Electrophysiological Indicators of Sleep-associated Memory Consolidation in 5- to 6-year-old Children

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Author contribution

A-KJ, SW, and MW-B designed the study; A-KJ and SW performed the experiments; A-KJ and MW-B analysed the data; A-KJ and MW-B wrote the manuscript. All authors revised the manuscript.

Competing interests

The authors declare no competing interests.

Author notes

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ABSTRACT

In young adults, memory consolidation during sleep is supported by a time-coordinated interplay of sleep spindles and slow oscillations. However, given tremendous developmental changes in sleep spindle and slow oscillation morphology, it remains elusive whether the same mechanisms as identified in young adults are comparably functional across childhood. Here, we characterise slow and fast sleep spindles and their temporal coupling to slow oscillations in 24 pre-school children. Further, we ask whether slow and fast sleep spindles and their modulation during slow oscillations are similarly associated with behavioural indicators of declarative memory consolidation as suggested from adult literature. Employing a development-sensitive, individualised approach, we reliably identify an inherent, development-specific fast sleep spindle type, though nested in the adult-like slow sleep spindle frequency range, along with a dominant slow sleep spindle type. Further, we provide evidence for the modulation of fast sleep spindles during slow oscillations, already in pre-school children. However, the temporal coordination between fast sleep spindles and slow oscillations is weaker and less precise than expected from adult research. While we do not find evidence for a critical contribution of the pattern of fast sleep spindle modulation during slow oscillations for memory consolidation, crucially, both inherent slow and fast sleep spindles separately are differentially related to sleep-associated consolidation of items of varying quality. While a higher number of slow sleep spindles is associated with stronger maintenance of medium-quality memories, more fast sleep spindles are linked to higher gain of low-quality items. Our results provide evidence for two functionally relevant inherent sleep spindle types in pre-school children despite not fully matured sleep spindle – slow oscillation coupling.

INTRODUCTION

It is widely agreed that rhythmic neuronal activity during sleep supports declarative memory consolidation (Diekelmann & Born, 2010; Watson & Buzsáki, 2015). Compelling evidence suggests that the underlying key mechanism is the reactivation of initially labile, learning-related, neuronal activity in the hippocampus and its integration into cortical networks (Peyrache et al., 2009; Wilson & McNaughton, 1994). This system consolidation results in more durable and integrated mnemonic representations (Diekelmann & Born, 2010). However, given profound developmental changes in rhythmic neuronal activity, it is still elusive whether the neuronal mechanisms facilitating sleep-associated system consolidation identified in young adults apply similarly to children of all ages.

The canonical view suggests that system consolidation is mainly taking place during non-rapid eye movement sleep (NREM) by the precise temporal co-occurrence of hippocampal activity with fast sleep spindles (SP, ~12-16 Hz), initiated by the UP-state of the slow oscillation (SO, < 1 Hz, Buzsaki, 1998; Clemens et al., 2007; Diekelmann & Born, 2010; Helfrich et al., 2018; Klinzing et al., 2016; Latchoumane et al., 2017; Mölle et al., 2009, 2011). SOs are marked by high amplitude UP- and DOWN-states, reflecting alternations in the membrane potential of large populations of cortical neurons between joint depolarisation and hyperpolarisation, respectively (Steriade et al., 1991, 1993). Via cortico-thalamic pathways, SO UP-state depolarisation creates conditions in the thalamus that initiate SPs (Contreras et al., 1997; Steriade, 2006). SPs arise through reciprocal interactions between reticular thalamic and thalamo-cortical neurons of which the latter transmits them to the cortex where they are thought to induce increased plasticity (Bonjean et al., 2011; Lüthi, 2014; Muller et al., 2016; Niethard et al., 2018; Rosanova & Ulrich, 2005; Timofeev et al., 2002). Fast SPs, in turn, have been repeatedly shown to orchestrate hippocampal activity and to facilitate hippocampal-cortical connectivity in rodents and humans (Andrade et al., 2011; Clemens et al., 2007; Siapas & Wilson, 1998; Sirota et al., 2003). Thus, fast SPs offer perfect conditions for the integration of hippocampal activity patterns into cortical networks (Muller et al., 2016; Niethard et al., 2018). Importantly, while fast SPs coupled with hippocampal activity can also occur independently of SOs, it is the triad of SOs, fast SPs, and hippocampal activity that seems to be beneficial for memory (Helfrich et al., 2018; Latchoumane et al., 2017; Muehlroth et al., 2019; Nir et al., 2011).

Besides a fast SP type, predominant in centro-parietal brain areas, there is also a slow, frontal SP type (~9-12 Hz, Andrillon et al., 2011; Mölle et al., 2011) identified in adult human surface electroencephalography (EEG). Slow SPs differ from the fast type in several aspects including e.g. frequency, topography, circadian regulation, preferred phase of occurrence during SOs, their expression across the lifespan, and role for memory (De Gennaro & Ferrara, 2003; Fernandez & Luthi, 2019). That is, contrary to fast SPs, slow SPs occur less numerous during the UP-state and rather during the

transition from the UP- to the DOWN-state. Furthermore, their role for system consolidation is less established. However, it has been hypothesised that rather than hippocampal-neocortical integration, slow SPs may be preferentially involved in cortico-cortical storage mechanisms (Astori et al., 2013; Ayoub et al., 2013; Doran, 2003; Rasch & Born, 2013; Timofeev & Chauvette, 2013).

During development, rhythmic neuronal activity patterns change drastically in their temporal expression, peak frequency, and topographical distribution (Clarke et al., 2001; Hahn et al., 2018; Purcell et al., 2017). The hallmark of the presence of a given rhythm is thereby the existence of an identifiable peak in the power spectrum (Aru et al., 2015; Kosciessa et al., 2020). Considering the adult pattern as a point of reference (slow SPs: 9 (11)-12 (13) Hz, frontal distribution; fast SPs: 12 (13)-16 (15) Hz, centro-parietal distribution; SOs: < 1 Hz, frontal distribution), the following age-differences were reported in developmental samples. Slow rhythmic neuronal activity (0.5-4 Hz), comprising SOs, is most strongly pronounced before the onset of puberty, attenuating thereafter i.e., in the SO power and the steepness of the slope (Campbell & Feinberg, 2009; Kurth et al., 2010a). Moreover, different to SOs in young adults, that predominantly originate in anterior cortical regions, SO onset and spectral dominance was located in central and posterior areas respectively in pre-pubertal children (Kurth et al., 2010b; Timofeev et al., 2020).

Unlike SOs, overall, SPs become more and more present after the age of 4 until early adulthood (Olbrich et al., 2017; Purcell et al., 2017; Scholle et al., 2007). Concerning the differentiation between slow and fast SPs, systematic research in children has been scarce so far. Whereas adult-like slow SPs already evolve early during childhood, adult-like fast SP development seems to be prolonged (D'Atri et al., 2018; Hahn et al., 2018; Purcell et al., 2017). Specifically until the age of 4 to 5 years, adult-like fast SPs are comparatively rare, evolving around puberty (D'Atri et al., 2018; Hahn et al., 2018; Purcell et al., 2017). In addition, it is typically challenging to provide evidence for separate SP types in children. The gold-standard for identifying more than one rhythm in the SP range in children would be two separate spectral peaks (Aru et al., 2015; Kosciessa et al., 2020). Independent of recording site, SP peaks usually fall in the adult-like slow SP frequency range suggesting a dominance of adult-like slow SPs during childhood (Hoedlmoser et al., 2014; Shinomiya et al., 1999). Across maturation, the peak frequency increases with an adult-like fast centro-parietal peak evolving around puberty (Campbell & Feinberg, 2009; Shinomiya et al., 1999; Tarokh & Carskadon, 2010).

In line with findings of less pronounced SPs across childhood, a recent study reported also lower coupling between SPs and SOs during childhood that increased across adolescence (Hahn et al., 2020). Together, the existing literature suggests that the assumed core mechanisms of sleep-associated memory consolidation, i.e., adult-like fast SPs and the temporal synchronisation of SPs by SOs, might not be fully functional in children, yet.

However, there is no reason to assume a-priori that functionally equivalent rhythmic neuronal events are expressed exactly in the same way across the lifespan (Clarke et al., 2001; Shinomiya et al., 1999). Nevertheless, analyses of sleep electrophysiology in children mostly rely on the application of fixed adult-derived, (nevertheless often inconsistent), criteria without ensuring the presence of a rhythm (i.e., a spectral peak) within the search space (but see Friedrich et al., 2019; Olbrich et al., 2017). As a result, it often remains elusive whether the rhythmic neuronal phenomenon of interest in a given child during a given developmental period is reliably captured or whether functionally different rhythmic neural events might be mixed (Cox et al., 2017; Ujma et al., 2015). Considering evidence from adults for distinct functions, this applies specifically to slow and fast SPs during childhood. A distinction into slow and fast SPs based on adult criteria may simply miss relevant developmental shifts. Therefore, it is unclear whether the scarce findings on fast SPs in children indeed reflect a missing fast SP rhythm or a bias of the analysis approach. Given well-known developmental frequency acceleration (Campbell & Feinberg, 2016; Marshall et al., 2002), it is conceivable, that a functionally relevant, development-specific fast SP type might be already present in children, though expressed at slower frequencies than in adults. Covered by the adult slow frequency range this might impede its detection (Olbrich et al., 2017). Thus, imprecisely capturing the within-person, age-specific neuronal rhythm of interest may pose specific challenges when aiming to uncover its mechanistic role in memory consolidation across development (Muehlroth & Werkle-Bergner, 2020).

Indeed, while numerous studies support the important role of sleep for declarative memories across childhood, evidence on the electrophysiological correlates of system consolidation mechanisms during sleep remains scarce and inconsistent (Ashworth et al., 2014; Backhaus et al., 2008; Friedrich et al., 2019, 2020; Hahn et al., 2018; Hoedlmoser et al., 2014; Kurdziel et al., 2013; Peiffer et al., 2020; Prehn-Kristensen et al., 2011; Wilhelm et al., 2008, 2013, 2020). Comparable to findings in adults, both SPs and slow neuronal activity were related to sleep-associated memory consolidation in children; though highly inconsistently across memory tasks and age groups (Friedrich et al., 2015, 2019; Hahn et al., 2018; Hoedlmoser et al., 2014; Kurdziel et al., 2013; Maski et al., 2015; Prehn-Kristensen et al., 2011, 2014; Wang et al., 2017). While most studies did not differentiate between slow and fast SPs, recent longitudinal findings suggest that the development of adult-like fast SPs and enhanced temporal synchrony between SPs and SOs supports effects of sleep on memory from pre-pubertal childhood to adolescence (Hahn et al., 2018; Hahn et al., 2020). In parts, the simple extrapolation of adult-derived criteria for the detection of sleep-associated neural rhythms may have impeded the identification of the neural mechanisms supporting system consolidation during development – especially in pre-school children.

