The association between overnight recognition accuracy and slow oscillation-spindle coupling is moderated by BDNF Val66Met

Halonen, Risto

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The association between overnight recognition accuracy and slow oscillation-spindle coupling is moderated by *BDNF* Val66Met

Risto Halonen [a], Liisa Kuula [a], Jari Lahti [b], Katri Räikkönen [b], Anu-Katriina Pesonen [a,*]

[a] *SleepWell Research Program, Faculty of Medicine, University of Helsinki, P.O. Box 9, Helsinki 00014, Finland*
[b] *Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, P.O. Box 9, Helsinki 00014, Finland*

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ABSTRACT

During sleep, memories are consolidated via oscillatory events that occur in temporal and phasic synchrony. Several studies show that sleep spindles peaking close to the depolarized positive peaks of slow oscillations (SO) associate with better retention of memories. The exact timing of this synchrony presumably depends on the properties of the related neural network that, in turn, is affected by certain genetic variants associated with brain development and function. Brain-derived neurotrophic factor (*BDNF*) Val66Met and Catechol-O-methyl-transferase (*COMT*) Val158Met are repeatedly reported to implicate the structure and function of prefrontal and hippocampal areas as well as molecular events promoting synaptic plasticity. In this study, we examined with a community-based sample of 153 adolescents (~17 years) whether these variants (1) affected the coupling properties between frontal SOs and spindles and (2) moderated the association between SO-spindle coupling and overnight recognition accuracy. We found SO-upstate-coupled fast (> 13 Hz) sleep spindles to associate with better recognition in the whole sample. Additionally, Val66Met moderated this association such that SO-spindle coupling was predictive of memory outcome only in those homozygous to Val_{BDNF} alleles but not in Met_{BDNF} carriers. Memory outcome was not associated with the SO-coupling properties of slow spindles nor affected by the interaction between Val158Met and coupling measures. Finally, in the whole sample we found that SO-upstate-coupled fast spindles were more strongly associated with the recognition of positive, relative to neutral, pictures. In conclusion, precise coupling of SOs and fast spindles associates with overnight recognition accuracy and this association is moderated by *BDNF* Val66Met.

1. Introduction

Sleep spindles and their synchronization with slow oscillations (SO) during non-rapid eye movement (NREM) sleep have received keen focus in memory research. When cortically-originated SOs reach thalamic reticular nucleus, they trigger spindle events that travel to the cortex via thalamo-cortical projections [1]. Especially fast spindles (≥ 12–13 Hz) tend to peak during the depolarized upstate of SOs [2], instantiating brief but potent windows of synaptic plasticity [3] and mediating hippocampal-neocortical communication [4]. Accordingly, experimental evidence has solidified the significance of SO-upstate preference of spindles in memory retention over sleep [5–8]. Scantly, however, has it been investigated what inter-individual properties promote the constancy, or accuracy, of the SO-upstate preference. One study found that the age-related differences in prefrontal gray matter integrity affected

the synchronization properties between SOs and spindles [8]. It becomes compelling to ask whether inherent factors contributing to prefrontal development and functioning, such as genes, would moderate the SO-spindle-coupling or its efficacy in sleep-dependent memory consolidation.

One such candidate gene is the one encoding brain-derived neurotrophic factor (BDNF), a mediator of activity-dependent plasticity [9, 10]. A polymorphism that substitutes valine (Val) to methionine (Met) in the codon 66 (Val66Met) results in impaired intracellular trafficking and reduced activity-dependent secretion of BDNF [10]. Anatomical and functional alterations in prefrontal-hippocampal network are reported in the carriers of a Met_{BDNF} allele [11–13]. Additionally, studies on sleep and learning are emerging. Val_{BDNF} homozygosity, relative to carrying Met_{BDNF} alleles, has been implicated with improved overnight learning [14,15], but also with higher vulnerability towards prolonged wake

[16]. In Val$_{BDNF}$ homozygotes only, memory outcome associates with slow oscillation (SO) power [15] and frontal fast sleep spindle density [17], propelling speculation if SO-spindle synchrony or its significance on memory consolidation is related to *BDNF* genotype.

Another gene associated with the development and function of prefrontal and hippocampal structures is catechol-O-methyltransferase (*COMT*) gene. A substitution of valine to methionine at codon 158 (Val158Met) leads to higher extracellular dopamine level in prefrontal cortex [18]. The polymorphism modulates the hippocampal-prefrontal coupling during memory processing [19] and associates with improved performance in prefrontally guided tasks relative to Val$_{COMT}$ homozygotes [20]. Val158Met has been shown to associate with memory outcome over wake [19,21]. However, in our previous study, its interaction with sleep was not significant, indicating that memory retention over sleep was not affected whether carrying Val$_{COMT}$ alleles or not [16]. Interestingly, fast sleep spindles are reduced dose-dependently along Val$_{COMT}$ alleles, presumably due to differences in cortical SO activity that modulates spindle generation [22]. No study yet has examined how such differences manifest in synchronized oscillatory activity in SO-spindle coupling.

Studies examining the associations between SO-spindle coupling and memory retention are often limited by two aspects. First, the focus is on fast spindles only. However, one study [8] reported that *slow* spindle activity that emerged during the descending SO slope after upstate correlated with worse memory retention. This was in contrast to fast spindle activity that was expectedly elevated closer to the positive SO peak, along with correlating positively with memory retention. Hence, confining investigation to SO-upstate-tied fast spindles may be insufficient. The second limitation is to examine *relative* coupling metrics only – that is, the tendency for consistent coupling direction or SO-upstate proximity, measured by resultant vector length [23], upstate percentage [5], mean circular distance between spindles and the positive SO peak [7] or mean SO angle of spindle peaks [5,6]. The relative proximity of upstate-coupled spindles may be equal even if the raw number of these events is not, even though the assumed effect of synaptic strengthening would possibly be better captured by the amount of the events.

Strongly emotional experiences evoke responses that originate from ensuring survival – dangers are better avoided and rewarding events pursued. Sleep-dependent consolidation is proposed to prioritize such salient memories over unimportant [24]. At encoding of emotional information, the activation of amygdala modulates hippocampal plasticity, which presumably 'tags' certain memories for future saliency [25]. During subsequent sleep, these memories get consolidated selectively [24], whereas unnecessary synaptic connections are downscaled according to synaptic homeostasis hypothesis [26]. Experimental evidence links sleep spindles with selective consolidation by their role in either activating salient information [27,28] or inhibiting non-relevant aspects [29]. Given the well-documented significance of especially SO-coupled spindles in memory consolidation, studies examining how the synchronization relates with emotional memory are sparse. However, it was recently reported [30] that the proportion of SO-coupled spindles correlated with *worse* recognition of pictures, but only in those participants that were experimentally stressed before the encoding. Moreover, the association was more evident regarding emotional, compared to neutral, pictures. While these findings indicate that affect interacts with SO-spindle coupling on memory consolidation, the topic requires further investigation.

