The association between sleep spindles and IQ in healthy school-age children

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A B S T R A C T

Recent studies have suggested that sleep is associated with IQ measures in children, but the underlying mechanism remains unknown. An association between sleep spindles and IQ has been found in adults, but only two previous studies have explored this topic in children. The goal of this study was to examine whether sleep spindle frequency, amplitude, duration and/or density were associated with performance on the perceptual reasoning and working memory WISC-IV scales, but that sleep spindle amplitude, duration and/or density were associated with performance on the IQ test. We used portable polysomnography to document sleep architecture in the natural home environment and evaluated IQ. We found that lower sleep spindle frequency was associated with better performance on the perceptual reasoning and working memory WISC-IV scales, but that sleep spindle amplitude, duration and density were not associated with performance on the IQ test.

1. Introduction

Studies involving children and adults have identified a significant relationship between poor or insufficient sleep and decreased cognitive capacity (Beebe, 2011; Bell-McGinty et al., 2004; Busby and Pivik, 1983; Caldwell et al., 2005; Carskadon et al., 1981; Chee and Choo, 2004; Chee et al., 2006; Choo et al., 2005; Dewald et al., 2010; Fallone et al., 2001; Gozal and Kheirandish-Gozal, 2007; Gruber et al., 2010; Habek et al., 2004; Lim et al., 2007; Mu et al., 2005a, 2005b; Nixon et al., 2008; Randazzo et al., 1998; Sadeh et al., 2003; Schabus et al., 2006; Touchette et al., 2007; Voderholzer et al., 2011; Wilhelm et al., 2012). Furthermore, longer habitual sleep duration in healthy school-aged participants has been associated with better performance on measures of perceptual reasoning and overall IQ (Gruber et al., 2010). These findings reveal an association between sleep duration and performance on IQ tests, but the mechanisms underlying this interplay remain unknown.

Several authors have proposed that sleep spindles may physiologically underpin intelligence or high-level general mental ability (Bodizs et al., 2005; Brière et al., 2000; Fogel et al., 2007; Nader and Smith, 2001). Sleep spindles are a feature of (predominantly) stage 2 Non-Rapid Eye Movement (NREM) sleep, and are characterized by recurrent and brief bursts of spindle-like EEG activity. Sleep spindles have a characteristic crescendo–decrescendo envelope and bursts are typically 0.5 to several seconds in duration (Rechtschaffen and Kales, 1968). Sleep spindles are generated by an interaction between the thalamic reticular nucleus (RT) and thalamocortical (TC) connections (Steriade and Deschenes, 1984, 1988) and are thought to arise from oscillations of the TC network (Amzica and Steriade, 2000; Steriade, 2000). The intra-spindle frequency is determined by an interplay between the GABAergic inhibitory neurons of the RT and the TC neurons. RT neurons impose hyperpolarization on TC neurons, activating a nonspecific cation current (Ih) that depolarizes TC neurons and activates low-threshold Ca++ + currents (UTC) and bursting. The latter provides feedback excitation to RT neurons, thus closing the loop. Each TC burst also imposes an excitatory post synaptic potential (EPSP) on pyramidal neurons, forming the basis for the spindle waves seen on EEG.

Regarding the electrical generators of spindles, EEG recordings in humans have demonstrated both superficial and deep frontal cortical sources, as well as sources in the ventrobasal thalamus that are often synchronous with those observed on scalp EEG (Schomer and Lopes da Silva, 2010). Spindles appear to be initiated by cortical activation of RT neurons, in phase with a sporadic slow cortical oscillation (~0.75 Hz) (Steriade, 2006) and during the A1 phase of the cyclic alternating pattern (De Gennaro and Ferrara, 2003). Thereafter, spindle
maintenance appears to involve signaling from the brainstem, hypothalamic and basal forebrain to the TC and cortex.

Cortical excitation of RT neurons is instrumental in spreading and synchronizing spindles through TC and cortico-cortical excitation. These two modes of firing relay information to specific TC neurons and the so-called “non-specific” intralaminar nuclei. Cortical activation of the latter acts with recurrent cortico-cortical excitation to widely spread the spindle rhythm across the cortex. The initially waxing amplitude of the EEG waves is grossly correlated to the amplitude of neuronal EPSPs and reflects the gradual recruitment of additional neurons. This confers the high amplitude EEG signal seen in the middle of the spindle. The waning phase of the signal is due to deterioration of synchronization across increasing TC sectors. Their asynchronous feedback to the thalamus renders the RT neurons out of phase to each other; this eventually reaches enough cortical neurons to depolarize TC neurons (via feedback), terminating the rhythm. Notably, increasing arousal interferes with spindles. For example, cholinergic afferents from the brainstem excite TC neurons and inhibit RT neurons during the waking and REM states, inhibiting the rhythms that prevail in NREM sleep (i.e., spindles and delta) (Urakami et al., 2012).

Spindles may be characterized quantitatively using several parameters including frequency (number of waveforms per second), density (number of spindle bursts/min of NREM sleep), amplitude (peak-to-peak difference in spindle voltage), and duration of spindle bursts. The role of sleep spindles was historically debated, but it is now believed that they contribute to sleep promotion and maintenance in the contexts of sensory gating, motor representation development, cognition consolidation, and memory consolidation (Gais et al., 2002; Rosanova and Ulrich, 2005; Schabus et al., 2007; Steriade, 2006).