Besides potential biases induced when assessing neuronal rhythms across development on adult-based criteria, it has been suggested that ignoring the encoding strength of individual memories (i.e., the quality) prior to sleep might account for additional inconsistencies across tasks (Muehlroth et al., 2020; Wilhelm et al., 2012, 2020). Depending on the quality of a memory, the outcomes and underlying processes of memory consolidation might differ. That is either the maintenance of memories already accessible prior to sleep or the gain of items previously not consciously available (Dumay, 2016, 2018; Fenn & Hambrick, 2013). Several studies indicated that sleep-associated system consolidation mechanisms preferentially act on the maintenance of memories of weak to intermediate quality (Denis et al., 2020; Drosopoulos et al., 2007; Fenn & Hambrick, 2013; Muehlroth et al., 2020; Schapiro et al., 2018; Schreiner & Rasch, 2018; Wilhelm et al., 2012; but see Schoch et al., 2017; Tucker & Fishbein, 2008). Relying on the average memory may thus introduce further unwanted noise (Tulving, 1967) when trying to disentangle the functions of sleep oscillations for memory consolidation across development. Hence, examining how sleep supports memory consolidation across childhood needs appropriate assessment of the electrophysiological and memory processes involved.

The present study targeted two main questions: Firstly, we asked whether the specific electrophysiological indicators of sleep-associated memory consolidation can be detected reliably in pre-school children. Therefore, we set out to characterise slow and fast SPs and their temporal interaction with SOs using individualised rhythm detection in pre-schoolers. Secondly, we asked whether SPs and their temporal modulation by SOs in 5- to 6-year-olds would show comparable associations with the behavioural indicators of memory consolidation as suggested by findings in adults. To control for inter-individual differences in memory quality, we adapted a paradigm developed to control for memory quality of individual items in single adult participants (Fandakova et al., 2018; Muehlroth et al., 2019) for the use in pre-school children.

METHODS

PARTICIPANTS

Thirty-six pre-school children (19 female, $M_{ag\ e}$= 69.53 mo, SD_{age} = 6.50 mo) were initially enlisted to participate in our exploratory study on the role of sleep oscillations in memory consolidation in pre-school children. Participants were recruited from day-care centres in Berlin, Germany and from the database of the Max Planck Institute for Human Development (MPIB). Five participants did not complete the study protocol. Data collection from four children was incomplete due to technical failures during one of the two polysomnographic (PSG) recordings. Additionally, three participants were excluded from further analyses because they failed to complete the behavioural task. Therefore, the final sample consisted of 24 children (14 females; M_{age} = 70.71, SD_{age} = 7.28 mo). The participants were randomly assigned to one of two learning conditions. One, in which children studied 50 scene-object associations

(N = 14, M_{age} = 68.57, SD_{age} = 7.51 mo) and another one, in which children studied 100 scene-object associations (N = 10, M_{age} = 73.70, SD_{age} = 6.08 mo). The two groups did not differ significantly in their mean age (Z = -1.76, p = 0.078, $CI_{2.5,\ 97.5}$ [-2.44; 0.00]). All participants were native German speakers without current or chronic illness, use of medications, personal or family history of mental and sleep disorder, obesity (body mass index > 28kg/m²), respiratory problems (e.g. asthma), and without evidence of a learning disability. All participants completed a short screening prior to study participation. Subjective sleep quality was assessed by the "Children's Sleep Habit Questionnaire" (CSHQ, Schlarb et al., 2010) and the "Children's Sleep Comic" (SCC, Schwerdtle et al., 2012). The Strengths and Difficulties Questionnaire (SDC, Goodman, 1997) was used to screen for behavioural and emotional conspicuousness. In addition, parents filled in the Children's Chronotype Questionnaire (Werner et al., 2009), a short demographic questionnaire, and a sleep log starting three days prior to the first PSG-night. Children received a gift for their participation and the families received monetary compensation. The study was designed in agreement with the Declaration of Helsinki and was approved by the local Ethic Committee of the MPIB.

GENERAL PROCEDURE

The experimental protocol for each participant encompassed seven days and included two nights of electrophysiological sleep recordings (Figure 1). Sleep was recorded in the participants' familiar environment using ambulatory PSG (SOMNOScreenplus; SOMNOmedics, Germany). PSG-recordings started and ended corresponding to each participant's individual bedtime habits. The first night served as adaption and baseline night (Figure 1, baseline night). The second night was flanked by an associative scene-object memory task with cued recall before and after sleep (Figure 1, learning night). We contrasted indicators of sleep quality (see Methods) between the two nights and found no differences between baseline and learning night (Table S1). All behavioural assessments took place in a standardised laboratory environment at the MPIB. Three days before the first night, children's sleep was stabilised according to their habitual bed and wake times and monitored by sleep logs filled in by the parents together with their children.

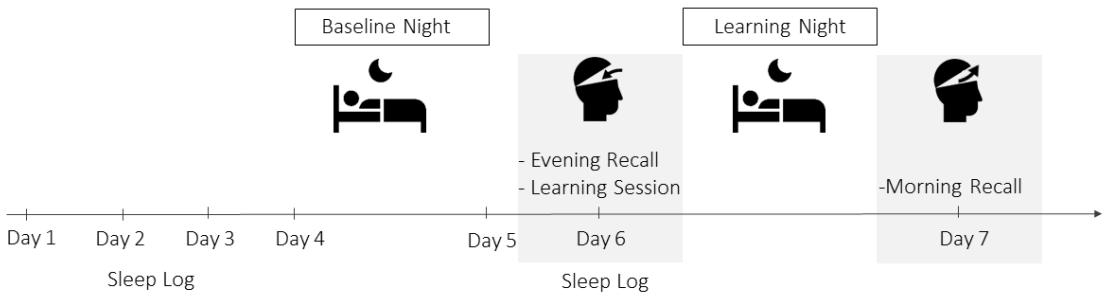

Figure 1. Experimental Procedure. Sleep was monitored for two nights (baseline and learning night) using ambulatory PSG. Participants started filling in a daily sleep log three days prior the baseline night and continued throughout the whole procedure. The memory task took place before and after the learning night (grey boxes).

MEMORY TASK

The memory task used in the present study was a child-adapted version of an associative scene-word memory paradigm designed to trace the quality of associative memories within individuals using repeated cued recall sessions (Fandakova et al., 2018; Muehlroth et al., 2019). In order to adapt the task to our population of 5- to 6-year-old children, where reading abilities are only starting to evolve, we replaced the written nouns with photographs of everyday objects. During the *encoding phase* (encoding, Figure 2), scene-object pairs were presented for 4000 ms. Each pair was followed by the presentation of a 3-point Likert scale for 2000 ms where participants were asked to indicate how well they were able to apply a previously trained imagery strategy (see below). A fixation cross of 1000 ms separated individual trials. Immediately after the encoding session, a *cued recall plus feedback session* followed (recall & feedback, Figure 2). The scenes served as cues and participants were asked to verbally recall the object corresponding to the scene within a 8000 ms interval. Correctness of answers was coded by the experimenter and, in addition, aurally recorded. Subsequently, the correct pairing was again presented for 2000 ms irrespective of the previous answer. This feedback was intended to provide an additional learning opportunity. The availability of specific scene-object associations before and after sleep was tested by a cued recall test prior to bedtime (*evening recall*, Figure 2) and during a cued recall test in the morning (*morning recall*, Figure 2). The evening recall took place in the evening following a 10 min break after the cued recall plus feedback session. The morning recall was performed in the morning, two hours after the participant woke up. Preceding the main memory paradigm, participants were instructed to remember a scene-object pair by integrating the scene and the object into one joint vivid mental image. Participants trained applying this imagery strategy in 10 trials that were not part of the main task. To further adapt task procedures for young children, we reduced the original number of stimuli to adjust task difficulty and attention requirements. Due to a lack of comparable studies in this age group but based on comparable studies in children of older age (Hoedlmoser et al., 2014; Urbain et al., 2016), we created two lists of different trial length: one with 50 and another one with 100 non-associated pairs of scenes and objects. This resulted in two groups learning a different amount of scene-object associations (from now on called $Group_{50}$ and $Group_{100}$). As we could not determine the appropriate number of scene-object pairs for 5-to 6-year-old children a priori, the trial length manipulation was initially intended to explore the task-difficulty space in this age-range. However, as it turned out in the analyses, trial-length groups did not differ with regard to their memory performance (Table S2, Figure S1). Hence, for most analyses, we collapsed across both groups. Despite collapsing across groups, we indicate group membership in result plots. The whole learning session lasted

maximally 30 min ($Group_{100}$, including breaks). Pairs of scenes and objects were presented on black background on a 15.6'' screen. Scenes were always displayed in the left hemifield and objects in the right hemifield. The order of presentation was randomised across learning and cued recall sessions but not across participants. In addition, the first 50 trials were equal between $Group_{50}$ and $Group_{100}$. The task was implemented using PsychToolbox (Kleiner et al., 2007) for Matlab (MathWorks, Natick, MA).

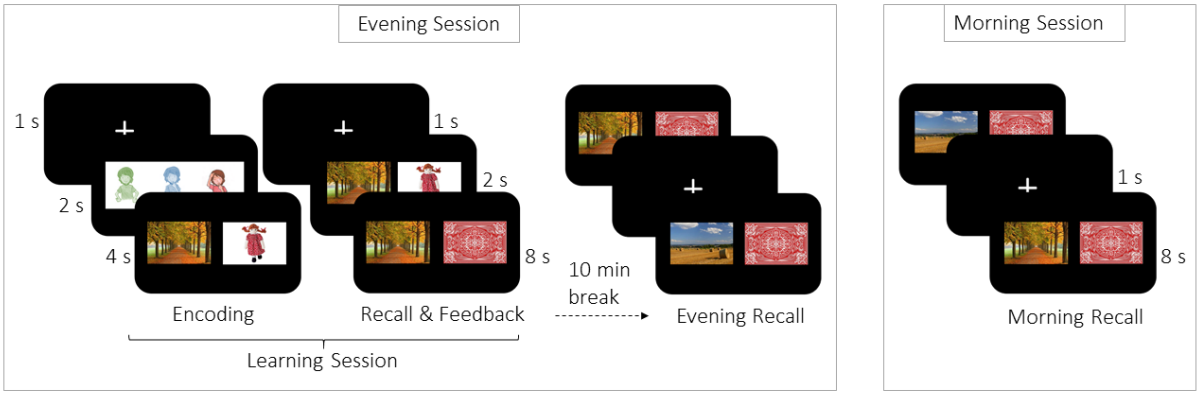

Figure 2. Associative Memory Task. During the evening session, participants studied scene-object pairs in two runs (learning session; encoding, recall & feedback) and were tested for their memory of the learned pairs during the evening recall. In the morning, participants were again probed for their memory of the learned scene-object pairs with a cued recall task (morning session; morning recall).