In the present study, we primarily aimed to resolve if Val66Met and Val158Met associate with SO-spindle coupling dynamics and if they moderate the relation between coupling and overnight visual recognition. As noted above, these genetic polymorphisms are known for anatomical and functional implications in frontal and hippocampal structures. Yet, no previous study has investigated how SO-spindle synchrony is moderated by these genetic variants. Second, our examination of this synchrony consists of both relative and absolute metrics to discern if a tendency for spindles to peak near SO upstate associates with memory outcome similarly than the number of such events. Finally, by deploying pictures of varying emotionality, we can observe if the interplay of SOs and spindles favor certain types of memories.

This study is conducted in a sizable sample of community-based adolescents (~17 y). Within the cohort, we have previously reported that (1) *BDNF* Val66Met moderated the association between recognition accuracy and frontal fast sleep spindles [17] and that (2) the level of emotion in the memorized pictures affected their recognition accuracy [16]. We hypothesize that *BDNF* Val66Met moderates the timing of frontal fast SO-spindle coupling such that Val$_{BDNF}$ homozygotes show more precise coupling with the positive SO peak relative to Met$_{BDNF}$ carriers. Additionally, we expect that the properties of SO-spindle coupling underlie the relatively better recognition of emotional items [16].

2. Methods

2.1. Participants

The participants comprised an urban community-based cohort composed of 1049 healthy singletons born between March and November 1998 in Helsinki, Finland [31]. Detailed descriptions of the cohort and follow-up participation are found elsewhere [32,33]. In the current study, the adolescents who lived within a 30 kilometer radius of Helsinki and whom had participated in the previous follow-up and given consent for further contact, were recruited by phone and were offered 50 € for their effort. Out of the 196 adolescents that participated in this follow-up, 173 were genotyped at an earlier follow up. Complete and technically valid polysomnography (PSG) and memory task data was obtained from 152 adolescents.

The Ethics Committee of the Children's Hospital in Helsinki University Central Hospital approved the study protocol (177/13/03/03/ 2014). Informed written consent was obtained from the participants. All parts of the study were conducted in accordance with the Declaration of Helsinki.

2.2. Memory task

The study was conducted at the homes of the adolescents. Instead of determined sleep schedules, the participants adhered to their normal sleep routines. The study flow, variation in sleep and wake times as well as memory task details have been described in detail previously [16].

In the evening, the participants memorized 100 pictures from the International Affective Picture System (IAPS) [34] shown on a laptop screen for 1000 ms with 1500 ms intervals. The pictures were divided into six categories based on their normative arousal (2 levels: low and high) and valence (3 levels: negative, neutral, positive) ratings. The normative arousal/valence levels differed within the dimension categories (p values <0.001) whereas they were balanced across the categories (e.g. equal valence in low and high arousal pictures; p values $\geq$ 0.629) and balanced between target and sham pictures (p values $\geq$ 0.675). Next morning, the participants were shown the 100 target pictures, mixed with 100 unseen sham pictures (distributed equally between arousal and valence categories). If they recognized the picture, the participants were instructed to press space bar as quickly as possible. Only space bar presses given while the picture was visible (1000 ms) were counted as responses.

Recognition accuracy (*d'*) was calculated for all picture categories. The measures of *d'* were calculated as the difference between the hit rate and the false rate (standardized proportion of correctly/incorrectly recognized target/sham pictures of all target pictures) to correct for response bias [35]. Because of false alarm rates of 0, we applied log-linear approach [36].

2.3. Polysomnography protocol and preprocessing

All recordings were performed using SOMNOscreen plus (SOMNO-medics GmbH, Germany). The trained research nurse attached gold cup electrodes at 6 electroencephalography (EEG) locations (frontal (F) hemispheres: F3, F4; central (C): C3, C4; occipital (O): O1, O2), and two for the mastoids (A1, A2). The electro-oculogram (EOG) and the electromyogram (EMG) were measured by using disposable adhesive electrodes (Ambu Neuroline 715, Ambu A/S, Denmark), two locations for EOG and three locations for EMG. An online reference Cz and a ground electrode in the forehead were used. The sampling rate was 256 Hz (the hardware filters for SOMNOscreen plus are 0.2–35 Hz). PSG data were scored manually using the DOMINO program (v2.7; SOMNOmedics GmbH, Germany) in 30-sec epochs into N1, N2, N3, REM and wake, according to AASM guidelines (The AASM Manual for the Scoring of Sleep and Associated Events) [37].

The manually scored PSG signals were converted to EDF format and then further analyzed using the functions of EEGlab 14.1.2b [38] running on MATLAB R2018a (Mathworks, Inc., Natick, MA, USA). All signals were digitally band-passed and filtered offline from 0.2 to 35 Hz (with a Hamming windowed sinc zero-phase FIR filter; cut-off, −6 dB), at 0.1 Hz and 35.1 Hz, respectively, and re-referenced to the average signal of A1 and A2 electrodes. According to our hypotheses and what is previously reported on genotypic moderation regarding frontal spindles [17], the primary analyses were confined to F3 and F4 electrodes. We examined C3 and C4 data in Appendix 1.

2.4. Spindle analysis

The pre-processed EEG data were further band-pass filtered (order 2816) in the slow (10–13 Hz) and fast (13–16 Hz) frequency bands. From the filtered signal, slow and fast spindles were extracted during NREM sleep (N2 + N3) using a method adapted from an automated detection algorithm described by Ferrarelli et al. [39]. The threshold values for finding the spindle peak amplitude in each channel were defined by the mean of the channel amplitude (μV) multiplied by 5. The putative spindle's amplitude was required to stay over the mean channel amplitude multiplied by 2 for 250 ms in both directions from the peak maximum, resulting in a minimum spindle duration of 0.5 s. The maximum cut-off for spindle length was set to 3.0 s and the maximum peak amplitude was set to 200 μV. In addition, the signal amplitude between spindles was required to stay under the lower threshold for 78.1 ms, which is approximately the duration of one period of sine at 13 Hz; this requirement was implemented in order to prevent false alarms. Finally, we excluded spindle-like bursts that occurred during arousals. We calculated spindle densities by dividing the spindle number by the minutes spent in NREM (N2 + N3) sleep, and further averaged the values from different hemispheres to denote frontal (F3, F4) or central (C3, C4) spindle density.