Investigators have further suggested that sleep spindles can serve as a physiological markers of both intellectual ability (Bodizs et al., 2005; Fogel and Smith, 2011; Geiger et al., 2011) and neurophysiological maturation (De Gennaro and Ferrara, 2003; Nagata et al., 1996; Shinomiya et al., 1999). Several authors found correlations between the extent of spindle activity and performance on various IQ tests (Bodizs et al., 2005; Fogel et al., 2007; Nader and Smith, 2001; Schabus et al., 2006). In adults, significant positive correlations were evident between individual averages of spindle numbers/night and performance on the IQ subscale of the Multidimensional Aptitude Battery II (MAB-II) test (Gaillard and Blois, 1981). Similarly, strong associations have been reported between spindle numbers and performance on the Raven Progressive Matrices Test (RPMT; Bodizs et al., 2005) and the Raven Advanced Progressive Matrices Test (APMT; Schabus et al., 2006). Fogel et al. (2007) reported that the number of stage-2 spindles was positively correlated with IQ test performance. Furthermore, spindle numbers are reportedly reduced in individuals with dementia (Petit et al., 2004; Reynolds et al., 1985). These observations have led several authors to suggest that the usual pattern of individual sleep spindles in adults is associated with the “g” factor of general mental ability (Anderson, 1995). This could be related to the fact that during wakefulness, the RT is a key component of a larger attentional network that enables the TC system to encode and process information more efficiently (Pinault, 2004). Efficient information processing is an important factor for intelligence, and efficient allocation of attention is critical to learning efficiency (Howard and Polich, 1985).

Although relatively few studies have examined the interplay between sleep spindle activity and IQ in children, the sleep spindle patterns of children with cognitive challenges reportedly differ from those of typically developing children. For example, Gibbs and Gibbs (1962) observed that children with mental disabilities had spindles of greater amplitude and longer duration than those in normal children. Shibagaki and Kiyono (1983) found that children with below-normal IQ scores had unusual spindles that resembled those of children with epilepsy. More recently, Bruni et al. (2009) found that increased spindle activity and EEG sigma power were associated with the extent of dyslexic impairment in children with dyslexia. Although these studies were important initial examinations of the association between sleep spindles and IQ in children, they did not examine this association in typically developing children. Thus, it is unclear whether the observations made in clinical populations with cognitive impairments could be generalized to healthy children, or whether they are associated with the underlying cognitive deficits.

Only two prior studies (Chatburn et al., 2013; Geiger et al., 2011) directly explored the relationship between sleep spindle characteristics and IQ in typically developing children. Geiger et al. reported a negative association between the average peak spindle frequency or sigma power and full-scale IQ. Chatburn et al. (2013) found that spindle activity was unrelated to IQ but similar to Geiger et al. sleep spindle frequency was negatively associated with performance on neurocognitive measures associated with the executive functions (working memory and planning), and with fine motor skill.

Together, these findings suggest a potential contrast between adult studies, in which a positive association has been repeatedly found between sleep spindle activity and cognitive performance (Bodizs et al., 2005; Briefer et al., 2000; Fogel et al., 2007; Gaillard and Blois, 1981; Nader and Smith, 2001; Schabus et al., 2006), and the pediatric literature, in which sleep spindle activity is suggested to be negatively associated with cognitive performance. Clearly, additional studies in children are needed.

Developmental research has shown that the frequency, amplitude, duration and number of sleep spindles change with age such that there is a progressive decrease in sleep spindle number, density, duration and a progressive increase in intra-spindle frequency with age (Nicolas et al., 2001). Some findings of Geiger et al.’s study were not consistent with previous reports that the peak frequency of sleep spindles increases with age. Geiger et al. found a negative association between sleep spindle frequency and IQ scores: the lower the sleep spindle peak frequency in the power spectra, the higher the full-scale IQ score. Other studies examining developmental changes in sleep spindles found that older children show higher sleep spindle frequencies compared to younger children. If we assume that children with higher IQ scores are developmentally advanced, these findings seem contradictory (Tarokh and Caruskadon, 2010; Shinomiya et al., 1999).

Furthermore, these studies examined spindle frequencies at various stages of sleep, but they did not measure spindle duration, or amplitude. Thus, it is not yet clear if these spindle features influence the performance of children on IQ tests. Also, although the cited works were well-designed, the results should be interpreted with caution because the population size was small and the data were collected during sleep in a sleep laboratory, which creates stress that can negatively affect sleep (Beebe et al., 2008; Le Bona et al., 2001), memory, and learning. It is therefore important to evaluate the associations of multiple aspects of sleep spindle properties with IQ in a larger sample of children sleeping in their home environments. Notably, portable polysomnography (PSG) has been validated and successfully employed in work with children (Beebe et al., 2008; Goodwin et al., 2001; Gruber et al., 2009; Kawashima et al., 2009). Such non-intrusive monitoring enhances the ecological validity of sleep studies in children by reducing the problems associated with laboratory recordings, such as stress or adjustment difficulties that manifest in distinct sleep characteristics (e.g., longer sleep latency and/or lower sleep efficiency) (Goodwin et al., 2001).

Although the existing studies provide convincing evidence that sleep duration is associated with IQ, the underlying mechanism remains unknown. It is important to understand how sleep and intelligence interact, because such information could promote the development of innovative approaches to optimize cognitive development. For example, current educational policies aimed at improving academic excellence and enriching cognitive development do not emphasize the importance of obtaining sufficient sleep. Sleep deprivation is highly
prevalent in school-age children, yet no consistent effort is being made to address it. Evidence demonstrating that sleep plays an essential role in IQ and the cognitive processes underlying learning will help facilitate policies that encourage healthy sleeping and support efforts to disseminate information on the critical importance of sleep for optimal development and academic success (Gruber, 2013). Thus, such work could fundamentally advance the field of developmental neuroscience, as well as form the basis for important advances that will allow children to achieve their potential for optimal growth and development.

