving and avoidant coping strategies (Davey et al., 1992). A positive association between spindle activity and worry in youth converges with findings from a sample of young children where avoidant coping and denial were inversely related to spindle activity (Mikoteit et al., 2012). We suggest that rather than overall severity of anxiety or depressive symptoms, particular cognitive features of affective disorders (e.g., worry, rumination) and forms of coping may more closely map onto spindle generation and activity. Repetitive thought processes such as worry and rumination are characterized by increased activation of underlying thalamocortical circuits (Cooney et al., 2010; Mandell et al., 2014) and spindle generation similarly represents repeated activation of thalamocortical or hippocampocortical networks (Astori et al., 2013; De Gennaro and Ferrara, 2003). Spindles may therefore interact with these repetitive cognitive processes via synchronized neural activity that serves as the basis for memory consolidation.

Relationships between cognitive-affective processing style and spindle activity might also inform understanding of commonly observed sex differences in spindle activity. Specifically, while greater spindle activity has been found in adult and adolescent females with MDD (Mikoteit et al., 2013), rumination is a core feature of depression that parallels worry in its perseverative, negative focus. Females, particularly depressed females, ruminate at higher rates than their male counterparts (Johnson and Whisman, 2013).

A second explanation for our primary findings is that the relationship between spindle activity and affective psychopathology is directly moderated by stage of development. Our sample was purely comprised of pre-pubertal children (Tanner stages 1 and 2). The most dramatic changes in sleep architecture occur with the onset of puberty, between 9 to 12 years of age (Crone and Dahl, 2012; Tarokh et al., 2016). Likewise, spindle frequency, duration, and amplitude undergo marked changes across development, with gradual increases observed in childhood prior to declines beginning around the age of 13 (Nagata et al., 1996; Scholle et al., 2007), paralleling underlying neuroplasticity and cognitive ability. We also note that the only study to find higher (rather than lower) spindle activity in youth with MDD compared to healthy controls was comprised entirely of pre-pubertal children (Goetz et al., 1983). Spindle activity may therefore serve as a nonspecific correlate of affective disorders prior to the pubertal transition.

Evidence of increased spindle activity in youth completing PSG in the laboratory compared to in the home was unexpected, but the sensory gating theory of sleep spindles may explain

this result. Since sleep spindles restrain cortical transmission of external stimuli in the service of sleep maintenance (Antony and Paller, 2017; Dang-Vu et al., 2011, 2010) a night of sleep in a novel sleep laboratory environment might be expected to instigate greater production of spindles than sleep in a familiar setting. Along these lines, we also expected that sleep spindle activity would correlate with reports of better sleep quality. Rather than inferring sleep quality from objective measures of sleep we examined child reports of sleep quality the morning following PSG monitoring. However, this association was non-significant. It is possible that our measure of sleep quality may have lacked adequate nuance to capture a relationship with spindles, but Goetz and colleagues (1983) similarly found no association between spindles and sleep complaints in their study of pre-pubertal youth. The fact that spindle activity (and slow wave sleep) is highest during childhood, making sleep relatively robust to disruption (Ringli and Huber, 2011; Urakami et al., 2012) may account for this lack of association. Moreover, the fact half of our sample was comprised of youth with GAD who consistently report poorer sleep quality in the absence of objective sleep disturbance should be considered (Alfano et al., 2015; Mullin et al., 2017).

The non-significant association observed between IQ and spindle density may seem surprising in light of consistent evidence of a positive relationship in adults (Fogel et al., 2007; Fogel and Smith, 2011). However, findings are more equivocal in child samples and point toward a change in the direction of this relationship across development undergirded by neuromaturation (see Reynolds et al., 2018). It is also possible that the higher than average mean IQ observed among our participants may have also limited our ability to detect a significant relationship.

Limitations:

This study had a number of strengths, including a well-characterized sample of youth with GAD with clinical characteristics representative of this population (e.g., high rates of comorbidity; Alfano, 2012; Moffitt et al., 2007), comprehensive diagnostic assessment, and multi-modal assessment of sleep. These results, should however, be interpreted in the context of several limitations. First, failure to detect a difference in spindle activity based on diagnostic group or sex may be attributable to inadequate statistical power. Although our sample size is comparable to that of other studies (e.g., Lopez et al., 2010) a larger sample would have been more ideal. Our measure of sleep quality immediately followed the PSG night but has not been validated previously. The 3-point Likert scale used may have restricted children's responses and obscured potential relationships with sleep spindles. Still, the inclusion of a subjective rating of sleep quality represents a relative strength of the current study, as many studies infer sleep quality from various objective measures of sleep (e.g., Purcell et al., 2017).