2.5. Slow oscillation detection

NREM (N2 + N3) SOs were detected with an adapted algorithm developed by Ngo and colleagues [40] using the Wonambi EEG analysis toolbox ([64], Wonambi: EEG analysis toolbox 1). The signal was first low-pass filtered at 3.5 Hz. All negative and positive amplitude peaks were identified between consecutive positive-to-negative zero-crossings, comprising a full phase cycle. Zero-crossing intervals within the duration of 0.8–5 s were included, corresponding to the 0.2–1.25 Hz frequency range. Finally, mean values for positive and negative peak potentials were calculated, and these events were denoted as SOs where the negative peak was lower than the mean negative peak and where the positive-to-negative peak amplitude difference exceeded the mean

amplitude difference. Frontal (F3, F4) and central (C3, C4) slow oscillations were averaged across hemispheres.

2.6. Slow oscillation-spindle coupling

We examined SO-spindles in an event-locked manner, i.e. focusing the analyses on the synchronization of discrete sleep spindle and SO events. First, in each EEG channel, we identified spindles where the amplitude peaked within a SO cycle (i.e., SO-spindles). Next, we band-pass filtered the EEG signal to 0.2–1.25 Hz, Hilbert-transformed the SO signal, and extracted the instantaneous phase at the amplitude maximums for each SO-spindle. Using CircStat toolbox [41], we extracted mean coupling phase and resultant vector length (RVL) for each participant. We also calculated the probability for spindles to occur simultaneously with SOs, i.e. SO-spindle%.

Regarding memory outcome, we were especially interested in the directional preference of SO-spindles. That is, fast spindles tend to peak close to the positive peak of slow oscillations (0°) [2] which is shown to associate with memory outcome [5]. While the memory implications of slow SO-spindles are less understood and possibly negative [8], slow spindles accumulate at the up- to downstate transition of SOs [2,8]. Hence, as a reference phase for memory outcome associations we used 0° for fast spindles as literature suggests, and explored how the tendency of slow spindles to couple with the up- to downstate transition (90°) associated with memory outcome.

We examined directional coupling in relative and absolute terms. As a relative measure we used mean coupling distance that was defined by averaging the absolute phase differences (in radians, obtained with CircStat toolbox [41]) between individual spindle peaks and either 0° (fast spindles) or 90° (slow spindles). While coupling distance is a relative measure and does not capture the amount of the concerned events, we also calculated the number of SO-spindles peaking at different phases within a SO cycle. To this end, we divided the SO cycle into eight bins of equal phase angle, i.e. 45° each, starting from the negative peak at −180° into Bin1 (−180° to −135°), Bin2 (−135° to −90°), Bin3 (−90° to −45°), Bin4 (−45° to 0°), Bin5 (0–45°), Bin6 (45–90°), Bin7 (90–135°) and Bin 8 (135–180°). Then we counted the number of sleep spindle peaks occurring within each bin (Fig. 1). In the analyses regarding memory outcome, we focused a priori on fast SO-spindles peaking within ± 45° from 0° (i.e. Upstate#) or slow SO-spindles peaking within ± 45° from 90° (i.e. Descending#).

For further analyses, we averaged the SO-spindle measures across hemispheres to represent frontal (F3, F4) or central (C3, C4) coupling. While we were primarily interested in frontal coupling according to our hypothesis, we also examined the SO-coupling of central fast spindles as they have been previously shown consequential in memory retention [6, 8]. NREM (N2 + N3) sleep was investigated as a whole. We did not confine our analyses to N3 only because also N2 events are shown to associate with memory outcome (even though coupling is more pronounced during N3 sleep) [5] and because Val66Met was observed to moderate the association between memory and specifically N2 spindles [17].

2.7. General cognitive ability

It has been previously reported that neuroanatomical integrity influences the oscillatory synchrony between SOs and sleep spindles [8]. Whether general cognitive ability relates with such properties, and subsequently, is reflected by SO-spindle coupling properties has thus far been unstudied. To enable controlling for the impact of general cognitive ability on the association between SO-spindle coupling and memory outcome, we assessed intellectual ability with a shortened version of the Wechsler Adult Intelligence Scale III (WAIS-III) [42]. The assessment included five WAIS-III subtests in the following order: Vocabulary, Block Design, Similarities, Matrix Reasoning and Digit Span. General cognitive score was calculated by averaging the Z scores of the subtests.
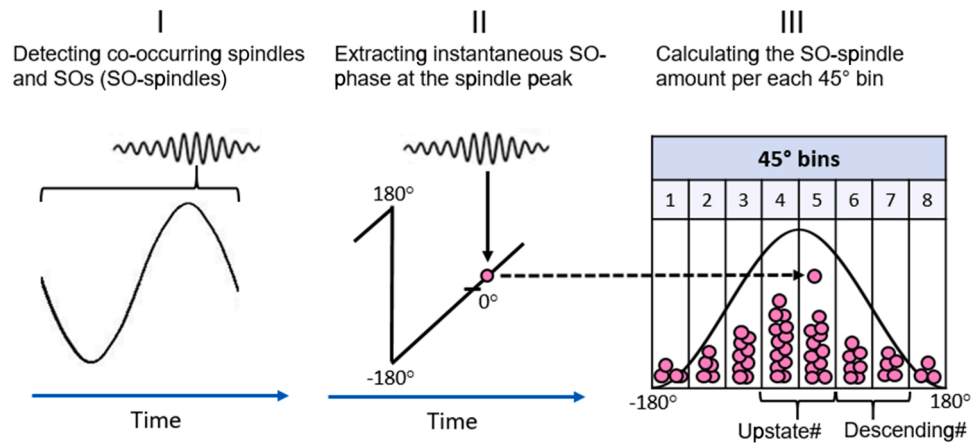

Fig. 1. The delineation of slow oscillation-spindle binning. 1) Detecting slow oscillations with a temporal overlap with a spindle peak. 2) After Hilbert-transformation, extracting the slow oscillation phase at the instant of the spindle peak. 3) Calculating the frequencies of spindles that peak in each 45° bins of the full slow oscillation cycle (depicted in black). Upstate# for fast spindles and Descending# for slow spindles comprised of ± 45° from 0° or 90°, respectively.