BEHAVIOURAL ANALYSES

General performance during recall sessions was calculated as the ratio of correctly recalled objects to the total number of trials (i.e., 50 or 100) multiplied by 100. The effect of sleep on memory consolidation was measured as the percentage of successfully recalled items during the morning recall relative to the total number of items recalled during the evening. Given the two recall sessions in the evening (recall & feedback, evening recall), we were able to analyse memory consolidation contingent on each item's recall history during the evening session (Figure 2, Dumay, 2016; Muehlroth et al., 2020). Therefore, we distinguished three categories of items and assessed the effect of sleep on memory consolidation within these three categories separately. Firstly, items never recalled during the evening were categorised as ***low memory quality*** items. Secondly, items correctly remembered during both evening recalls (recall & feedback and evening recall) were categorised as ***high memory quality*** items. Lastly, items recalled correctly only once during the learning session *were considered as of* ***medium memory quality***. Hereby, we took items both remembered during the evening recall but not during the recall & feedback session, as well as items remembered during the recall & feedback session but not during the evening recall into account. Even though theoretically less likely, the ability to recall an item during the recall & feedback session but not during the evening recall was evident in 13 out 24 participants and applied to only a small number of items except for one subject where it applied to 39 items. Conceptually, the distinction

of low-, medium-, and high-quality memories allows for different outcomes of memory consolidation in the morning (Dumay, 2016; Fenn & Hambrick, 2013; Muehlroth et al., 2020). There might be 1) memory gain in the case of successfully recalled low-quality memories (not accessible during the evening session) and 2) memory maintenance for medium- and high-quality memories (accessible already during the evening session).

SLEEP POLYSOMNOGRAPHY ACQUISITION AND ANALYSES

DATA ACQUISITION

Sleep was recorded using an ambulatory PSG-system (SOMNOscreen plus, SOMNOmedics GmbH, Randersacker, Germany). For EEG recordings, a total of 15 gold electrodes were placed according to the international 10-20 System (Jasper, 1958) including left and right horizontal electrooculogram (HEOG), two submental electrodes referenced against one chin electrode for electromyogram (EMG), and seven active scalp electrodes (F3, F4, C3, Cz, C4, Pz, Oz). The ground electrode was placed at AFz. Two electrodes were placed on the left and right mastoids (A1, A2) for later re-referencing. EEG-data was recorded between 0.2-75 Hz at a sampling rate of 128 Hz against the common reference Cz. In addition, cardiac activity was recorded using two electrocardiogram (ECG) derivations. Impedances were kept below 6 kΩ, prior to start of the recordings.

EEG PRE-PROCESSING

Initially, PSG data was offline filtered and re-referenced against the averaged mastoids (A1, A2) for visual sleep stage identification using BrainVisionAnalyzer 2.1 (Brain Products, Germany). Sleep stages were then visually classified for epochs of 30 s by two scorers according to the rules of the American Academy of Sleep Medicine (Berry et al., 2015) using the program SchlafAus (Gais, 2005). Based on the visual scoring, the following indicators of the sleep quality (Ohayon et al., 2017) were calculated: (1) total sleep time (TST, the time spent in N1, N2, N3 and R), (2) percentage N1, N2, N3, R (the time spent in a respective sleep stage relative to TST), and (3) wake after sleep onset (WASO, the time awake between sleep onset and final awakening). Afterwards, using Matlab R2016b (Mathworks Inc., Sherbom, MA) and the Fieldtrip toolbox (Oostenveld et al., 2011), EEG data was semi-automatically cleaned for the detection of rhythmic neuronal events during sleep. In a first step, bad EEG channels were rejected based on visual inspection. Then, an automatic artefact detection algorithm was implemented for the remaining channels on 1 s epochs to exclude segments with strong deviations from the overall amplitude distribution. Therefore, mean amplitude differences were z-standardized within each segment and channel. Segments were marked as bad if either visually identified as body movements or if they exceeded an amplitude difference of 500 µV. Furthermore, segments with a z-score exceeding 5 in any channel were excluded (see Muehlroth et al., 2019 for similar procedures).

DETECTION OF RHYTHMIC NEURONAL ACTIVITY

SLEEP SPINDLE DETECTION

SPs were detected during NREM sleep (N2 and N3) using an established algorithm (Klinzing et al., 2016; Mölle et al., 2011; Muehlroth et al., 2019) with individually adjusted frequency bands and amplitude thresholds (Muehlroth & Werkle-Bergner, 2020). Given evidence for a slow SP type being more prevalent in frontal areas and a fast SP type predominant in central and parietal areas (Anderer et al., 2001; De Gennaro & Ferrara, 2003), we firstly identified the individual SP peak frequency between 9-16 Hz in averaged frontal and centro-parietal electrodes. Power spectra were calculated by applying a Fast-Fourier Transform (FFT) on every 5 s artefact-free epoch using a Hanning taper. On the assumption that the EEG background spectrum is characterized as A*f(-a) (Buzsáki & Mizuseki, 2014), the resulting power spectra were then fitted linearly in the log (frequency)-log (power) space using robust regression to model the background spectrum. The estimated background spectrum was then subtracted from the original power spectrum (Figure 3 (A) to (B)). Using this approach, the resulting peaks in the power spectrum represent rhythmic, oscillatory activity (Kosciessa et al., 2020). Finally, the frontal and centro-parietal peak frequency was identified in the corrected power spectra with an automated algorithm combining a first derivative approach (Grandy et al., 2013) with a classical search for maxima (Figure S2 for all individual power spectra). Individual frequency bands for SP detection in frontal, central, and parietal electrodes were defined as frontal or centro-parietal peak frequency ± 1.5 Hz, respectively (Mölle et al., 2011). EEG data was then band-pass filtered using a Butterworth two-pass filter of 6th order for the respective frequency bands and the root mean square (RMS) was calculated at every sample point using a sliding window of 0.2 s. The resulting RMS signal was smoothed with a moving average of 0.2 s. A SP was detected, whenever the amplitude of the RMS signal exceeded the mean of the filtered signal by 1.5 SD for 0.5-3 s. Succeeding SPs with boundaries within an interval of 0.25 s were merged if the resulting event did not exceed 3 s. Within such a merging run, one SP could only be merged with one other SP. The merging process was repeated iteratively until no further merging was possible (Mölle et al., 2011; Muehlroth et al., 2019). Only detected SP events in artefact-free segments were considered. Given the results of our time-frequency analyses of the temporal association between SPs and SOs, we additionally extracted SPs in frontal, central, and parietal electrodes higher than the individually identified upper limit for the event coupling analyses (peak frequency + 1.5 Hz < “high” SPs < 16 Hz, Figure 3 (B), Table S3 for descriptive measures of individually identified and “high” SPs).

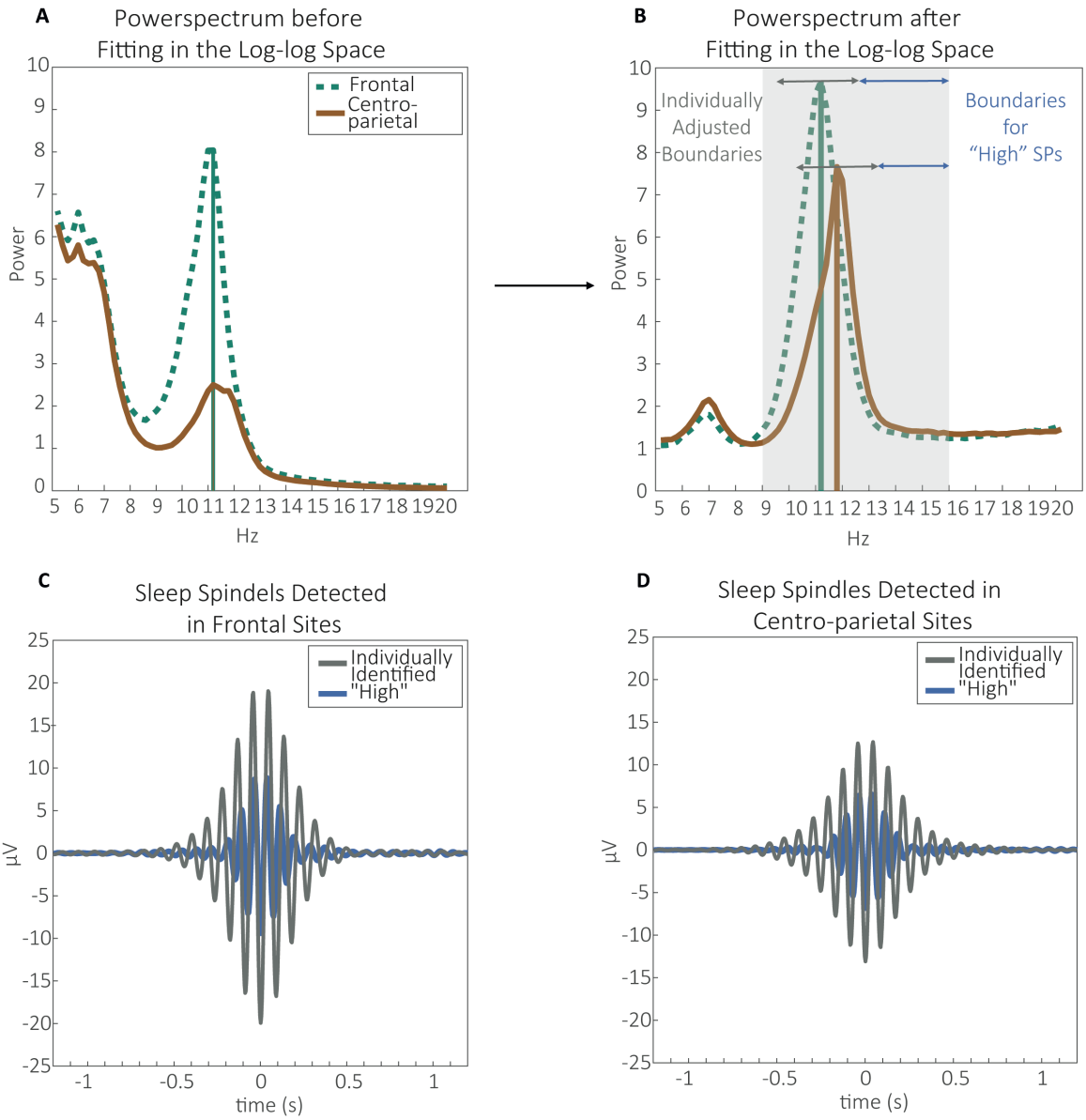

Figure 3. Schematic of the approach to define SP frequency boundaries based on the individual peak frequency and "high" SPs in averaged frontal and centro-parietal electrodes. **(A)** The original power spectra were **(B)** corrected by their background spectra. Based on the first derivative and the maximum peak, SPs were individually identified within ± 1.5 Hz around the respective peaks. We additionally extracted SPs specifically higher than our individually identified upper boundary (**(B)** "High" SPs) for coupling analyses between SPs and SOs. **(C & D)** Shape of averaged individually identified and "high" SPs detected in **(C)** frontal and **(D)** centro-parietal sites.

SLOW OSCILLATION DETECTION

Given the evidence that in children slow rhythmic neuronal activity during sleep shows a posterior rather than an anterior prevalence (Kurth et al., 2010b), SOs were detected at all electrodes. Detection was based on Mölle et al. (2011) and Muehlroth et al. (2019) using an individualised amplitude criterion. The EEG signal was first filtered between 0.2-4 Hz using a Butterworth two-pass filter of 6th order. Following, zero-crossings were detected in the filtered-signal and positive and negative half waves were identified.

A negative half-wave, combined with a succeeding positive half-wave with a frequency between 0.5-1 Hz was considered a potential SO. A potential SO was finally considered a proper SO, when its peak-to-peak amplitude exceeded 1.25 times the average peak-to-peak amplitude of all potential SOs and when the amplitude of the negative peak only exceeded 1.25 times the average negative amplitude of all putative SOs. Finally, only SOs that did not overlap with artefact segments were extracted.