Although analyses controlled for PSG type, ideally, all children would have completed the PSG night in the same setting. Further, spindles were examined during a single night of PSG. However, because spindle activity appears to be heritable (Purcell et al., 2017) and relatively stable across different nights (De Gennaro et al., 2005; Gaillard and Blois, 1981) the impact of potential 'first night effects' is unclear. The use of automated scoring may be viewed as a potential weakness as well. Spindle amplitude and density may be independent

in their predictive value and reliance on spindle density alone may miss important differences in spindles (Purcell et al., 2017). Finally, our sample was predominantly Caucasian (60%) and relatively affluent, with a median family income of \$100,000/(year), which potentially limits the generalizability of our findings.

Conclusion:

Overall, findings provide new insight into relationships between sleep spindle activity and emotional health in pre-pubertal children and call for developmentally-sensitive approaches in examining these relationships. Results also suggest that rather than broad-based measures of affective symptom/disorder severity, transdiagnostic approaches that focus on specific coping strategies and cognitive-affective features of childhood disorders may serve to greatly advance knowledge in this domain. Longitudinal studies are also needed to explore potential reciprocal relationships between spindle characteristics and individual affective risk across development.

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Highlights:

- Similar sleep spindle density characterizes sleep in children with GAD and healthy controls
- Sleep spindles are positively associated with worry symptoms, but not anxiety severity
- Sleep quality is unassociated with spindle density
- Cognitive aspects of worry may drive spindle activity

Table 1.

Demographic, sleep, and symptom characteristics

	Full Sample Mean (SD) / % (n)	GAD Mean (SD) / % (n)	Healthy Controls Mean (SD) / % (n)
Age	8.86 (1.47)	8.77 (1.48)	8.94 (1.48)
Gender			
Female	51.7% (30)	46.2 (12)	56.3 (18)
Male	48.3% (28)	53.8 (14)	43.8 (14)
Race/Ethnicity			
White	60.3% (35)	61.5 (16)	59.4 (19)
African-American	6.9% (4)	3.8 (1)	9.4 (3)
Asian	1.7% (1)	3.8 (1)	0 (0)
Hispanic	15.5% (9)	15.4 (4)	15.6 (5)
Other	15.5% (9)	15.4 (4)	15.6 (5)
Full Scale IQ	117.57 (13.03)	115.25 (12.78)	119.48 (13.13)
Sleep Characteristics			
Total Sleep Time (min.)	495.65 (67.94)	497.78 (40.62)	493.93 (84.47)
Sleep Onset Latency (min.)	33.33 (29.1)	32.82 (29.96)	33.74 (29.45)
Wake After Sleep Onset (min.)	41.49 (33.92)	39.06 (33.88)	43.45 (34.39)
Sleep Efficiency	87.13% (7.07)	87.64 (6.70)	86.71 (7.44)
Anxiety Symptom Severity			
SCARED	21.09 (14.49)	28.92 (15.25)	14.34 (9.80)
PSWQ-C	13.98 (8.54)	18.58 (8.78)	10.13 (6.20)
CGAS (GAD only)	59.62 (5.78)	59.62 (5.78)	-
PSG Night Self-Reported Sleep Quality	1.61 (.64)	1.76 (0.62)	1.5 (0.64)

Notes. SCARED = Screen for Child Anxiety Related Disorders. PSWQ-C = Penn State Worry Questionnaire. CGAS = Children's Global Assessment Scale (reported for the anxious group only). Frontal N2 SD = N2 sleep spindle density at frontal site. Frontal N3 SD = N3 sleep spindle density at frontal site. Central N2 SD = N2 sleep spindle density at central site. Central N3 SD = N3 sleep spindle density at central site.

Table 2.

Bivariate Correlations among Variables of Interest for all Participants

	1	2	3	4	5	6	7	8	9	10	11
1. Age											
2. Race/Ethnicity	-.22										
3. Income	-.08	-.30 [*]									
4. IQ	.02	-.23	.26								
5. SCARED	.07	.01	-.08	-.16							
6. PSWQ-C	.13	-.10	-.06	-.04	.74 ^{**}						
7. CGAS	-.04	.12	.04	-.33	-.35	-.52 ^{**}					
8. PSG Night SQ	.12	-.02	.23	.15	.07	.01	-.45 [*]				
9. Frontal N2 SD	.17	-.03	.20	-.17	.05	.35 ^{**}	-.39 [*]	.20			
10. Frontal N3 SD	.16	-.08	.15	-.08	.19	.35 ^{**}	-.51 ^{**}	.15	.74 ^{**}		
11. Central N2 SD	.16	-.24	.14	-.14	-.03	.25	-.33	.21	.84 ^{**}	.56 ^{**}	
12. Central N3 SD	.02	-.22	.03	-.03	.03	.19	-.38	.10	.57 ^{**}	.75 ^{**}	.70 ^{**}

Notes.^{***}
p .001,^{**}
p .01,^{*}
p < .05.