2.8. Genotyping

DNA was extracted from blood (22%) and saliva samples (78%) collected at the 2009–2011 follow-up. Genotyping was performed with the Illumina OmniExpress Exome 1.2 bead chip at the Tartu University, Estonia, in September 2014 according to the standard protocols. Regarding both rs6265 and rs4680 we assessed the frequencies of GG (Val/Val), GA (Val/Met) and AA (Met/Met) genotypes.

2.9. Statistical analyses

Genotypic differences in sample characteristics, RVL, coupling distance, SO-spindle% and Upstate#/Descending# were tested with one-way analysis of variance (ANOVA). We used paired-samples t-test to compare RVL and coupling distance between (1) fast and slow spindles and (2) between frontal and central fast spindles. Rayleigh's test of non-uniformity was used to test the circular distribution of the mean SO-spindle phase values. We compared mean phase distributions between (1) fast and slow SO-spindles, (2) genotypic subgroups and (3) frontal and central SO-spindles with Watson-Williams test.

Mixed ANOVAs were used to test the associations between recognition accuracy (2 levels of arousal, 3 levels of valence) and SO-spindle measures (coupling distance and Upstate#/Descending# as continuous independent variables). Genotype (Val66Met or Val158Met) was used as a between-subjects variable when examining the interactions between SO-spindle measures and genotype. Mixed ANOVAs were used to investigate the interactions between SO-spindle measures and the emotional dimensions (arousal and valence) of the picture categories. We did not test the effect of genotype or picture categories on recognition outcome, as those results have been previously reported within the same cohort [16]. Follow-up analyses exploring the interactions within-group were mixed ANOVAs and linear regressions.

In order to address the possible effect by confounders in the analyses regarding memory outcome, we included sex, sleep duration and the total time spent awake between memory encoding and recall as covariates. We considered the sleep and wake measures important due to the unequal retention interval, having previously shown them consequential in the cohort [16]. Further possible confounders on the associations between coupling measures and memory outcome we considered general cognitive ability, spindle density, SO amount or SO-spindle%, whose associations with recognition accuracy or SO-spindle coupling were first tested with partial correlation. Then, we assigned each of these potential confounders as a covariate in the tests regarding SO-spindle coupling and recognition accuracy to examine their effect on the associations.

The nominal level of statistical significance was set at $p < 0.05$. In follow-up analyses where several parallel variables were tested, we used false discovery rate (FDR) correction [43] with q-value 0.05: 8 tests for mixed ANOVAs between bin-wise SO-spindle amount and overall recognition accuracy, and 48 tests when the associations between SO-spindle bins (8) and picture categories (6) were tested with linear regression. Significant one-way ANOVAs on three subgroups of Val158Met were followed-up with Bonferroni-corrected post-hoc comparisons.

Follow-up regression results within the genotypic subgroups were further re-analyzed using Bayesian linear regression in order to quantify the evidence for null hypotheses. Bayes Factor (BF) describes the marginal likelihood ratio between the null and alternative hypothesis [44]. A BF of 1 thus indicates no evidence for either hypothesis, whereas lower BFs indicate increasingly stronger evidence for the null hypothesis (i.e. 1–1/3 anecdotal, 1/3–1/10 moderate, 1/10–1/30 strong, 1/30–1/100 very strong and $< 1/100$ extremely strong evidence) [44]. BF was estimated using Jeffreys–Zellner–Siow (JZS) priors.

Statistical analyses on linear variables, including Bayesian regression analyses, were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp, Armonk, NY, US). CircStat toolbox [41] was used to calculate circular variables (mean phase, RVL, circular distance) and run tests on circular (Rayleigh's test and Watson-Williams test).

3. Results

3.1. Genotyping

BDNF Val66Met showed genotyping success rate $\geq$ 95%, minor allele frequency of 0.16, and was in Hardy–Weinberg equilibrium (p-value > 0.05). In the analytic sample, there were 105 (68.6%), 41 (26.8%), and 7 (4.6%) of GG (Val/Val), GA (Val/Met), AA (Met/Met) genotypes, respectively. Due to low number in Met_{BDNF} homozygotes, Val/Met and Met/Met groups were combined, resulting into subgroups of 105 Val_{BDNF} homozygotes and 48 Met_{BDNF} carriers. Val/Met and Met/Met groups did not differ in terms of sample characteristics (Table 1) or sex distribution (p values $\geq$ 0.141).

COMT Val158Met showed genotyping success rate $\geq$ 95%, minor allele frequency of 0.41, and was in Hardy–Weinberg equilibrium (p-value > 0.05). In the sample, there were 27 (17.6%), 70 (45.8%), and 56 (36.6%) of GG (Val/Val), GA (Val/Met), AA (Met/Met) genotypes.

Table 1

Sample characteristics, compared between the genotypic subgroups.

	ALL N = 153			BDNF (VV/VM+MM) N = 105/48	COMT (VV/VM/MM) N = 27/70/56
	Mean	SD	Range	p	p
Age	16.89	0.12	16.64 – 17.17	0.36	0.49
TST (hh:mm)	7:39	1:10	3:10 – 10:46	0.39	0.66
N1%	11.0	5.0	2.8 – 28.7	0.95	0.91
N2%	40.9	5.8	25.7 – 55.6	0.93	0.25
N3%	27.2	6.4	13.5 – 46.1	0.19	0.36
REM %	20.7	4.9	4.9 – 32.4	0.18	0.28
Sleep efficiency %	93.0	6.2	58.9 – 98.9	0.76	0.92
Fast spindle density	2.9	0.9	1.1 – 5.9	0.91	0.33
Slow spindle density	4.1	0.9	0.6 – 6.8	0.88	0.86
SOs / channel	939	224	474 – 1513	0.55	0.12
Fast SO-spindle%	17.6	6.0	5.8 – 42.0	0.40	0.89
Slow SO-spindle%	14.3	4.7	3.8 – 30.1	0.16	0.64

VV = Val/Val. VM = Val/Met. MM = Met/Met. SD = standard deviation. p: p-value of the genotypic difference. TST = Total sleep time. N1–3: Non-rapid eye movement sleep stages 1–3. REM = rapid eye movement sleep. SO = slow oscillation. SO-spindle% = the percentage of SO-coupled spindles of all spindles. p = p value of the genotypic difference in one-way ANOVA.