In sum, an association between sleep spindles and IQ has been found in adults, but only two previous studies have explored this topic in children. Here, we examined the possible association between spindle activity and IQ in typically developing children. We examined whether spindle frequency, amplitude, duration, and/or density were associated with performance on the perceptual reasoning, verbal comprehension, working memory, and processing speed composite scores of the Wechsler Intelligence Scale for Children-IV (WISC-IV; Wechsler, 2003).

2. Materials and methods

2.1. Participants

The study population consisted of 29 children (age 7–11 years; mean 8.79 years; SD 0.94 years; 15 boys and 14 girls). Most participants were Caucasian (73.3%) with the remainder being Asian (13.3%) and “other” (of mixed ethnicity; 13.4%). The average IQ was 108 (SD 13.89). A subject was excluded from the study if that subject had (1) an IQ of less than or equal to 80, as measured by WISC-IV; (2) a history of psychiatric illness, a developmental disorder, or psychosis; (3) a sleep-disordered breathing subscale score of over 0.33 on the Pediatric Sleep Questionnaire (Chervin et al., 2000) and a hypopnea/central apnea index >1.5/h or a periodic leg movement index value >5/h; (4) any medical or psychiatric condition (e.g., depression or anxiety) that might interfere with sleep; and/or, (5) any medical condition or impairment that might interfere with the ability to complete testing. (6) any medication.

Participants were recruited from elementary schools of a district of Montreal inhabited predominantly by families of the mid-socioeconomic class. Parents responded to flyers sent to all parents by local school boards. The participation rate of families that contacted our laboratory was 90%. The study was approved by the Research Ethics Board of the Douglas Mental Health University Institute (Montreal, Canada); informed consent was obtained from all parents; and all participants agreed to participate in the study.

2.2. Study design

Children were first screened for eligibility to participate. During the initial contact, an over-the-phone assessment of sleep-disordered breathing (SDB) and restless leg syndrome (RLS) was conducted using validated questionnaires (Chervin and Hedges, 2001; Owens et al., 2000). Children who passed the over-the-phone screening were then invited to participate in the study.

Enrolled children were told to abstain from caffeine-containing products. Parents were instructed to maintain the child’s habitual sleep/wake schedule, and to keep a sleep diary containing detailed information on bedtime, wake-up time, and any medication given in the week prior to the study. Daytime sleepiness was assessed using the Modified Epworth Sleepiness Scale (Melenclendes et al., 2004).

The package that was given to parents included a sleep assessment battery, a demographic questionnaire, and a consent form. They were asked to document the child’s bedtime over three nights, using actigraphy, to assess bedtime routine prior to our application of standard multichannel overnight PSG on the fifth night. On the PSG night, standard overnight multichannel PSG evaluation was performed at each child’s home by an experienced sleep technician using a portable PSG device. The sleep technician arrived at each subject’s home 1 h prior to the child’s habitual bedtime and hooked up the sleep recording apparatus. Meanwhile, a research assistant presented an explanatory video that introduced the device. The child and family were then given time to become comfortable with the device, which is very small and has little or no impact on normal activities. Recording commenced at the child’s habitual bedtime, whereupon the sleep technician left to allow the child to sleep as usual. The sleep technician and research assistant were available on call if needed. In the morning, the technician returned to pick up the device. Sleep recordings were supervised by a licensed sleep technician in electrophysiology under the auspices of the Center for Sleep Research (Centre d’Etude du Sommeil) at the Hôpital du Sacré-Cœur [Montreal, Quebec]. The sleep technicians had worked extensively with children, affixed all sensors and electrodes. Cognitive performance was assessed in the laboratory using the WISC-IV.

2.3. Measures

2.3.1. Intelligence

The WISC-IV (Wechsler, 2003) measures intelligence in children aged 6–16 years. The instrument contains 10 core subtests, the data from which yield the Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). The 10 core subtests were administered in the prescribed order, following the standard procedures found in the administration manual. The VCI, which is designed to measure language expression, comprehension, listening and concept formation skills, includes data from subtests measuring detection of similarities, comprehension, and vocabulary. The PRI, which is designed to measure fluid reasoning in the perceptual domain with tasks that primarily assess nonverbal fluid reasoning and perceptual orientation ability, includes data from matrix reasoning, picture concepts, and block design subtests. The WMI, which is designed to measure the ability to sustain attention, concentrates and exerts mental control, includes letter–number sequencing and digit spans. Finally, the PSI, which is designed to measure visual perception, organization, scanning, and the efficient production of multiple motor responses (i.e., through tasks that require executive control and sustained effort for quickly working on simple visual material, as well as the fine motor dexterity needed to manipulate a pencil), includes data on coding and symbol searching. Data from all four indices contribute to the full-scale IQ score.