STATISTICAL ANALYSES

Statistical analyses were conducted using the open-source toolbox Fieldtrip (Oostenveld et al., 2011) for Matlab (R2016b, Mathworks Inc., Sherbom, MA) and R 3.6.1 (R Core Team, 2014). Due to violations of the assumption of normality in some variables (Shapiro-Wilk Test) and given our small sample size, most analyses were based on non-parametric approaches. For correlations, pairwise-comparisons, and regression analyses we provide the 95-% simple bootstrap percentile confidence interval (*CI*) of the respective parameter estimate, based on 5000 case re-samples. For regression analyses, we turned to robust methods whenever there were indicators for outliers, high leverage observations, or influential observations (QQ-Plot, Cook's Distance). For repeated measure Analyses of Variance (ANOVA), degrees of freedom were Greenhous-Geisser ($\mathcal{E} < 0.75$) or Huyn-Feld ($\mathcal{E} > 0.75$) corrected in case of violations of sphericity. The generalised eta-squared (η^2_G) is provided as a measure of effect size. Planned comparisons and post-hoc analyses for ANOVAs were conducted using non-parametric Wilcoxon rank-sum tests for independent comparisons and using Wilcoxon signed-rank tests for dependent comparisons. Missing data was handled by list wise exclusion. All post-hoc tests were corrected for multiple comparisons using the Bonferroni-Holm method (Eichstaedt et al., 2013).

TIME-FREQUENCY ANALYSES OF THE TEMPORAL ASSOCIATION BETWEEN SLEEP SPINDLES AND SLOW OSCILLATIONS

To describe the modulation of SPs by SOs, a first set of analyses explored power modulations during SOs (Muehlroth et al., 2019). Analyses were conducted during NREM sleep (N2 and N3) on artefact-free segments only. Trials containing SOs were selected by centring the data ± 3 s around the DOWN-peak of SOs. To allow for the interpretation of any SO-related power de- or increase, we matched every SO trial with a randomly chosen SO-free 6 s segment from the same electrode and sleep stage. Subsequently, time-frequency representations between 5-20 Hz were derived for trials with and without SOs using a Morlet wavelet decomposition (12 cycles) in steps of 1 Hz. Time-frequency representations during SO trials were then compared to SO-free trials within every participant using independent-sample *t*-tests. Given the high incidence of SOs during N3, we often identified a lower number of SO-free as compared to SO trials. To account for this, 100 random combinations of SO and SO-free trials were drawn and contrasts of power during SO- compared to SO-free trials were calculated for all 100 combinations and averaged afterwards. The ratio of N2 to N3 trials was maintained during

this procedure. The resulting *t*-maps represent power in- and decreases between 5-20 Hz during SO-compared to SO-free trials within every individual. Finally, we conducted a cluster-based permutation test (Maris & Oostenveld, 2007) with 5000 permutations within a time segment of -1.2-1.2 s (centred to the DOWN-Peak of the SO) to compare *t*-maps against zero on a group-level. This time segment was chosen to cover one complete SO cycle (0.5-1 Hz, 1-2 s).

ANALYSES OF THE TEMPORAL RELATION BETWEEN DISCRETE SLEEP SPINDLES AND SLOW OSCILLATIONS

The general co-occurrence of discrete SPs and SOs was determined by identifying the percentage of SP centres (SO DOWN-peaks) during NREM (N2 & N3) occurring within an interval of ± 1.2 s around the DOWN-peak of SOs (SP centre), relative to all SPs (SOs) detected during NREM sleep. To explore the temporal coordination of SPs with respect to the SO cycle, we created peri-event time histograms (PETH) by determining the percentage of SP centres occurring within bins of 100 ms during an interval of ± 1.2 s around the SO DOWN-Peak. Percentage values within bins reflect the frequency of SP centres occurring within one bin relative to the total number of SP centres during the complete SO ± 1.2 s time interval (multiplied by 100). To test, whether the occurrence of SPs within each bin was specific to the SO cycle, differing from spontaneous occurrence, the individual percentage frequency distributions of SP centre occurrence were tested against surrogate distributions using dependent *t*-tests. The surrogate distributions were obtained separately for every individual by randomly shuffling the temporal order of the PETH bins 1000 times and then averaging across the 1000 sampling distributions. A cluster-based permutation test with 5000 permutations was applied to control for multiple comparisons.

RESULTS

INDIVIDUALLY ADJUSTED SLEEP SPINDLE DETECTION REVEALS A SLOW SLEEP SPINDLE TYPE IN FRONTAL REGIONS AND A FAST SLEEP SPINDLE TYPE IN CENTRO-PARIETAL REGIONS

Based on scarce evidence on the expression of fast SPs in children, we explored the possibility that already 5- to 6-year old children express two inherent types of sleep spindles: A slow frontal and fast centro-parietal SP type. After having established two distinguishable peaks in frontal and centro-parietal recording sites (Figure S2), we tested for evidence for two SP types by applying separate repeated measure ANOVAs with the within-person factors NIGHT (baseline vs. learning) and ELECTRODE (F3, F4, C3, Cz, C4, Pz) on individually identified SP frequency, density, and amplitude during NREM (N2 & N3) sleep. Overall, none of the SP measures differed between nights ($F_{frequency}(1,18) = 0.27$, $p = 0.613$, $\eta^2_G < 0.01$; $F_{density}(1,18) = 0.001$, $p = 0.970$, $\eta^2_G < 0.01$; $F_{amplitude}(1,18) = 0.65$, $p = 0.431$, $\eta^2_G < 0.01$). However, as expected, individually identified SPs varied overall in their frequency ($F(1.18,21.28) = 32.68$, $p < 0.001$, $\eta^2_G = 0.33$), density ($F(2.92,52.55) = 14.98$, $p < 0.001$, $\eta^2_G = 0.18$), and amplitude ($F(1.53,27.53) = 53.41$, $p < 0.001$, $\eta^2_G = 0.42$, Figure 4 (A)-(C)) across electrodes. Planned contrasts comparing SP measures in frontal electrodes with central and parietal recording sites revealed significantly lower frequency in F3

and F4 as compared to C3, C4, Cz, and Pz (Figure 4, Table S4 (A), all $Z < -5.00$, all $p < 0.001$). Inversely, density and amplitude was significantly higher in frontal as compared to central and parietal recording sites (Figure 4, Table S4 (A), all $Z < -2.00$, all $p < 0.040$). These effects did not differ between the baseline and learning night (interaction effects: $F_{frequency}(2.28,40.94) = 0.81$, $p = 0.465$, $\eta^2_G < 0.01$; $F_{density}(2.58,46.49) = 1.07$, $p = 0.363$, $\eta^2_G < 0.01$; $F_{amplitude}(2.72,48.88) = 0.71$, $p = 0.536$, $\eta^2_G < 0.01$).

Given the consistent differences between frontal and centro-parietal SP characteristics, we collapsed across nights and frontal (F3, F4) and centro-parietal (C3, Cz, C4, Pz) recording sites, creating measures representing a slow (frontal) and fast (centro-parietal) SP type for all following analyses.

The mean frequency of averaged slow (frontal) SPs was 11.07 Hz (min = 9.90 Hz, max = 12.69 Hz) while the averaged fast (centro-parietal) SPs had a mean frequency of 11.84 Hz (min = 11.19 Hz, max = 12.92 Hz). Please note that despite the fact that (a) separate peaks were identifiable and (b) slow (frontal) and fast (centro-parietal SPs) differed reliably in their peak frequency, the faster SPs in our pre-school children were still below the typical fast SP frequency range in adults (Andrillon et al., 2011; Klinzing et al., 2016; Mölle et al., 2011).

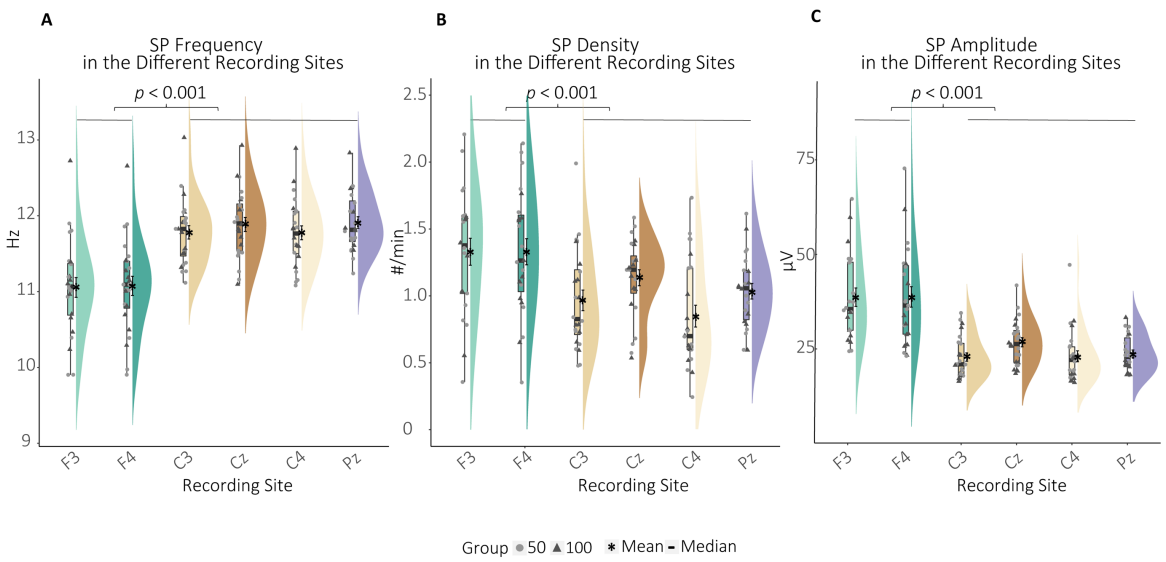

Figure 4. Individually identified SP **(A)** frequency, **(B)** density, and **(C)** amplitude in frontal, central, and parietal electrodes. *P*-values represent the results from Wilcoxon signed-rank tests comparing the average frontal and centro-parietal measures (Table S4 (B)). Frontal SPs differed from centro-parietal SPs in all three measures implying the presence of a dominant slow frontal and a fast centro-parietal SP type.

Spearman's rank correlations indicated that higher frequency, density, and amplitude of slow SPs was associated with higher corresponding values of fast SPs ($\rho_{frequency} = 0.50$, $p = 0.014$, $CI_{2.5,\ 97.5}$ [0.13, 0.75], $\rho_{density} = 0.72$, $p<0.001$, $CI_{2.5,\ 97.5}$ [0.44, 0.88], $\rho_{amplitude} = 0.84$, $p<0.001$, $CI_{2.5,\ 97.5}$ [0.62, 0.94]). Furthermore, neither the percentage of NREM sleep nor age were associated with slow or fast SP

frequency, density, or amplitude (all $-0.5 < \rho < 0.5$, all $p > 0.09$, Figure S3). In sum, individually identified SPs in frontal and centro-parietal sites differed in their characteristics indicating the presence of a slow and a fast SP type already in 5- to 6-year-old children.