3.2. Sample characteristics

Table 1 presents the age, sleep architecture and frontal spindle and SO measures of the sample (N = 153, 86 female subjects / 56%). No significant differences were found between either *BDNF* or *COMT* subgroups (p-values $\geq$ 0.16). Sex ratio did not differ between *BDNF* ($p_{\chi 2}$ = 0.23) nor *COMT* ($p_{\chi 2}$ = 0.68) subgroups.

Our preliminary analyses on the distributions of the dependent and independent variables revealed a major outlier regarding overall recognition accuracy (+3.5 SD). We excluded this participant from further analyses. Furthermore, to prevent distortion by extreme coupling values, we excluded those participants whose total number of SO-spindles was less than 30, or if bin values exceeded the mean by at least 3.5 SD. These exclusions concerned 1–3 values per bin.

3.3. SO-spindle coupling and recognition accuracy

Testing the non-uniformity of the frontal spindle peak distribution over SO cycle with Rayleigh's test showed that both fast and slow spindles were non-uniformly distributed (p values < 0.001). The grand mean phases for fast and slow spindles were $-24.8°$ and $84.0°$, respectively, differing significantly (Watson-Williams test p < 0.001). Resultant vector length was higher for fast, relative to slow, spindles (fast RVL = 0.32 vs. slow RVL = 0.25, p < 0.001). Mean coupling distance was shorter for fast (from $0°$) than slow (from $90°$) spindles (1.21 r vs. 1.26 r, respectively; t = -3.224, p = 0.002). Fig. 2A shows the distribution of frontal fast and slow SO-spindles over the SO cycle, both mean phases and pooled over all SO-spindle events. See Appendix 1 for central fast spindle coupling measures.

Examining the associations between frontal fast SO-spindle coupling and recognition accuracy revealed significant associations regarding mean coupling distance (from $0°$) ($F_{(1, 147)}$ = 9.522, p = 0.002) and Upstate# ($F_{(1, 146)}$ = 6.421, p = 0.012). The mean coupling distance of slow spindles (from $90°$) or Descending# were not significant (p-values $\geq$0.059). See Fig. 2B for the association between frontal fast SO-spindle coupling and averaged recognition accuracy. Central fast spindle coupling measures were not significantly associated with recognition accuracy (p values $\geq$ 0.253) (Appendix 1).

We further investigated whether the associations between SO-spindle coupling and recognition accuracy were independent of general cognitive ability or fast spindle and SO activity as such. Preliminary investigation with partial correlations (sex controlled) showed general cognitive ability to associate significantly with recognition accuracy (p < 0.001) but not with fast SO-spindle coupling measures (p $\geq$ 0.323). Coupling distance correlated with fast spindle density and slow oscillation amount (p $\leq$ 0.010), and Upstate# correlated additionally with

SO-spindle% (all p values $\leq$ 0.005). Thus, we ran again the analysis concerning fast spindle coupling distance and Upstate# with additionally controlling for general cognitive ability, fast spindle density, frontal SO number or SO-spindle%. None of these covariates affected the significance statuses of coupling distance (p $\leq$ 0.006) or Upstate# (p $\leq$ 0.038).

We explored bin-wise associations with recognition accuracy in the whole sample and found a positive association between Bin4 and recognition accuracy ($F_{(1, 147)}$ = 6.649, p = 0.011) and a negative association regarding Bin8 ($F_{(1, 145)}$ = 7.440, p = 0.007). No bin-wise significant associations were found regarding slow SO-spindles. See Appendix 2 for heat-mapped Pearson's correlations between bin frequencies and category-wise recognition accuracies.

3.4. BDNF Val66Met

The non-significant main effects of *BDNF* Val66Met on recognition accuracy within the cohort have been reported previously [16,17].

Val_{BDNF} homozygotes and Met_{BDNF} carriers did not differ in terms of fast and slow spindle phase distribution (Watson-Williams test p = 0.841 and p = 0.438, respectively), RVL ($F_{(1, 151)}$ = 0.021, p = 0.885 and $F_{(1, 151)}$ = 0.219, p = 0.641), coupling distance ($F_{(1, 151)}$ = 0.011, p = 0.917 and $F_{(1, 151)}$ = 0.258, p = 0.652) or Upstate#/ Descending# ($F_{(1, 151)}$ = 2.319, p = 0.130 and $F_{(1, 151)}$ = 0.710, p = 0.410). However, regarding fast spindles, Val66Met moderated the association between recognition accuracy and Upstate# ($F_{(1, 144)}$ = 4.669, p = 0.032) but not coupling distance ($F_{(1, 145)}$ = 0.011, p = 0.917). Slow spindle coupling measures did not interact with Val66Met on recognition accuracy (p-values $\geq$ 0.612).