2.3.2. Sleep

2.3.2.1. Polysomnography. PSG was performed in-home, allowing all children to sleep in their natural environments. PSG recordings were obtained using a digital ambulatory sleep recorder (Vitaport-3; TEMEC Instruments BV, Kerkrade, the Netherlands) that incorporated electroencephalography (EEG), submental electromyography (EMG), electro-oculography (EOG), and finger pulse oximetry. Because there might be important differences in sleep spindle activity measured at various locations on the scalp (Barakat et al., in press; Tanguay et al., 1975; Martin et al., 2013; Zeitloher et al., 1997; Ueda et al., 2001), where sleep spindles might mature at different times (Shimomiya et al., 1999; Nagata et al., 1996), we measured spindle features using EEG electrodes placed bilaterally along the anteroposterior axes at locations F3, F4, C3, C4, P3, P4, O1, and O2 using a bilateral referential montage EEG signals that were filtered at 70 Hz (low pass) with a 1-s time constant and digitized at a sampling rate of 256 Hz using commercial software (Columbus, The Netherlands).

Consistent with standard AASM criteria (Iber et al., 2007), sleep stages were scored visually onscreen (LUNA; Stellate Systems, Montreal, Canada), primarily through the use of central derivations (the referential
derivations were to linked ears). The variables used in the present study were sleep duration, the amount of time spent in each stage of sleep, and sleep efficiency. Scoring of sleep parameters was performed by certified sleep technicians blinded to all assessments and survey data.

To assess breathing effort, two respiratory belts (measuring chest and abdominal movement) were used to detect episodes of hypopnea and central apnea, and pulse oximetry was used to measure oxygen saturation. A diminution of ≥50% in the signal from the chest or abdominal belt was considered to reflect hypopnea, whereas a complete absence of respiratory effort was defined as central apnea. Any subject with a hypopnea/central apnea index > 1.5/h of sleep was referred for complete assessment of sleep-related breathing disorders. EMG leg electrodes were used to record leg movements during sleep. A periodic leg movement index value ≥5/h of sleep was considered to reflect abnormal elevation; any such subject was excluded from the study.

2.3.2.1.1. Automatic detection of sleep spindles. Sleep spindles were automatically detected during artifact-free NREM epochs in left and right parasagittal scalp derivations (i.e., left: F3, C3, P3, and O1; right: F4, C4, P4, and O2). Data were bandpass-filtered from 11 to 15 Hz using a linear phase Finite Impulse Response (FIR) filter design with a passband from 11 to 14.9 Hz. Forward and reverse filtering was performed to ensure zero-phase distortion and to double the filter order. The root mean square of each filtered signal was next calculated within a 0.25 s time window and a threshold established at the 95th percentile (Schabus et al., 2007). A spindle was identified when at least two consecutive root mean square time points exceeded the threshold, and the duration criterion (0.5 s) was met.

Four spindle characteristics were derived; these were density (number of spindles/min of N2 and N3 sleep); amplitude (peak-to-peak difference in voltage, expressed in microV); duration (in s); and frequency (number of cycles/s, in Hz). Spindle characteristics were assessed over the entire duration of NREM sleep and, separately, for each NREM sleep period (NREMP). An NREMP was defined as at least 15 min of NREM sleep followed by at least 5 min of REM sleep (Aeschbach and Borbely, 1993).

2.3.2.2. Actigraphy. Nighttime sleep was monitored by using actigraphy; the technique employs a wristwatch-like device (AW-64 series; Mini-Mitter Co, Inc, Bend, OR) to evaluate sleep via measurement of ambulatory movement. Actigraphy has been shown to be a reliable method of sleep evaluation, and the Actiware Sleep algorithm for scoring of sleep indices has been previously validated, displaying a high degree of correspondence with polysomnographic data (Hyde et al., 2007; Kushida et al., 2001; Littner et al., 2003; Werner et al., 2008). The actigraphic data were analyzed in 1-minute epochs, and Actiware Sleep 3.4 (Mini-Mitter) served as the sleep-scoring software. The total number of activity events was computed for each 1-minute epoch, and if the threshold sensitivity value of the mean score during the active period was exceeded, the epoch was considered to be waking in nature. Otherwise, the epoch was considered to be sleep. Actigraphic sleep measures included bed-time and wake-up time.

2.3.2.3. Subjective sleep measures. Daily sleep logs (Manber et al., 1996) were completed by parents and included information regarding children’s bedtimes and waking times. 2) A modified version of the Epworth Sleepiness Scale (ESS) (Melendres et al., 2004), an eight-item questionnaire assessing individual propensity to fall asleep during common daytime situations, was used to measure the general level of child daytime sleepiness.

2.3.3. Behavioral and physical measures

1) Overall behavioral functioning was examined using the Child Behavioral Checklist (CBCL) (Achenbach, 1991), a 113-item parental questionnaire assessing behavioral and emotional problems. The CBCL two broadband problem scales, internalizing (e.g., anxiety, depression, withdrawal) and externalizing (e.g., aggression, impulsivity, delinquency) were utilized in this study. Using this measure, externalizing and internalizing symptoms were differentiated at the level of global scores. The CBCL yields good metric characteristics and excellent representative norms, and the reliability and validity of the test have been repeatedly demonstrated (Achenbach, 1991); 2) A modified version of Petersen’s puberty development scale (Carskadon et al., 1993) was used to assess pubertal development. The PDS has a male and female version and gathers information on physical changes associated with puberty. The development of each pubertal characteristic is rated on a 4-point scale ranging from 1 (no development) to 4 (development complete), with the exception of menarche, which is scored dichotomously (1 = has not occurred or 4 = has occurred); 3) Information on parental educational level, marital status, income, and profession was collected by administration of a background questionnaire, and a SES score was calculated using the 4-factor index of Hollingshead (Hollingshead, 1975); this assigns scores to various professions and educational levels, and incorporates income and marital status, to yield a family SES.