NO EVIDENCE FOR AN ANTERIOR OR POSTERIOR PREDOMINANCE OF SLOW OSCILLATIONS

Given the evidence that in children slow rhythmic neural activity during sleep shows a posterior rather than an anterior prevalence (Kurth et al., 2010b), we compared SO characteristics in averaged frontal (F3 & F4), averaged midline centro-parietal (Cz & Pz), and midline occipital (Oz) regions to examine any potential anterior or posterior predominance that might affect our following SP-SO coupling analyses. We decided to concentrate on midline derivations whenever possible, as SOs tend to travel along a midline anterior-posterior path (Murphy et al., 2009). We conducted separate repeated-measure ANOVAs on SO frequency, density, and amplitude with the within-person factors NIGHT (baseline vs. learning) and TOPOGRAPHY (frontal, centro-parietal, occipital).

SOs differed neither in their frequency ($F(1,22) = 0.20$, $p = 0.888$, $\eta^2_G < 0.01$), density ($F(1,22) = 2.00$, $p = 0.147$, $\eta^2_G = 0.02$), nor amplitude ($F(1,22) = 2.14$, $p = 0.129$, , $\eta^2_G = 0.03$) between topographical locations (Figure 5 (A)-(C)). This effect did not differ between baseline and learning night (interaction effects: $F_{frequency}(2,44) = 0.65$, $p = 0.528$, $\eta^2_G < 0.01$; $F_{density}(2,44) = 1.11$, $p = 0.337$, $\eta^2_G < 0.01$; $F_{amplitude}(2,44) = 0.74$, $p = 0.482$, $\eta^2_G < 0.01$). Furthermore, frequency and amplitude did not differ between the two PSG nights ($F_{frequency}(1,22) = 1.82$, $p = 0.191$, $\eta^2_G < 0.01$; $F_{amplitude}(1,22) = 3.65$, $p = 0.069$, $\eta^2_G < 0.01$). However, density was significantly higher during the baseline as compared to the learning night ($F(1,22) = 5.85$, $p = 0.024$, $\eta^2_G = 0.03$). Taken together, analyses did not indicate any topographical predominance of SOs in the present pre-school sample.

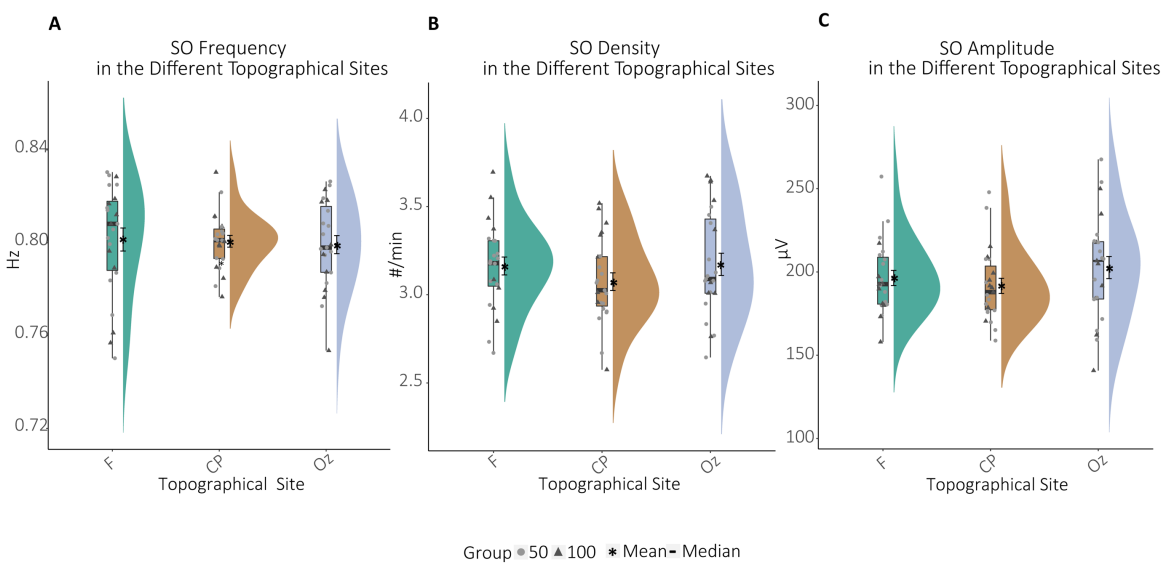

Figure 5. Main effects of the topographical differences between SO **(A)** frequency, **(B)** density, and **(C)** amplitude. Main effects from separate repeated-measure ANOVAs indicated no differences between topographical sites for any SO measure.

EXPLORATION OF SLEEP SPINDLE MODULATION DURING SLOW OSCILLATIONS

POWER MODULATIONS DURING SLOW OSCILLATIONS

After having established the existence of separable slow and fast SPs we were interested in their temporal relation to SOs. In a first step, we explored SP power modulation during SOs on a descriptive level by contrasting power (5-20 Hz) during SOs (centred ± 1.2 s around the DOWN-peak) with power during trials without SOs (Muehlroth et al., 2019). As there was no evidence for an anterior or posterior predominance of SOs, we examined frontal and centro-parietal SP power during averaged frontal (F3, F4), averaged midline centro-parietal (Cz, Pz), and occipital SOs (Oz). Cluster-based permutation tests revealed one cluster of increased power during SOs for both frontal and centro-parietal SP power (all cluster *p*s < 0.001). SP power was increased across the entire SP frequency range (9-16 Hz, Figure 6, dashed outline) and basically across the whole SO interval (Figure 6, results for frontal and occipital SOs see Figure S4). Although this effect was apparent across SOs in all recording sites, it seemed most pronounced for centro-parietal SOs. The strongest frontal and centro-parietal SP power enhancements during SOs were observed during the transition from the DOWN- to the subsequent UP-peak in frequencies ≈>12 Hz. Specifically for centro-parietal SOs, this enhanced power in the adult-like fast SP range (12-15 Hz, Mölle et al., 2011; 13– 16 Hz; Anderer et al., 2001; Schabus et al., 2007) was maintained throughout the UP-state.

To summarise, we observed enhanced frontal and centro-parietal SP power during SOs, with a strong increase in power in the adult-like fast SP frequency range before and during the SO UP-peak. Hence, we observed evidence for SO-SP coupling in pre-school children. On a descriptive level, the peak increase in the adult-like fast SP frequency range observed here, appears slightly earlier than what is reported in the adult literature (Helfrich et al., 2018; Klinzing et al., 2016; Muehlroth et al., 2019).

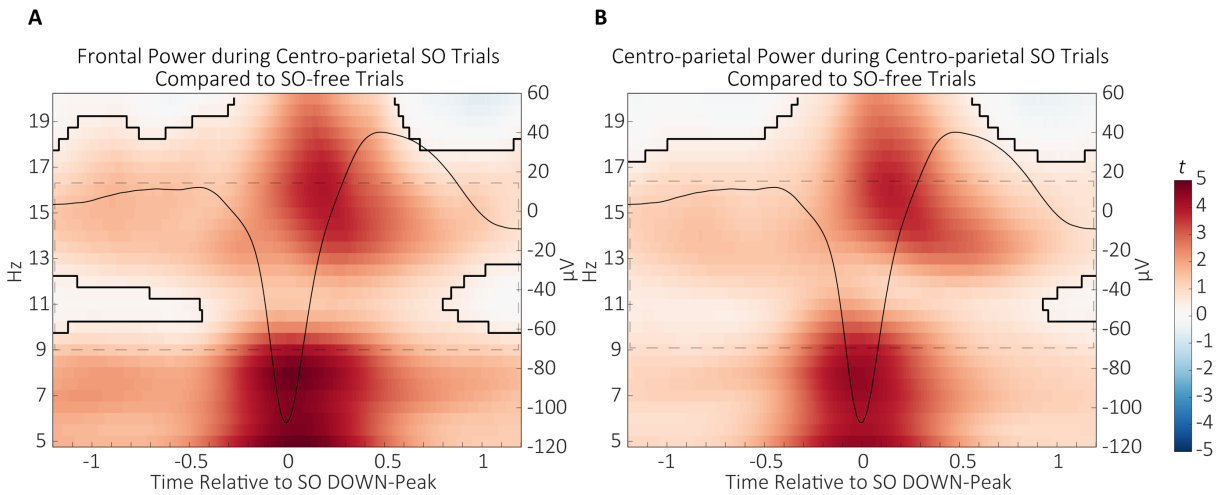

Figure 6. Differences in **(A)** frontal and **(B)** centro-parietal wavelet power during centro-parietal SOs compared to trials without SOs (*t*-score units). Significant clusters (cluster-based permutation test, $p < 0.05$) are outlined. The SP frequency range is indicated by the reference window outlined in dashed lines. The average centro-parietal SO is projected onto the power differences to illustrate their relation to the SO phase (scale in µV on the right side of each time-frequency plot).

MODULATION OF DISCRETE INDIVIDUALLY IDENTIFIED SLEEP SPINDLES DURING SLOW OSCILLATIONS

Despite apparent power modulations within the SP frequency range during SOs, it is important to stress, that these results do not necessarily need to reflect modulations of discrete individually identified slow and fast SPs, given that for both SP types the mean frequency was identified at a lower frequency range (see SP results). Therefore, in a second step, we were interested in how the occurrence of individually identified slow and fast SPs was related to the SO cycle.

To examine whether SPs and SOs actually co-occurred, we firstly determined the percentage of slow and fast SP centres (SO DOWN-peaks) occurring within an interval ± 1.2 s around the DOWN-peak of SOs (SP centres, Muehlroth et al., 2019). We tested differences in SP-SO co-occurrence across SP types and SOs recorded in different locations using two separate repeated measure ANOVAs with the within-person factors SP TYPE (slow, fast) and SO TOPOGRAPHY (frontal, centro-parietal, occipital) on the percentage of SP events during SOs (SO DOWN-peaks during SPs).

The percentage of SP centres co-occurring with SOs was overall significantly different between slow and fast SPs ($F(1,23) = 21.59$, $p < 0.001$, $\eta^2_G = 0.11$) and across SOs in different topographical locations ($F(1.49,34.35) = 103.24$, $p < 0.001$, $\eta^2_G = 0.32$). Furthermore, the difference in SP centre occurrence between SP types was modulated by the topographical location of SOs (interaction effect: $F(2,46) = 4.48$, $p = 0.017$, $\eta^2_G < 0.01$). Post-hoc tests showed that the percentage of both slow and fast SPs was considerably higher during SOs in centro-parietal compared to frontal and occipital recording sites (all $Z < -3.00$, all $p<0.001$, Figure 7 (A); Table S5 (A)). Furthermore, in line with a general predominance of slow SPs, a significantly higher percentage of slow SPs, compared to fast SPs, co-occurred with frontal, centro-parietal, and occipital SOs (all $Z < -3.00$, all $p < 0.001$, Figure 7 (A), Table S5 (B)). Results for SOs co-occurring with SPs revealed similar results (Figure 7 (B), Table S6).

In sum, our analyses show that in general individually identified SPs co-occur with SOs, with more slow SPs coinciding with SOs and centro-parietal SOs showing the highest incidence with SPs.