Within-group follow-up tests showed that Upstate# associated with recognition accuracy in Val_{BDNF} homozygotes ($F_{(1,99)}$ = 12.933, p < 0.001) but not in Met_{BDNF} carriers ($F_{(1, 42)}$ = 0.024, p = 0.877). Due to unequal subgroup sizes, we conducted a Bayesian linear regression on Met_{BDNF} carriers to test the result, which supported the null hypothesis with moderate strength (BF = 0.116). Further exploring bin-wise associations in Val_{BDNF} homozygotes showed significant associations regarding Bin4 ($F_{(1, 99)}$ = 9.634, p = 0.002) and Bin5 ($F_{(1, 99)}$ = 13.044, p < 0.001), i.e. the bins comprising $\pm$ $45°$ from the positive SO peak ($0°$). An initial significant association concerning Bin3 ($F_{(1, 98)}$ = 4.397, p = 0.039) did not survive FDR correction. In Met_{BDNF} carriers, an association was found regarding Bin8 ($F_{(1, 41)}$ = 4.373, p = 0.043), but it did not remain significant after FDR correction. While Bayesian examination questioned the non-significance with anecdotal strength (BF = 1.56; other bins 0.116 – 0.362), no indication of *positive* associations with SO-coupled spindles and recognition accuracy in Met_{BDNF} carriers was found. Illustrating the associations with heat-mapped
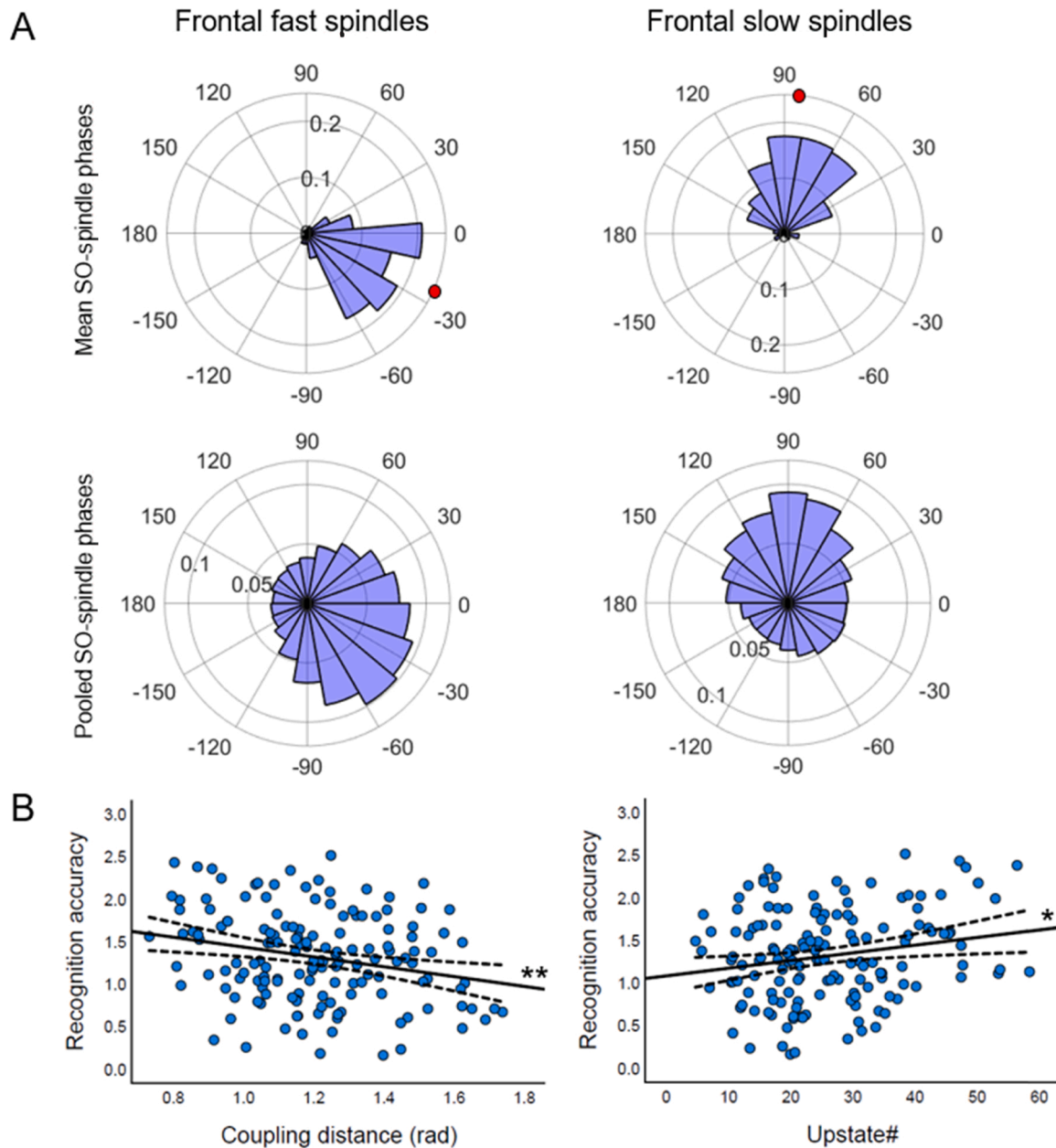
Fig. 2. Frontal slow oscillation-spindle coupling in the whole sample. (A) In the upper row, polar histograms illustrate the distribution of participant-wise mean phases on slow oscillation cycle for fast (left) and slow sleep spindles that peak during slow oscillation cycles (SO-spindles). The red dot denotes grand mean phase ($-24.8°$ and $84.0°$ for fast and slow SO-spindles, respectively). The mean phase distribution is significantly different between fast and slow spindles ($p < 0.001$). The lower row displays the distribution of all pooled SO-spindles. (B) Frontal fast spindle mean coupling distance (in radians) and Upstate# associate significantly with overnight recognition accuracy ($p = 0.002$ and $p = 0.012$, respectively). The displayed recognition accuracy scores are averaged over all picture categories and de-standardized after controlling for sex, sleep duration and total time awake. * $p < 0.05$. ** $p < 0.01$. Dashed lines represent 95% confidence intervals.

regression t coefficients between all fast spindle bin frequencies and category-wise recognition accuracy scores show that the proximity of SO upstate relates positively with better memory outcome in Val_{BDNF} homozygotes (Fig. 3).

The impact of controlling for general cognitive ability, fast spindle density, frontal SO number and SO-spindle% was examined regarding Val66Met. The interaction between Upstate# and Val66Met ($p \leq 0.046$) as well as the within-group (Val_{BDNF} homozygotes) association between Upstate# and recognition accuracy ($p \leq 0.005$) remained significant.

3.5. COMT Val158Met

The non-significant main effects of Val158Met on recognition

accuracy within the cohort have been reported previously [16].