3. Analyses

Descriptive statistics were computed for all relevant variables. To determine whether sleep duration on the PSG night was similar to those on the weeknights preceding PSG, Student’s t-test for related samples was used to compare the time in bed obtained in the four nights prior to PSG to the time spent in bed in the PSG night.

Principal component analyses (employing Varimax rotation) were used to reduce the number of variables and to aggregate measures on spindles into reliable indices reflecting spindle density, amplitude, and duration. A diminution of ≥50% in the signal from the chest or abdominal belt was considered to reflect hypopnea, whereas a complete absence of respiratory effort was defined as central apnea. Any subject with a hypopnea/central apnea index > 1.5/h of sleep was referred for complete assessment of sleep-related breathing disorders. EMG leg electrodes were used to record leg movements during sleep. A periodic leg movement index value ≥5/h of sleep was considered to reflect abnormal elevation; any such subject was excluded from the study.

Sleepiness score 47.45 ± 9.65

Percentage females 48.28 ± 9.00

Internalizing problems 49.28 ± 10.11

Externalizing problems 49.28 ± 9.00

Total N2 sleep 47.45 ± 9.65

Sleepiness score 47.45 ± 9.65

WISC-IV

Verbal comprehension 101.93 ± 14.54

Perceptual reasoning 111.34 ± 15.17

Processing speed 108.76 ± 12.18

Working memory 103.62 ± 11.94

Full scale IQ 108.00 ± 13.69

PSG characteristics

Sleep duration (min) 513.88 ± 58.09

Sleep onset latency (min) 23.28 ± 17.65

Sleep efficiency (%) 96.62 ± 2.87

Total REM sleep (min) 81.95 ± 24.03

Total NREM sleep (min) 431.93 ± 43.59

N1 sleep (min) 23.40 ± 12.31

N2 sleep (min) 189.45 ± 54.15

N3 sleep (min) 219.09 ± 55.89

REM sleep 15.95

NREM sleep 84.05

N1 sleep 4.55

N2 sleep 36.87

N3 sleep 42.63

Index of respiration 0.90 ± 0.60

Oximetry 97.70 ± 0.59

Hypopnea/central apnea index 0.90 ± 0.75

Leg movement 1.92 ± 1.36

Note: PSG refers to Polysomnography; SES refers to Socioeconomic Status; PDS refers to the Puberty Development Scale; CBCL refers to the Child Behavior Checklist; WISC-IV refers to the Wechsler Intelligence Scale for Children — Fourth Edition; REM refers to Rapid Eye Movement; NREM refers to Non-Rapid Eye Movement; N1 refers to Non-Rapid Eye Movement Stage 1; N2 refers to Non-Rapid Eye Movement Stage 2; N3 refers to Non-Rapid Eye Movement Stage 3.
duration, and frequency, across derivations from the left and right parasagittal scalp. Interpretation and labeling of each component were based on loadings of 0.6 or higher.

Because age, gender, socioeconomic status and pubertal status (Blair et al., 2012; Buckhalt et al., 2007; Sadeh et al., 2000, 2009) have been shown to affect sleep (Blair et al., 2012), we examined their association with the sleep spindle factors to determine which covariate adjustment should be made in our regression analyses. The objective was to choose the fewest pre-specified factors whose potential predictive value could be related to the predictors. To identify the potential impact of gender on sleep spindles, one-way analysis (ANOVA) was used, with child gender as the between-subjects factor and sleep spindle factors as the dependent variable. To determine the potential impact of puberty stage on sleep spindles, an additional ANOVA was run with child pubertal stage as the between-subjects factor and sleep spindle factors as the dependent variable. Spearman rank correlations were used to examine potential associations between SES or age and sleep spindle factors.

To explore whether sleep spindle features were associated with IQ scores, relationships between sleep spindle factors representing duration, frequency, amplitude, and density and performance on WISC-IV subscales were tested using multiple linear regression analyses, adjusted for the potential confounders of age, gender, and puberty status.

All analyses employed SPSS Version 20.0 for Windows and a p value of <0.05 was considered to indicate statistical significance.

4. Results

Table 1 and Fig. 1 show the demographics, behavioral and sleep characteristics, WISC-IV composite scores and spindle features (means and standard deviations) of all enrolled participants. Polysomnographic recordings indicated that the participants slept for a mean nightly duration of 513.88 min (SD = 58 min). The mean reported bedtime was 21:25 (SD = 57 min), and the mean rising time 07:23 (SD = 52 min). Mean sleep efficiency was 96.6% (SD = 2.8%). No significant differences between the bed time and wake up time in the three nights preceding PSG evaluation and the sleep PSG night measured by PSG were evident (see Fig. 2).

4.1. Factor analyses

4.1.1. Spindle frequency

Principal-component analysis using Varimax rotation produced a one-factor solution for spindle frequency (Table 2). The factor accounted for 51.55% of the variance (the eigenvalue was 6.63). This factor was

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**Table 1** and **Fig. 1** show the demographics, behavioral and sleep characteristics, WISC-IV composite scores and spindle features (means and standard deviations) of all enrolled participants. Polysomnographic recordings indicated that the participants slept for a mean nightly duration of 513.88 min (SD = 58 min). The mean reported bedtime was 21:25 (SD = 57 min), and the mean rising time 07:23 (SD = 52 min). Mean sleep efficiency was 96.6% (SD = 2.8%). No significant differences between the bed time and wake up time in the three nights preceding PSG evaluation and the sleep PSG night measured by PSG were evident (see Fig. 2).