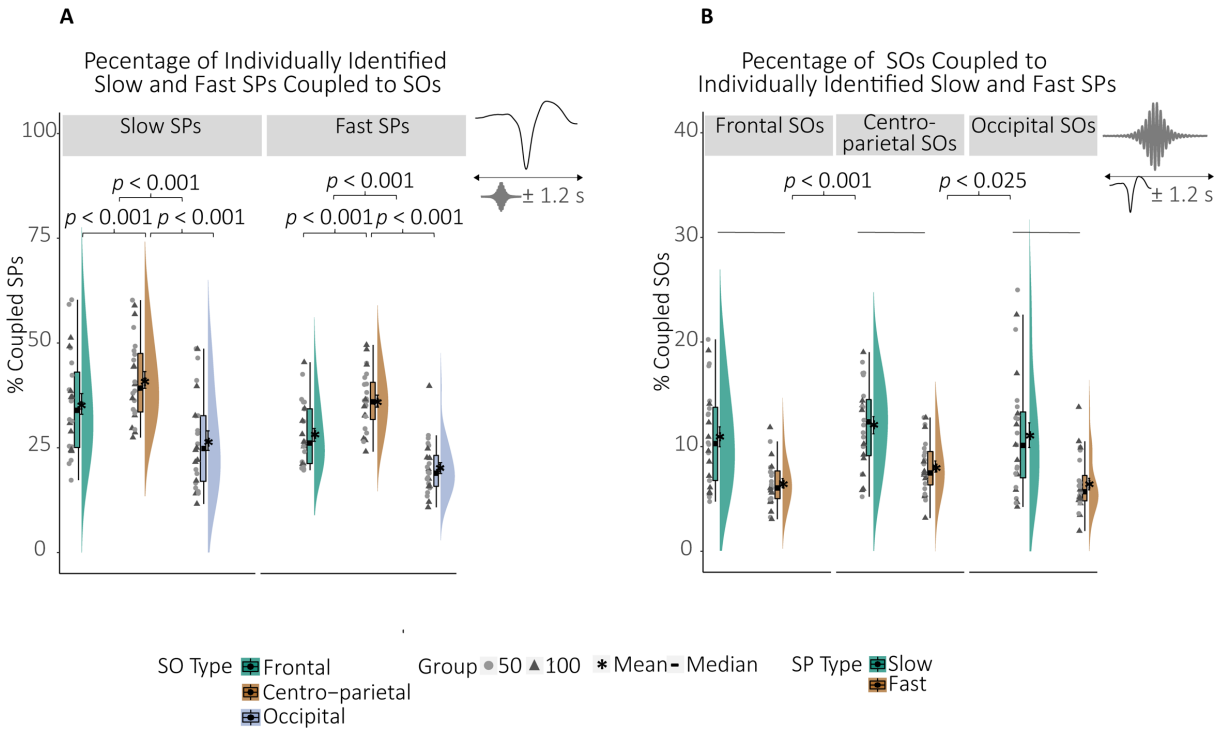

Figure 7. **(A)** Percentage of individually identified slow and fast SPs co-occurring with frontal, centro-parietal, and occipital SOs. *P*-values represent the results from the post-hoc Wilcoxon signed-rank tests. **(B)** Percentage of frontal, centro-parietal, and occipital SOs co-occurring with individually identified slow and fast SPs. *P*-values represent the results from the post-hoc Wilcoxon signed-rank tests on the main effect "SO Topography" comparing centro-parietal SO DOWN-peak co-occurrence with individually identified SPs against frontal and occipital SO DOWN-peak co-occurrence with individually identified SPs.

Given the general presence of individually identified SPs during SOs, we were interested in the precise temporal modulation of these SPs during the SO cycle. Thus, we separately determined the percentage of slow and fast SPs within specific 100 ms bins during an interval of ± 1.2 s around SO DOWN-peaks to generate PETHs. To assess whether the modulation of SP occurrence within a bin was specific to the SO cycle, we compared the percentage distribution of SP centre occurrence with its randomly shuffled surrogate. Given the higher co-occurrence of SPs with centro-parietal SOs, we focus on results during centro-parietal SOs (results for frontal and occipital SOs see Figure S5).

For fast SPs, we found an increased occurrence during the SO UP-peak preceding the DOWN-peak (cluster $p = 0.005$; -700 ms to -400 ms; UP-peaks = -453.00 ms & 484.400 ms) and an attenuated incidence during the end of the SO (cluster $p < 0.001$, 900 ms to 1200 ms, Figure 8 (B)). Similarly, slow SPs were reduced during the end of the SO cycle (cluster $p = 0.002$, 1000 ms to 1200 ms, Figure 8 (A)). However, the observed modulation of individually identified slow and fast SPs during SOs does not look strong and matches neither the previous time-frequency results nor what we would expect from the adult literature (e.g. Muehlroth et al., 2019)

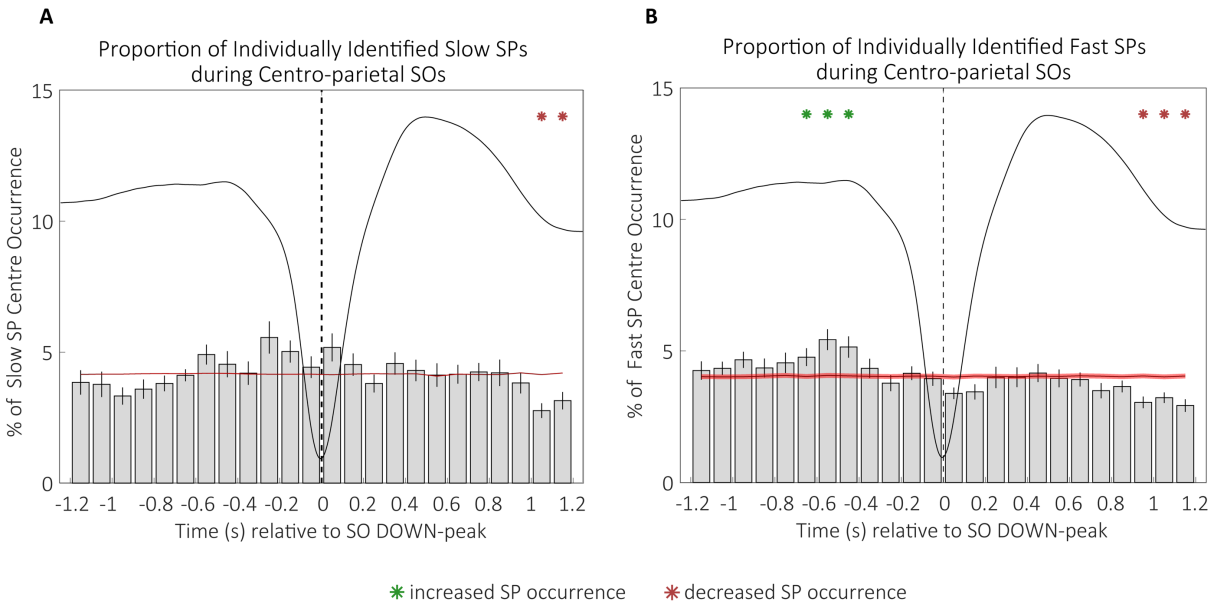

Figure 8. Percentage of individually identified **(A)** slow and **(B)** fast SPs occurring within 100 ms bins during centro-parietal SOs. Green asterisks indicate increased (positive cluster, cluster $p < 0.05$) and red asterisks indicate decreased (negative cluster, cluster $p < 0.05$) SP occurrence compared to random occurrence (black horizontal line with standard error of the mean indicated in red). Dashed vertical lines represent the SO-DOWN peak. The average centro-parietal SO is depicted in black.

Given that SP power modulation in the time-frequency analyses happened to be most pronounced in a range higher than the individually identified SPs, we exploratorily extracted SPs specifically higher in frequency than our individually defined upper SP frequency boundaries (from now on called "high" SPs) and repeated the PETH analyses. These discrete events should more accurately reflect the frequency range of peak power modulations in our time-frequency analyses. Indeed, frontal "high" SPs showed a mean frequency of 13.22 Hz (min = 12.36, max = 14.10 Hz) and centro-parietal "high" SPs had an average frequency of 13.58 Hz (min = 12.80, max = 14.33 Hz, see Table S3 for further descriptive measures of "high" SPs). Even though we could not identify a dominant peak in the "high" SP frequency range in any of the participants' power spectra, this does not proof the complete absence of such adult-like fast SPs (Figure S2 for overall spectra; Figure S6 for spectra during trials with "high" SPs only). Especially given the results of the time-frequency analyses, there might be a small number of discrete SPs in this range not powerful enough to elicit a peak in the power spectrum. However, resembling the fast SPs in adult humans, these SPs might still co-occur with SOs and show a relevance for behaviour (Figure S7 and Tables S7 and S8 for general co-occurrence results).

Cluster-based permutation tests did not reveal any statistically significant modulation of "high" frontal SP occurrence during centro-parietal SOs (Figure 9 (A), results for frontal and occipital SOs see Figure S8). However, "high" centro-parietal SPs showed a pattern of increased SP occurrence before the UP-peak preceding the DOWN-peak (cluster $p = 0.020$; -1000 ms to -800 ms) and during the transition from the DOWN- to the successive UP-peak, including the UP-peak (cluster $p < 0.001$, 100 ms to 500

ms). Furthermore, “high” centro-parietal SPs were attenuated starting before the UP-peak prior to the DOWN-peak lasting throughout the transition into the DOWN-peak (cluster $p < 0.001$, -500 ms to - 200 ms) and during the transition from the UP-peak following the DOWN-peak until the end of the SO cycle (cluster $p < 0.001$, 700 ms to 1200 ms, Figure 9 (B)). This pattern reflects the power modulations of the time-frequency analyses more closely than the pattern of individually identified SPs, supporting the notion of slightly earlier adult-like fast SP modulation in pre-school children during the SO cycle.

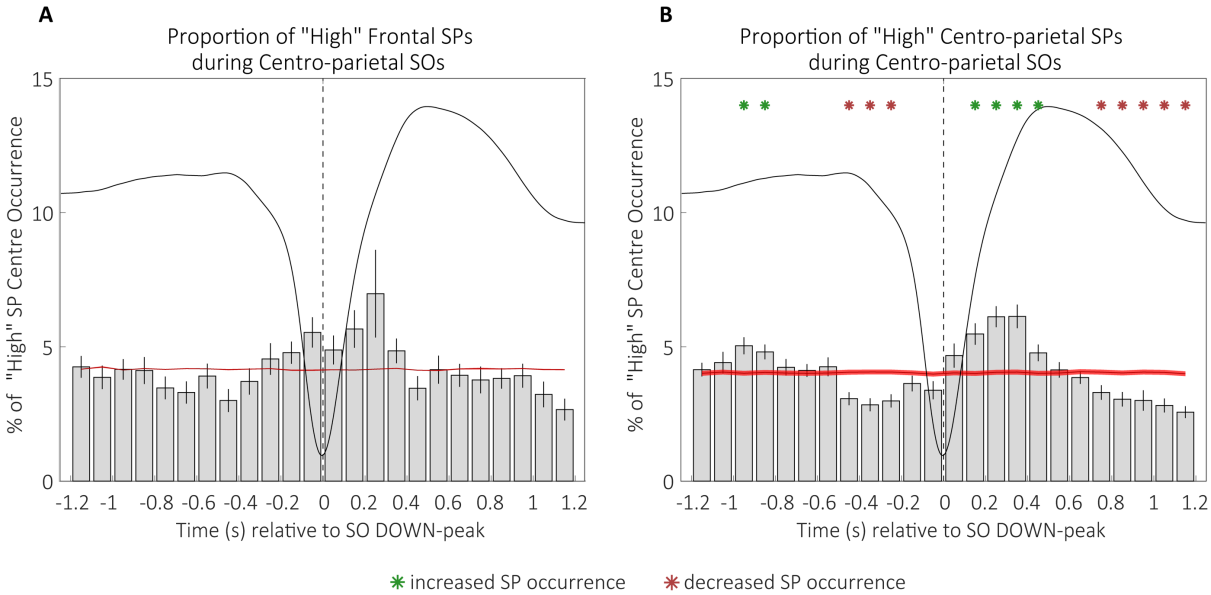

Figure 9. Percentage of “high” **(A)** frontal and **(B)** centro-parietal SPs occurring within 100 ms bins during centro-parietal SOs. Green asterisks indicate increased (positive cluster, cluster $p < 0.05$) and red asterisks indicate decreased (negative cluster, cluster $p < 0.05$) SP occurrence compared to random occurrence (black horizontal line with standard error of the mean indicated in red). Dashed vertical line represents the SO-DOWN peak. The average centro-parietal SO is depicted in black.