COMT Val158Met did not associate with fast or slow phase distribution (pair-wise Watson-Williams test $p \geq 0.302$ and $p \geq 0.292$, respectively), RVL ($F_{(1, 151)} = 0.392$, $p = 0.676$ and $F_{(1, 151)} = 2.262$, $p = 0.108$) or Upstate#/Descending# ($F_{(1, 151)} = 0.110$, $p = 0.896$ and $F_{(1, 151)} = 0.481$, $p = 0.619$). However, coupling distance differed significantly regarding slow ($F_{(1, 151)} = 3.209$, $p = 0.043$) but not fast spindles ($F_{(1, 151)} = 0.557$, $p = 0.574$). Examining slow spindle coupling distance showed it shortest in Val_{COMT} homozygotes (1.17 rad; Val_{COMT}/Met_{COMT}: 1.29 rad; Met_{COMT} homozygotes: 1.27 rad), differing significantly from the heterozygotes ($p = 0.039$, Bonferroni-corrected). The interactions between Val158Met and SO-spindle coupling measures on recognition accuracy were not significant regarding either fast (p-values
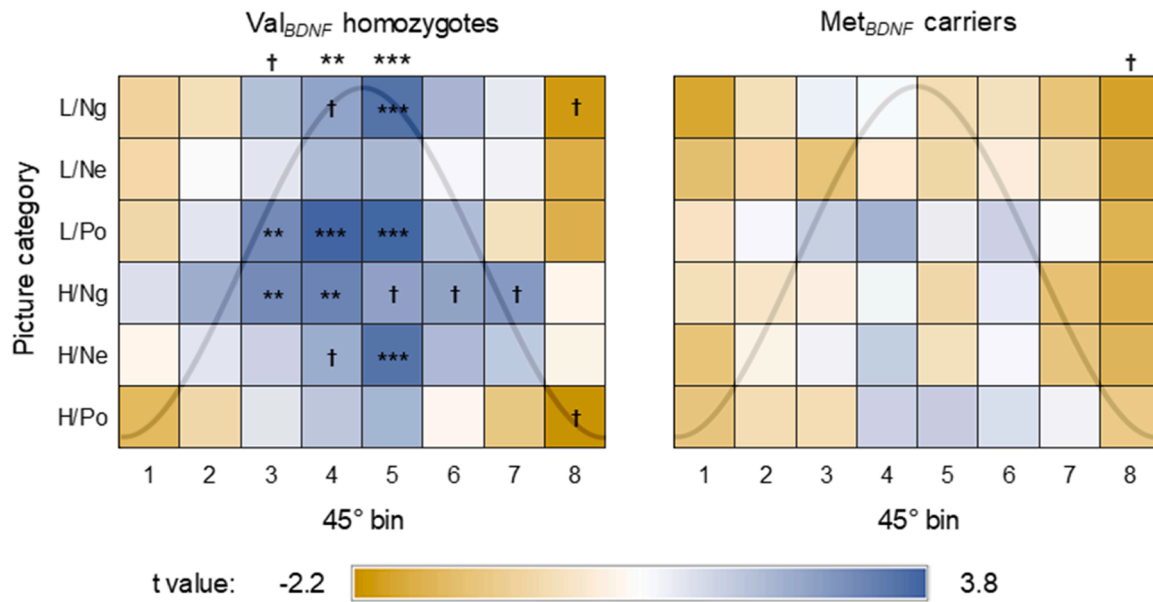
Fig. 3. Heat-mapped linear regression t values between bin-wise SO-spindle frequencies and recognition accuracies per picture categories (arousal/valence; L = low, H = high, Ng = negative, Ne = neutral, Po = positive). In Val$_{BDNF}$ homozygotes, significant associations accumulate close to the positive slow oscillation peak. The significance of linear mixed model analyses on overall recognition accuracy (averaged across the picture categories) shown above the grid. No significant associations were found in Met$_{BDNF}$ carriers. Covariates: sex, sleep duration and total time awake. *** p < 0.001; ** p < 0.01. † not significant after the correction for multiple tests.

$\geq$ 0.886) or slow (p-values $\geq$ 0.768) SO-spindles.

3.6. The effect of arousal and valence

We investigated whether SO-spindle measures or genotype interacted with picture category. Here we confined our analyses on fast spindles because of their significant associations with memory outcome. Significant interaction was observed regarding valence dimension and Upstate# (F$_{(2, 292)}$ = 3.345, p = 0.037) while coupling distance was non-significant (F$_{(2, 292)}$ = 2.126, p = 0.121). Arousal dimension did not interact significantly with SO-spindle measures (p-values $\geq$ 0.224).

Next, we explored the significant interaction between Upstate# and valence. Quadratic (F = 5.036, p = 0.026) but not linear (F = 2.089, p = 0.150), contrasts were significant. We calculated recognition accuracy difference scores for the valence category pairs, i.e.

Fig. 4. Upstate# associates with the difference between positive and neutral recognition accuracy (p = 0.010). The *positive-neutral* difference scores are de-standardized after controlling for sex, sleep duration and total time awake. * p < 0.05. Dashed lines represent 95% confidence interval.

Positive–Neutral, Negative–Neutral and Positive–Negative. Linear regression tests showed significant associations between Upstate# and Positive–Neutral (t = 2.594, p = 0.010) but not regarding Negative–Neutral (t = 1.092, p = 0.277) or Positive–Negative (t = 1.445, p = 0.150). The scatterplot in Fig. 4 illustrates the significant association.

Regarding genotypic interaction, we previously reported [16] that Met$_{COMT}$ homozygotes had higher recognition accuracy for high, compared to low, arousal pictures, that pattern replicated in the present study (not shown). BDNF Val66Met did not interact with arousal or valence. In the present study, three-way 'genotype x SO-spindle measure x arousal/valence' interactions were not significant regarding Val66Met (p-values $\geq$ 0.169) or Val158Met (p-values $\geq$ 0.096).

4. Discussion

In this study, we set to investigate genotypic moderation on the precise coupling between slow oscillations and sleep spindles and its associations with overnight visual recognition memory. We focused on polymorphisms previously associated with functional and structural neural implications as well as memory performance, namely BDNF Val66Met and COMT Val158Met. Fast, but not slow, spindles coupled with SO upstate associated with memory outcome. Val66Met moderated this association such that precise coupling appeared beneficial for Val$_{BDNF}$ homozygotes but not Met$_{BDNF}$ carriers, although the SO-spindle coupling measures as such did not differ between these subgroups. Additionally, in the whole sample, picture valence interacted with SO-spindle coupling: the recognition of positively valenced pictures was relatively most robustly predicted by SO-upstate-coupled fast spindles.

In the whole sample, we found an expected [5,8] pattern where fast sleep spindles preferentially peaked during the depolarized upstate of slow oscillations. The 'accuracy' of this coupling associated with memory outcome, in accordance with previous studies [5–8], whereas the amount of spindles peaking near the SO trough correlated negatively with recognition accuracy. These observations conform with the view that fast spindles coinciding with SO upstate form a potent window for memory consolidation due to a strong calcium influx into neurons [3]. Conversely, memory reactivations during a nonoptimal SO phase may
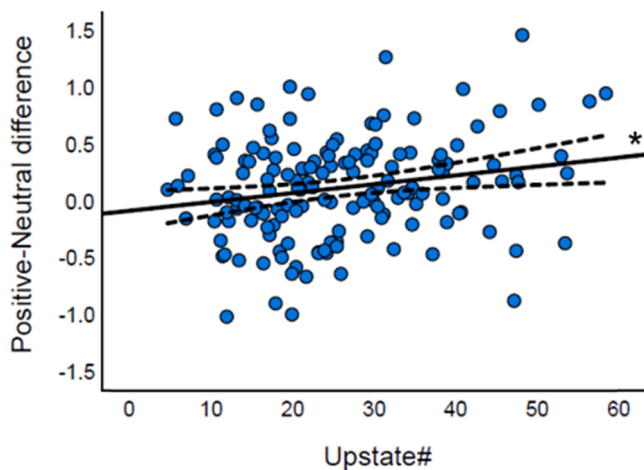
activate cascades leading to memory depression [45]. It is of note that the associations predicting memory outcome were only observed regarding frontal fast SO-spindles, even though central fast SO-spindles showed more consistent coupling with the depolarized SO peak. This pattern aligns with the findings from some previous studies [7,46] and is theoretically supported by a work demonstrating that prefrontal SO-spindle coupling mediates hippocampal-neocortical information transfer [4].