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**Fig. 1.** Spindle number, frequency, amplitude, duration and density in each Non-Rapid Eye Movement (NREM) sleep cycle for each electrode derivation. F3 and F4 refer to left and right frontal electrodes; C3 and C4 refer to left and right centrocephalic electrodes; P3 and P4 refer to left and right parietal electrodes; O1 and O2 refer to left and right occipital electrodes.
weighted by spindle frequency scores from all derivations (F3, F4, C3, C4, P3, P4, O1, and O2) and was therefore termed Spindle Frequency.

4.1.2. Spindle amplitude

Principal-component analysis using Varimax rotation produced two distinct factors for spindle amplitude (Table 2). These factors accounted for 66.5% and 18.9%, respectively, of the variance (the eigenvalues were 5.32 and 1.52, respectively). The first factor was weighted by spindle amplitude values on the derivations F3, F4, C3, and C4 and was therefore termed Spindle Amplitude FC. The second factor was weighted by a spindle amplitude values from derivations P3, P4, O1, and O2 and was therefore termed Spindle Amplitude PO.

4.1.3. Spindle duration

Principal-component analysis using Varimax rotation produced two distinct factors for spindle duration (Table 2). These factors accounted for 67.2% and 15.9%, respectively, of the variance (the eigenvalues were 5.38 and 1.28, respectively). The first factor was weighted by spindle duration scores on the derivations C3, C4, P3, P4, O1, and O2. This component appears to reflect sleep spindle durations derived from most regions and was therefore termed Spindle Duration. The second factor was weighted by a spindle duration score from derivations F3 and F4 and was therefore termed Spindle Duration F.

4.1.4. Spindle density

Principal-component analysis using Varimax rotation yielded one distinct factor solution for spindle density (Table 2). This factor accounted for 70.5% of the variance (the eigenvalues were 5.64). This component reflects sleep spindle density from all regions and was therefore termed Spindle Density.

4.2. Analyses of potential confounding variables

One-way ANOVAs revealed that girls had higher scores on the Sleep Spindle Frequency Factors \( F(1,28) = 4.04, p < 0.05 \) and children with the highest pubertal scores had higher factor scores on Spindle Duration \( F(1,28) = 3.15, p < 0.01 \). Spearman correlations between Sleep Spindle Factors and age revealed correlation with the Spindle Frequency Factor \( r = -0.49; p < 0.007 \). No significant association was found between any Sleep Spindle Factor and SES. We therefore adjusted for age, pubertal stage and gender in our regression analyses.
4.3. Associations between the frequency, amplitude, duration, and density of sleep spindles and performance on WISC-IV subscales

Sleep spindle frequency was negatively associated with scores on the perceptual reasoning ($R^2 = 0.53, p < 0.05$) and working memory ($R^2 = 0.51, p < 0.05$) WISC-IV subscales independent of age, gender, and pubertal status (Fig. 3).

5. Discussion

The principal goal of our present study was to explore associations between sleep spindle characteristics (duration, frequency, amplitude and density) and performance on WISC-IV measures in healthy typically developing children. Our main finding was that lower sleep spindle frequency was significantly associated with better perceptual reasoning and working memory WISC-IV composite scores in a manner independent of age, gender, and pubertal status. We identified no significant association between sleep spindle density, duration, or amplitude with performance on the WISC-IV. Factor analyses revealed that spindle frequency from the scalp derivations used loaded on similar factor; in our sample, therefore, there were no significant differences noted for the association between sleep frequency and cognition by different scalp locations.

Our finding of a significant negative association between sleep spindle frequency and IQ test performance is consistent with those of the only two previous studies examining the association between sleep spindle features and IQ in children (Chatburn et al., 2013; Geiger et al., 2011). Our results are also consistent with those of previous work showing increased spindle frequency in children with dyslexia (Bruni et al., 2009). Together, these data suggest that there is an inverse relationship between sleep spindle frequency and efficient cognitive processing in children. Higher spindle frequency is associated with poorer information processing, while lower frequency is associated with better processing. These findings are in contrast to the adult studies, in which spindle frequency has been associated with better cognitive functioning (Bodizs et al., 2005; Brière et al., 2000; Fogel et al., 2007; Gaillard and Blois, 1981; Nader and Smith, 2001; Schabus et al., 2006).

Previous studies have found that sleep spindle frequency, amplitude, duration, and density all change as a child matures (Jenni et al., 2004; Louis et al., 1992; Nicolas et al., 2001; Shibagaki et al., 1982; Shinomiya et al., 1999; Tanguay et al., 1975). Specifically, sleep spindle number, density, and duration decrease with age, while spindle frequency progressively increases over time (Nicolas et al., 2001; Shinomiya et al., 1999). Accumulating data in children have indicated associations between reduced spindle frequency and improved cognitive ability, and between higher spindle frequency and the existence of cognitive difficulties. These findings challenge the notion that increased spindle frequency is associated with better cognitive functioning. More research is needed to clarify the nature and direction of any associations among sleep spindle frequency, cognitive functioning, and maturation, and whether the age-related rise in sleep spindle frequency is associated with improvements in the cognitive ability of children.

Our findings are consistent with those of Geiger et al. (2011) and Chatburn et al. (2013), who found a significant association between reduced sleep spindle frequency and working memory performance among children. In addition, we found associations between sleep frequency was significantly associated with better perceptual reasoning and working memory WISC-IV composite scores in a manner independent of age, gender, and pubertal status. We identified no significant association between sleep spindle density, duration, or amplitude with performance on the WISC-IV. Factor analyses revealed that spindle frequency from the scalp derivations used loaded on similar factor; in our sample, therefore, there were no significant differences noted for the association between sleep frequency and cognition by different scalp locations.