CGAS = Children's Global Assessment Scale (reported for the anxious group only). SCARED = Screen for Child Anxiety Related Disorders. PSWQ-C = Penn State Worry Questionnaire. PSG Night SQ = Self-reported PSG night sleep quality. Frontal N2 SD = N2 sleep spindle density at frontal site. Frontal N3 SD = N3 sleep spindle density at frontal site. Central N2 SD = N2 sleep spindle density at central site. Central N3 SD = N3 sleep spindle density at central site.

Table 3.

Spindle Characteristics

	Full Sample Mean (SD)	GAD Mean (SD)	Healthy Controls Mean (SD)	Girls Mean (SD)	Boys Mean (SD)
Frontal N2 Spindle Density	.29 (.22)	.32 (.18)	.26 (.24)	.31 (.21)	.27 (.23)
Frontal N3 Spindle Density	.35 (.39)	.44 (.34)	.28 (.42)	.31 (.26)	.39 (.50)
Central N2 Spindle Density	.26 (.19)	.28 (.19)	.24 (.20)	.26 (.17)	.25 (.22)
Central N3 Spindle Density	.17 (.19)	.18 (.19)	.16 (.19)	.15 (.13)	.20 (.23)

Table 4.

Symptom Severity Predicting Sleep Spindles

	Frontal										Central									
	N2					N3					N2					N3				
	β	b	SE	95% CI	Adj. R^2	β	b	SE	CI	Adj. R^2	β	b	SE	CI	Adj. R^2	β	b	SE	CI	Adj. R^2
SCARED	.105	.001	.005	-.002, .002	.024	.216	.002	.001	.000, .004	.011	.077	.000	.001	-.001, .001	.177	.090	.000	.001	-.002, .001	.045
PSWQ-C	.362**	.003	.001	.001, .005	.158	.358**	.004	.002	.001, .008	.106	.263***	.002	.001	.000, .004	.242	.201*	.001	.001	.000, .003	.084
CGAS (GAD only)	-.380	-.004	.002	-.008, .001	.080	-.579*	-.010	.003	-.017, -.003	.225	-.206	-.002	.025	-.007, .002	.120	-.307	-.003	.002	-.008, .001	.095

Notes.

 $p < .001$,

**
 $p < .01$,

*
 $p < .05$.

Standardized and unstandardized estimates are reported. SCARED = Screen for Child Anxiety Related Disorders. PSWQ-C = Penn State Worry Questionnaire. CGAS = Children's Global Assessment Scale (reported for the anxious group only).

Table 5.

Spindle Density Predicting Sleep Quality

	β	b	SE	95% CI	Adj. R^2
Frontal					
NREM 2	.16	1.37	1.28	−1.21, 3.10	.04
NREM 3	.13	.77	0.86	−0.96, 2.49	.03
Central					
NREM 2	.14	1.35	1.54	−1.74, 4.44	.03
NREM 3	.06	.62	1.43	−2.26, 3.50	.02

Notes. Standardized and unstandardized estimates are reported. 95% Confidence Intervals.

Table 6.

Sleep Characteristics by Sleep Location

	In-Lab (n=32)		At-Home (n=26)	
	GAD (n=14) Mean (SD)	Healthy Controls (n=18) Mean (SD)	GAD (n=12) Mean (SD)	Healthy Controls (n=14) Mean (SD)
Total Sleep Time (min.)	481.38 (36.08)	472.79 (37.29)	515.55 (38.96)	519.60 (116.01)
Sleep Onset Latency (min.)	52.15 (27.51)	32.24 (29.03)	11.88 (14.56)	35.57 (30.94)
Wake After Sleep Onset (min.)	37.38 (35.19)	33.44 (21.25)	40.88 (33.85)	55.61 (43.40)
NREM 1 (%)	1.33 (0.93)	1.92 (1.36)	2.82 (1.85)	1.88 (1.46)
NREM 2 (%)	50.18 (4.67)	52.08 (5.37)	48.45 (6.75)	44.75 (7.80)
NREM 3 (%)	24.69 (5.55)	24.70 (3.75)	26.53 (5.87)	28.45 (5.72)
REM (%)	23.80 (3.51)	21.29 (3.17)	22.18 (3.56)	21.90 (6.34)
Total Frontal NREM Sleep Spindles	144.39 (79.99)	125.23 (111.14)	134.39 (79.25)	83.64 (66.70)
Total Central NREM Sleep Spindles	126.06 (80.29)	113.61 (72.25)	83.78 (54.92)	61.31 (50.71)
Sleep Efficiency	84.54 (6.74)	88.18 (6.18)	91.01 (4.95)	84.92 (8.62)
PSG Night Self-Reported Sleep Quality	1.86 (0.53)	1.61 (0.70)	1.57 (0.79)	1.30 (0.48)