RECALL SUCCESS AFTER A NIGHT OF SLEEP IS CONTINGENT ON MEMORY QUALITY

Having established the presence of a slow and a fast SP type and a modulation of SPs by SOs, we were interested in their relation with memory consolidation. As our associative memory task allows distinguishing memories based on their learning trajectory during the evening into memories of varying quality, we firstly tested whether there was a difference in memory consolidation for low-, medium-, and high-quality memories. We applied a mixed factorial ANOVA with the between-person factor GROUP ($Group_{50}$, $Group_{100}$) and the within-person factor MEMORY QUALITY (low, medium, high) on the percentage of remembered items during morning recall. Similar to previous analyses on the difference between groups in general recall performance (Figure S1, Table S2), groups did not differ in the magnitude of memory consolidation ($F(1,22) = 0.32$, $p = 0.580$, $\eta^2_G < 0.01$). However, the extent of memory consolidation was different for low-, medium-, and high-quality memories ($F(2,44) = 182.93$, $p < 0.001$, $\eta^2_G = 0.85$). Overall, post-hoc tests revealed, that the percentage of remembered items after a night of sleep was highest for items of high memory quality as compared to medium- ($Z = -3.13$, $p =$

0.002, $CI_{2.5,\ 97.5}$ [-3.91, -1.326]) and low-quality memories (Z = -4.24, p < 0.001, $CI_{2.5,\ 97.5}$ [-4.10, -3.90]). Furthermore, the success to recall medium-quality memories was higher than for low-quality memories (Z = -5.30, p < 0.001, $CI_{2.5,\ 97.5}$ [-4.10, -4.09], Figure 10 (A)). The difference in the consolidation of memories of varying quality was not different between groups (interaction effect: $F(2,44) = 0.27$, p = 0.769, $\eta^2_G < 0.01$). Moreover, Spearman's rank correlations revealed that the consolidation rates of low-, medium-, and high-quality memories were not correlated ($\rho_{low*medium} = 0.11$, p = 0.618, $CI_{2.5,\ 97.5}$ [-0.35, 0.53], $\rho_{low*high} = -0.12$, p = 0.575, $CI_{2.5,\ 97.5}$ [-0.54, 0.30], $\rho_{medium*high} = 0.18$, p=0.400, $CI_{2.5,\ 97.5}$ [-0.19, 0.51]).

In sum, the extent of memory consolidation was contingent on memory quality with recall success after one night of sleep increasing with higher memory quality.

INDIVIDUALLY IDENTIFIED SLOW SLEEP SPINDLES ARE ASSOCIATED WITH MEMORY MAINTENANCE OF MEDIUM-QUALITY MEMORIES AND FAST SLEEP SPINDLES ARE ASSOCIATED WITH GAIN OF LOW-QUALITY MEMORIES

Given that research in adults and children suggested that not only the mere presence but especially the learning-induced change in SP density is linked to the extent of sleep-associated memory consolidation (Friedrich et al., 2019; Gais et al., 2002; Lustenberger et al., 2015; Schabus et al., 2004), we calculated difference scores of SP density between the two PSG nights, separately for individually identified slow and fast SPs. A positive difference score represents higher SP density during the learning as compared to the baseline night.

For slow rhythmic neuronal activity, usually power measures are associated with memory consolidation (Marshall et al., 2006). Therefore, we took the average SO amplitude across frontal and midline recording sites as our measure of interest. We then examined the effect of learning induced slow and fast SP density change and SO amplitude on the consolidation of memories of low-, medium-, and high-quality using separate bootstrapped robust regressions. To control for a potential influence of chronological age on sleep-memory associations, age was included as a covariate. All variables were z-standardised to enhance interpretability of bootstrap percentile CIs around the regression coefficients.

Concerning consolidation of medium quality memories, results revealed that, besides age (β = 0.37, p = 0.020, $CI_{2.5,\ 97.5}$ [-0.01, 0.82]), higher slow SP density change from baseline to learning night (β = 0.53, p = 0.001, $CI_{2.5,\ 97.5}$ [0.14, 0.82]) was reliably associated with higher maintenance of medium-quality memories (Figure 10 (B)). The effect of SO amplitude (β = 0.28, p = 0.054, $CI_{2.5,\ 97.5}$ [0.02, 0.55]) narrowly missed the significance level of 0.05.

With regard to consolidation of low-quality memories, the increase in fast SP density during the learning night was significantly associated with a higher recall success (β = 0.41, p = 0.031, $CI_{2.5,\ 97.5}$ [-0.02, 1.13]) i.e., a memory gain (Figure 10 (C)). No associations between sleep electrophysiological

markers and maintenance of high-quality memories was observed (a complete listing of all regression results can be found in Tables S9-S11).

Taken together, age and learning-induced slow SP density change were related to memory maintenance of medium-quality memories while experience-related increase in fast SP density was associated with memory gain of low-quality memories.

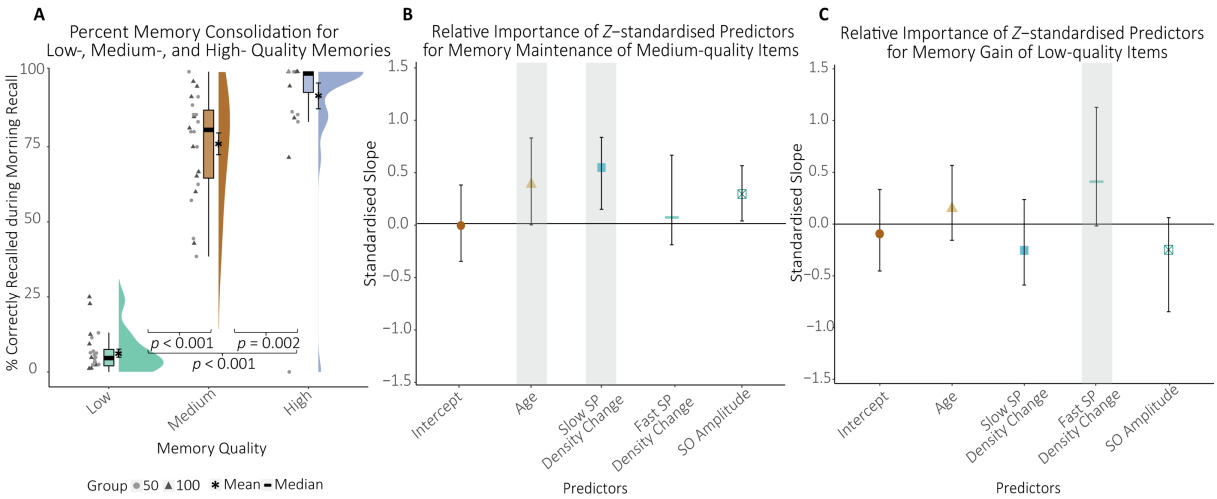

Figure 10. **(A)** Effect of sleep on memory consolidation for memories of varying quality. The better the memory quality the more items were recalled after one night of sleep. *P*-values represent the results from post-hoc Wilcoxon signed-rank tests. **(B & C)** *Z*-standardised regression coefficients for memory consolidation of **(B)** medium- and **(C)** low-quality memories with their 95-% simple bootstrap percentile confidence interval. Significant predictors are highlighted by the grey boxes. **(B)** Higher age and higher slow SP density during the learning compared to the baseline night (Slow SP Density Change) was associated with stronger memory consolidation of memories of medium quality. **(C)** Higher fast SP density during the learning compared to the baseline night (Fast SP Density Change) was associated with stronger memory consolidation of memories of low quality.

EXPLORATORY ANALYSIS OF THE ASSOCIATION BETWEEN SLEEP SPINDLE MODULATION BY SLOW OSCILLATIONS WITH MEMORY CONSOLIDATION

The most prominent views on system consolidation suggest the precise modulation of SPs during SOs, rather than the mere presence of each, as a key mechanism underlying sleep-associated memory consolidation (Diekelmann & Born, 2010; Helfrich et al., 2018, 2019; Muehlroth et al., 2019). Hence, we asked whether and how the identified SP power modulations during SOs are associated with memory consolidation in the present sample of pre-schoolers. As the time-frequency analyses revealed a cluster of increased power during the whole SO cycle in a broad frequency range, we restricted our exploratory correlation analyses to the peak power increase during SOs, which covers the strong increase in the adult-like fast SP frequency range (Figure 6, Figure S4). We therefore identified a mask of the 5% highest *t*-values between 11-20 Hz (based on the increase visible in Figure 6) from the group-level contrast. These *t*-values were in a frequency range between 14-17.5 Hz. The mask was used to extract the *t*-values within this area for every subject. Afterwards the *z*-standardised averaged value was correlated

with memory consolidation of low-, medium-, and high-quality memories. These exploratory correlations did not yield any significant associations (all $-0.5 < \rho < 0.39$; all $p > 0.06$, Figure S9 (A); see Figure S9 for all exploratory results on an association between indicators of SP-SO coupling and memory consolidation).

DISCUSSION

The present study aimed to characterise slow and fast SPs, their temporal interaction with SOs, and their relation to behavioural indicators of memory consolidation in pre-school children. Employing individualised rhythm detection methods, we found evidence for two separable SP types: A faster SP type in centro-parietal areas in addition to a more numerous, slower SP type in frontal sites. Individually identified fast SPs were nested in the adult-like slow SP range and already slightly modulated by the SO cycle. Surprisingly, we observed a clearer modulation of SPs higher than the individually identified SPs, roughly matching the adult-like fast SP range, during centro-parietal SOs. This modulation pattern seemed to be comparable to similar observations in adults, though with adult-like fast SPs in children peaking earlier than expected. While the pattern of SP modulation during SOs was not related to memory consolidation, importantly, the increase in individually identified frontal SPs was reliably associated with sleep-associated memory maintenance of medium-quality items. Further, individually identified fast SPs promoted the gain of low-quality memories. Together, our results indicate that, despite the core-mechanisms of sleep-associated system memory consolidation being not fully matured in pre-school children, sub processes in their development-specific expression (i.e., slow and fast SPs) support sleep-associated memory consolidation during childhood.