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Table 2
Means, SDs, and rotated factor loadings for the sleep spindle parameters.

<table>
<thead>
<tr>
<th>Spindles frequency</th>
<th>Factor loading</th>
<th>Spindles amplitude</th>
<th>Factor loading</th>
<th>Spindles duration</th>
<th>Factor loading</th>
<th>Spindles density</th>
<th>Factor loading</th>
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<td>1</td>
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<td>1</td>
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<td>1</td>
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<tr>
<td>F3</td>
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<td>0.84</td>
<td>15.20</td>
<td>0.94</td>
<td>0.13</td>
<td>0.80</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>SD 0.20</td>
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<td>5.77</td>
<td></td>
<td>0.08</td>
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<td>0.23</td>
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<td>0.79</td>
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</tr>
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<td>0.33</td>
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<td>0.77</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
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<tr>
<td></td>
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<td>2.03</td>
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<td>0.22</td>
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<tr>
<td>O2</td>
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<td>1.95</td>
<td></td>
<td>0.06</td>
<td></td>
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</tr>
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</table>

Factor scores
1 M −.05
SD 1.03
2 M –
SD –

Note: F3 and F4 refer to left and right frontal electrodes; C3 and C4 refer to left and right centrotemporal electrodes; P3 and P4 refer to left and right parietal electrodes; O1 and O2 refer to left and right occipital electrodes.

Of COMT on cognition has been a subject of keen research interest. In some measures, such as switching ability on the Wisconsin Card Sorting Test (WCST) (Joober et al., 2002; Malhotra et al., 2002; Rosa et al., 2004) and the N-Back test of working memory (Goldberg et al., 2003), Met-Met homozygosity predicts better task performance for both healthy and clinical adult populations. This suggests that variations in COMT genotype affect performance on prefrontal cortex-dependent tasks, such as working memory and switching or shifting attention. In addition, the Val158Met polymorphism of COMT has been associated with intelligence in a number of studies in typically developing participants (e.g., Barnett et al., 2007), while several studies have suggested that the Met-Met genotype has an advantage with regard to working memory (Bruder et al., 2005) and full-scale IQ (Shashi et al., 2006).

COMT activity has been associated with sleep in narcolepsy (Dauvilliers et al., 2001) and Parkinson’s disease (Frauscher et al., 2004), wherein dopamine system dysfunctions are believed to play important etiological roles (e.g., Eisensehr et al., 2003; Maguire-Zeiss et al., 2005). It has been suggested that COMT activity contributes to sleep problems via its involvement in dopamine metabolism (Frauscher et al., 2004). Furthermore, in a healthy population of adults, COMT gene variations were associated with consistently lower EEG activity in NREM sleep, REM sleep, and wakefulness (Bodemmann et al., 2009a). Specifically, Val/Val allele carriers exhibited less activity than Met/Met homozygotes in both REM and NREM sleep. This difference was resistant against the effects of sleep deprivation and modafinil. These data demonstrate that COMT-related mechanisms contribute to individual differences in brain oscillations, which are functionally related to executive performance and sleep.

Bodemmann et al. (2009b) quantified the contribution of this polymorphism to the effects of sleep deprivation and modafinil on subjective state, cognitive performance and recovery sleep in healthy volunteers. They found that two 100-mg doses of modafinil improved vigor and well-being, and maintained baseline performance with respect to executive functioning and vigilant attention throughout sleep deprivation in Val/Val genotype subjects, but had little effect on subjects with the Met/Met genotype.

In sum, convergent lines of research indicate that COMT is associated with working memory and switching; two aspects of executive function.

spindle frequency and performance on perceptual reasoning tests (Table 3). Notably, all three studies yielded some strikingly similar results, in that different components of intellectual ability showed distinct relationships with physiological features of sleep spindles. In the cited studies and the present report, associations between sleep spindle features and cognitive variables were evident principally when the capacity to think logically and to solve problems arising in novel situations and the capacity to identify patterns and relationships were evaluated. These features are considered to reflect “fluid intelligence” (Cattell, 1963; Jaeggi et al., 2008) and are thought to be relatively independent of learning. In contrast, no association between sleep spindle and verbal IQ was found. Verbal IQ abilities are considered to be more dependent on learning (Ashby et al., 2005).

It might be argued that both sleep spindle frequency and “fluid intelligence” are linked to the “g” factor, a general brain property underlying the efficiency of neural processes associated with such ability (Duncan et al., 1995). Behavioral genetic research has established that “g” is highly heritable (Deary et al., 2009). The factor correlates with other biological measures, including brain size (McDaniel, 2005). Many studies have found that sleep patterns are also highly heritable (de Castro, 2002; Fisher et al., 2012; Heath et al., 1990; Partinen et al., 1983). We thus propose that the correlations evident between spindle frequencies and IQ scores reflect the influence of a common causal factor affecting spindle frequency and performance on some aspects of IQ tests reflecting inherent abilities (thus not influenced by the environment).

One potential candidate might be catechol-O-methyltransferase (COMT), which is an enzyme that degrades catecholamines in the prefrontal cortex (PFC) (Weinshilboum et al., 1999). A G-to-A base-pair substitution in exon 4 of the COMT gene (Grossman et al., 1992), which substitutes methionine for valine at codon 158 (Val158Met) (Lachman et al., 1996), results in significantly higher PFC catecholamine levels because the enzyme encoded by the Met allele has 3-4-fold lower activity than that encoded by the Val allele (Chen et al., 2004; Lachman et al., 1996).