SLOW AND FAST SLEEP SPINDLES IN PRE-SCHOOL CHILDREN

In the system consolidation framework, fast SPs are suggested as a central mechanism for sleep-associated memory consolidation (Peyrache & Seibt, 2020; Rasch & Born, 2013). While existing evidence indicates the dominance of slow SPs, the reliable presence of an inherent fast SP type is still elusive in children (D'Atri et al., 2018; Hoedlmoser et al., 2014). Based on discernable individual peaks in frontal and cento-parietal spectra, we found that individually identified SPs differed in anterior and posterior recording sites in frequency, amplitude, and density in the majority of pre-school children. Thus, consistent with previous studies, that started out on adult-derived frequency-based approaches (D'Atri et al., 2018; Hahn et al., 2018), our results support the presence of a dominant slow and a fast SP type in pre-school children.

Importantly, the individually identified, fast SPs were rather in the range of adult-like slow SPs and thus differed from those identified in previous studies comparing slow and fast SPs in children (D'Atri et al., 2018; Hahn et al., 2018). However, the mean frequency of the individually identified fast SPs matches

other studies that detected SPs individually in centro-parietal sites in 2- to 5-year-olds (Kurdziel et al., 2013; Olbrich et al., 2017). Further, it aligns well with findings demonstrating that SP frequency in general, and specifically in centro-parietal areas, is slower during childhood, over the course of maturation (Campbell & Feinberg, 2009; Shinomiya et al., 1999). Hence, these observations might indicate that canonical fast SPs are not yet fully matured in pre-school children

Of note, in most children, two peaks were only identifiable when separating the power spectrum based on topography due to the proximity of these peaks. Further, a small number of children expressed identical peak frequencies.

In general, varying features of neural rhythms likely reflect anatomical and functional properties of their underlying cortical and subcortical circuits (Andrillon et al., 2011; Buzsáki, 2006; Campbell & Feinberg, 2009; Piantoni et al., 2013; Saletin et al., 2013). Thus, two scenarios implying slightly different underlying developmental mechanisms are likely to account for developmental differences in the expression of fast SPs. Firstly, brain morphology undergoes strong developmental remodelling (Barnea-Goraly et al., 2005; Casey et al., 2000). Increasingly accelerated neural transmission allows for faster central processing. Hence, pruning (Campbell & Feinberg, 2009) and increased myelination (Nunez, 2000) in thalamo-cortical circuitries, and decreasing degree of thalamic hyperpolarization (Andrillon et al., 2011; Steriade & Llinás, 1988) could directly account for frequency acceleration of fast SPs across maturation. Secondly, it is also conceivable that changes in the generation mechanisms of SPs result in an increasing expression of SPs in the adult-like fast SP range across maturation. This would lead to power gains in the respective fast SP frequency range enabling the detectability of a peak, once a sufficient number of fast SPs is expressed, and also leading to findings of increased frequency in the broad SP band. Thus, the individually identified fast SPs in pre-school children could either reflect a slower expression of the adult-like fast SPs or a distinct rhythm that is not/no more present in adults. However, disentangling the two possibilities necessitates longitudinal studies with combined electrophysiological and anatomical recordings (Lindenberger et al., 2011)

Taken together, we found evidence for two dissociable SP types in pre-school children. Given the nesting of fast SPs within the adult-like slow SP band, our results further support the utility of individualised approaches (Cox et al., 2017; Mölle et al., 2011; Ujma et al., 2015) to uncover true rhythmic neural activity in pre-school children.

TEMPORAL RELATION BETWEEN SLEEP SPINDLES AND SLOW OSCILLATIONS

Recently it has been proposed, that a precise modulation of SPs by the SO UP-state might be inherent already to pre-pubertal children (~ 8-11 y; Hahn et al., 2020; Piantoni et al., 2013), though less intensively pronounced and growing stronger across maturation (Hahn et al., 2020). Indeed, extending

these results to pre-school children, we did observe a slight modulation of fast SP occurrence by the SO UP-state, which was not apparent for slow SPs. Surprisingly, power and occurrence of centro-parietal SPs in frequencies higher than the individually identified SPs and rather in the adult-like fast SP range, exhibited an even more pronounced modulation during SOs which seems to be comparable to the SP-SO coupling identified in adults, though slightly earlier (Klinzing et al., 2016; Muehlroth et al., 2019). This fits findings of SP-SO dispersion during aging (Helfrich et al., 2018; Muehlroth et al., 2019) and suggests for child development that together with the number of adult-like fast SPs, their precise timing to the SO UP-peak still needs to mature.

Hence, the pattern of individually identified fast SP coupling and of "high" centro-parietal SP modulation seem to imply two distinct mechanisms underlying the development of strong, precise SP-SO coupling (i.e., increasing strength vs. increasing temporal precision). While we cannot answer which of these mechanisms leads to the fully pronounced SP-SO coupling known in adults, our results cautiously suggest that they might act in concert. After all, it appears as if the increasing presence of adult-like fast centro-parietal SPs, renders SP-SO coupling more precise and pronounced. Further, it is elusive which of the involved components, SPs, SOs or both underlie developmental differences in SP-SO coupling.

Besides the maturation of adult-like fast SPs, the development of SOs themselves could contribute to the above findings. SOs are more numerous and powerful during younger age and do not yet show a prefrontal dominance (Kurth et al., 2010a, 2010b). While we neither observed a frontal, nor the expected central or posterior dominance of SOs (Kurth et al., 2010b; Timofeev et al., 2020), we found more SPs and a clearer SP modulation pattern for centro-parietal SOs. However, explicitly the co-ordination of fast SPs with frontal SOs (Hahn et al., 2020; Helfrich et al., 2018, 2019; Muehlroth et al., 2019) and, in children, frontal SOs in general (Prehn-Kristensen et al., 2014) were found to be behaviourally relevant. However, one can only speculate that the relative lack of prefrontal SO dominance might affect the SP-SO modulation pattern in children. Further, as SOs are supposed to be more powerful with younger age, it might be, that the level of depolarization exerted during the transition from the DOWN- to the UP-peak might be enough to elicit SPs. This might account for the rise in "high" centro-parietal SPs before the UP-peak already. To sum up, we found evidence for a weak and imprecise modulation of fast SPs by SOs already in pre-school children implying that overall, the hallmark system consolidation mechanism appears not yet fully matured in pre-school children.

BEHAVIOURAL RELEVANCE OF SLOW AND FAST SLEEP SPINDLES AND THEIR PATTERN OF CO-OCCURRENCE WITH SLOW OSCILLATIONS FOR MEMORY CONSOLIDATION

The prevailing view proposes that the precise coupling of hippocampal ripples to fast SPs during the SO UP-state supports system consolidation during sleep by providing a time window of enhanced cortical excitability that enforces the stabilisation of hippocampal mnemonic patterns in respective cortical areas (Clemens et al., 2007; Diekelmann & Born, 2010; Helfrich et al., 2019; Staresina et al., 2015). Despite the presence of a modulation of SPs during SOs, in the current study, we did not find evidence for a critical contribution to memory consolidation in pre-school children. This may suggest that the coordinated triad of hippocampal ripples, SPs, and SOs is not only not fully developed, but also not yet behaviourally relevant in pre-school children. Overall, these observations suggest that over the course of development, neural mechanisms supporting sleep-associated systems consolidation might require refined synchronization to fully support stabilization and integration of novel mnemonic contents.

While the precise interaction between SOs and SPs was not associated with memory consolidation, importantly both a higher learning-induced increase in individually identified slow and fast SPs during the learning night was related to stronger memory consolidation in pre-school children, independent of their co-occurrence with SOs. This resonates with findings demonstrating that both coupled and uncoupled SPs benefit memory in adults while the number of coupled SPs possibly needs to exceed a certain threshold to be additionally beneficial for memory (Denis et al., 2020). Thus, it is likely that isolated SPs compensate for the lack and imprecision of SP-SO coupling, challenging the view of SP-SO coupling as the central mechanism of sleep-associated memory consolidation (Diekelmann & Born, 2010; Latchoumane et al., 2017). While our results do not rule out that more precise coordination of SPs and SOs provides additional advantages for memory consolidation, all in all, our results imply, that slow and fast SPs in their development-specific expression support memory consolidation independent of their modulation by SOs.

SLOW AND FAST SLEEP SPINDLES ARE DIFFERENTIALLY ASSOCIATED WITH MEMORY MAINTENANCE AND GAIN – IMPLICATIONS FOR DIFFERENTIAL FUNCTIONS?

Individually identified slow and fast SPs were not only both associated with memory consolidation but showed a differential association with memory maintenance and gain. Stronger increase in slow SPs during the learning night was reliably related to higher maintenance of medium-quality memories while the rise in individually identified fast SPs was associated with gain of low-quality memories. Importantly, a given memory representation needs to be accompanied by a certain level of hippocampal and cortical activation for system consolidation mechanisms to act on (Schoch et al., 2017; Tucker & Fishbein, 2008). The lack of accessibility of low-quality items in the evening does not necessarily indicate the absence of a mnemonic representation but might be due to retrieval-rooted factors such as impaired retrieval search (Ackerman, 1985), 'retrieval-induced forgetting' (Aslan & Bäuml, 2010) and/or reduced attentional guidance. Thus, the gain effect for low-quality items most likely reflects the release from

recall perturbing factors overnight rather than a sleep-associated emergence of novel memory representations (Fenn & Hambrick, 2013; Muehlroth et al., 2020; Nettersheim et al., 2015). Previously, weakly encoded items were linked to increased hippocampal reactivation and SPs during sleep indicating preferential system consolidation for memories most prone to forgetting (Denis et al., 2020; Schapiro et al., 2018). Hence, the increased availability of low-quality items after sleep could reflect a strengthening of a weak mnemonic trace and/or a relief from retrieval inhibiting factors. Thus, fast SPs are not only functionally relevant, but may be already specifically involved in hippocampal-cortical system consolidation in pre-school children – even without a top-down co-ordination by SOs.

While the role of slow SPs in memory consolidation is still inconclusive, they could very well also represent hippocampal-cortical integration that compensates in children for the absence of fast SP-SO coupling. However, it has been suggested, that slow SPs might be involved in cortico-cortical rather than hippocampal-cortical communication (Astori et al., 2013; Doran, 2003; Rasch & Born, 2013; Timofeev & Chauvette, 2013). As the effect of sleep on memory consolidation depends on the level of cortical integration of a memory during encoding (Himmer et al., 2017), one could cautiously hypothesise that medium-quality items have already established a stronger cortical trace than low-quality memories. Hence, there might be a lower need for hippocampal-cortical communication but rather a need for cortico-cortical distribution, potentially reflecting a stabilisation process. The exact prerequisites and mechanisms for overnight gain and maintenance certainly require further interrogations. Nevertheless, the present results provide further evidence that SP-related processes contribute to over-night system-level consolidation, even in pre-school children.

CONCLUSIONS

Overall, the present results underscore the functional relevance of inherent slow and fast SPs for memory consolidation in pre-school children, despite not fully evolved SP-SO coupling. Even more, the development-specific expression of fast SPs was associated with sleep-associated memory gain while slow SPs were related to memory maintenance.

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