Among the catecholamines, dopamine (DA) critically modulates PFC cognition, particularly different aspects of executive function, such as working memory and switching abilities (Arnsten, 1997; Luciana and Collins, 1997; Williams and Goldman-Rakic, 1995). Thus, the impact of COMT on cognition has been a subject of keen research interest. In some measures, such as switching ability on the Wisconsin Card Sorting Test (WCST) (Joober et al., 2002; Malhotra et al., 2002; Rosa et al., 2004) and the N-Back test of working memory (Goldberg et al., 2003), Met-Met homozygosity predicts better task performance for both healthy and clinical adult populations. This suggests that variations in COMT genotype affect performance on prefrontal cortex-dependent tasks, such as working memory and switching or shifting attention. In addition, the Val158Met polymorphism of COMT has been associated with intelligence in a number of studies in typically developing participants (e.g., Barnett et al., 2007), while several studies have suggested that the Met-Met genotype has an advantage with regard to working memory (Bruder et al., 2005) and full-scale IQ (Shashi et al., 2006).
that are considered to be part of “fluid intelligence.” COMT genotypes have also been shown to be associated with EEG activity during sleep, and to modulate the impact of sleep deprivation on cognition function.

Future work on genetic factors associated with intelligence and sleep, such as the above-described COMT polymorphism, and on the brain mechanisms involved in sleep spindle production, could help clarify the physiological nature of the observed associations.

Although Geiger et al. (2011) examined several important aspects of sleep physiology, no information on sleep spindle density, amplitude, or duration was collected in their study. Our present study extends their findings by showing that sleep spindle density, duration, and amplitude are not linked to performance levels on IQ tests. This is important because these are the features of sleep spindles that are affected to a greater extent by the environment. For example, intra-subject variability in spindle amplitude is considerable; amplitudes may differ even between two EEG channel recordings from the same subject (Hasan, 1983). In addition, an increase in sleep spindle density and duration has been noted in response to environmental auditory stimulation (Dang-Vu, 2012; Dang-Vu et al., 2010; Kawada, 1995; Kawada and Suzuki, 1994), and increased spindle activity is evident after training on a declarative learning task. In contrast, sleep spindle frequencies are stable over nights of recording (Geiger et al., 2011) and have been proposed to be independent of the specific situations (Geiger et al., 2011). We suggest that different processes may underlie the observed associations between features of sleep spindles and intelligence. The “trait like” aspects of sleep spindles, such as sleep frequency, may be associated with stable heritable, “trait like” aspects of IQ, whereas the state dependent features of sleep spindles, such as spindle density or duration, may be related to the more plastic and situational aspects of learning (e.g., memory formation and consolidation) that have been shown to result in a temporary increase in sleep spindle density and duration. Future research should further explore the interactions between specific aspects of sleep spindles and particular features of intelligence, learning, and memory. It is important to delineate such associations and to understand the underlying mechanisms.

5.1. Limitations and future directions

The present study had certain limitations. First, although all of the participants scored below the accepted cutoff value of the Pediatric Sleep Questionnaire, exhibited no evidence of oxygen desaturations, and did not show paradoxical breathing at either the thoracic or abdominal level, the presence of SDB cannot be completely excluded because we did not place a nasal cannula or a thermistor which were not well tolerated by the children participating in ambulatory PSG. Thus, future research comparing data obtained with and without cannulas is needed to determine their impact on spindle formation. Second, although statistical power analysis indicated that our sample size was adequate to allow detection of significant effects and our sample size is larger than the previous studies on the same topic, the present sample is rather small and our results should be considered preliminary in nature. Third, our findings are correlational, so cause-and-effect connections cannot be determined. Fourth, we conducted PSG testing over only one night, and were thus unable to assess intra-individual stability in sleep spindle characteristics across several nights. Fifth, although we minimized interference with regular sleep habits and the sleep environment by acquiring data in the home environment, we are unable to state that we successfully excluded all environmental factors that might affect child sleep. Future studies should explore the physical and environmental factors that influence sleep spindle patterns. Finally, although our findings support the existence of an association between reduced sleep spindle frequency and intelligence in children, future research is needed to more precisely define the brain circuits involved. Little is known regarding the cerebral correlates of human spindles. Several studies in adults have suggested an activation pattern that includes both thalami, the anterior cingulate cortex, the left anterior insula, and (bilaterally) the superior temporal gyrus (see Pinault, 2004; Steriade and Deschenes, 1984, 1988). The thalamic signal is consistent with the known involvement of the thalamus in sleep homeostasis, while the limbic region’s signal is consistent with roles in memory consolidation. The relationship between sleep spindles and general cognitive ability suggest that sleep spindle measures may reflect anatomical and functional differences in the TC system (Finelli et al., 2001), such as in the myelination of TC fibers and the number or strength of TC connections (Fogel et al., 2007; Miller, 1994). Lower sleep spindle frequencies may reflect a more efficient TC system, which is associated with higher general cognitive abilities and enables the subjects to encode and process information more efficiently. To date, no study has examined the potential cerebral correlates of spindles in children. Such work is beyond the scope of the present study, but future efforts will be critical for our understanding of the processes underlying the association between sleep and IQ.
6. Conclusions

Our findings suggest that sleep spindle frequency in healthy school-age children is negatively associated with performance on the working memory and perceptual reasoning modules of the Wechsler Intelligence Scale for Children (WISC-IV).

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References