Essentially, the association between frontal SO-spindle coupling and memory outcome was moderated by *BDNF* Val66Met. Fast spindles peaking close to the positive SO peak associated robustly with better memory outcome in Val$_{BDNF}$ homozygotes only, the association diverging significantly from Met$_{BDNF}$ carriers. The finding parallels previous observations where sleep-related correlates of memory consolidation, such as slow oscillation power [15] and fast spindle density [17], seem to benefit specifically Val$_{BDNF}$ homozygotes. Based on the latter of these reports we assumed a difference in SO-spindle coupling dynamics between the genotypic subgroups, but this hypothesis was not supported in our data. Some studies [14,15], albeit not all [17,47] have found overnight memory benefits in Val$_{BDNF}$ homozygotes over Met$_{BDNF}$ carriers. One study reported steeper memory performance decline in Met$_{BDNF}$ carriers over the course of week, inciting the authors to speculate genotypic differences in memory consolidation [48]. Thus, while the presumed neurostructural and -functional implications by Val66Met [11,13] seem not to influence oscillatory synchrony as such, our result may be considered in terms of synaptic plasticity.

Met$_{BDNF}$ allele is attributed with impaired trafficking and activity-dependent secretion of BDNF [10], a neurotrophin promoting synaptic plasticity [49]. In particular, Val66Met could influence the strength of spindle-related potentiation via N-methyl-D-aspartate (NMDA) receptors. NMDA receptors are involved in triggering the calcium influx during spindles, which consequently leads to signaling cascades underlying long-term potentiation [50]. BDNF enhances the NMDA receptor function [51], and accordingly, carrying Met$_{BDNF}$ alleles may limit NMDA receptor -dependent plasticity [52]. In our study, the moderation by Val66Met concerned particularly absolute, but not relative, measures of upstate-coupled fast spindles. This provides tentative support for the speculation that the effect of SO-upstate-coupled fast spindles could differ between the genotypes. That is, the amount of potentiating events being consequential implies a mechanistic function of these events, whereas a relative variable (i.e. mean distance in our case) disregards the amount and may rather mirror the neurostructural properties coordinating the timing properties of the synchrony [23].

The speculation above alludes that the found associations between fast spindle SO-coupling and memory outcome – in the whole sample and Val$_{BDNF}$ subgroup – represent sleep-dependent memory consolidation. However, lacking a pre-sleep memory test necessitates alternative hypotheses. First, the constancy of SO-spindle coupling has been reported to reflect neurostructural integrity characteristics [8] that, in turn, may influence cognitive processes such as encoding ability. We mitigated this possibility by controlling for general cognitive ability from the association between SO-spindle coupling and recognition accuracy, and found that the significance statuses were unaffected. Second, it has been shown that successful pre-sleep learning can augment SO depolarizations [2], increase spindle activity [53,54] and modulate fast spindle coupling dynamics [55]. Hence, the increased coupling seen in high-performing participants could be indicative of more efficient encoding. This phenomenon would be emphasized in Val$_{BDNF}$ homozygotes [52,56], reflected by enhanced SO-spindle coupling. The exact underpinnings how *BDNF* Val66Met moderates the association between oscillatory synchrony and recognition requires further research.

Slow SO-spindles showed the tendency to peak around the up- to downstate transition of slow oscillation, as reported previously [2,8], but their coupling properties was not associated with memory outcome in our data. The learning implications of SO-coupled slow spindles is rather scarcely investigated. One study [8] reported a negative correlation between the retention of scene-word pairs and slow spindle activity during the transition to SO downstate. The authors proposed such a coupling pattern be characteristic of 'aged' brain, along with misaligned coupling between fast spindles and SO peak. On the other hand, SO-coupled fast and slow spindles have been reported to occur in a rather coordinated manner, upstate-tied fast spindles being followed by slow spindles closer to the up-to-down-state transition [2]. It was suggested that slow spindles may be involved in cortico-cortical processing of recent memory traces. Either way, the impact of slow spindles on memory outcome remains ambiguous and likely depends on factors not captured within the current study.

No significant interactions between Val158Met and SO-spindle coupling on memory outcome were found. This suggests that *COMT* and its implications on prefrontal dopamine [18], and subsequently, synaptic plasticity [57] are not mirrored by the dynamics between memory outcome and SO-spindle-coupling. However, age may be a factor here, as it interacts with Val158Met in terms of dopamine levels [58] and neural connectivity [59]. Hence, in our adolescent sample, the implications of Met$_{COMT}$ alleles on sleep-dependent memory consolidation may well diverge from what would be found from adults. Instead, we observed Val158Met to associate with the coupling distance (from 90°) of slow spindles, such that Val$_{COMT}$ homozygotes sported significantly shorter mean peaking distance from the up-to downstate transition, where slow spindles generally accumulate [8]. This suggests that neuroanatomical or functional differences exerted by Val158Met has an influence on slow spindles that are triggered by frontal slow oscillations. One study found Val$_{COMT}$ allele dose to correlate with reduced fast spindles [22], further increasing the interest of Val158Met for future sleep oscillation studies.

Emotion has been considered a prioritizing factor in sleep-dependent memory consolidation [24]. With the same cohort, we previously reported that pictures in the highly arousing aversive category, followed by low arousing positive category, were relatively better recognized than other pictures [16]. Here we investigated SO-upstate-coupled fast spindles in emotional memory and found them to interact with the valence dimension. Specifically, the higher the amount of SO-upstate spindles, the better were positive pictures recognized relative to neutral pictures. Evidence suggests that spindles are involved in emotional memory consolidation [27,29]. The relation between SO-spindle coupling and emotional memory has been scantly investigated, though. One previous study showed that the percentage of SO-coupled spindles – regardless of the phase timing of these events – correlated *negatively* with emotional picture recognition [30]. This effect was only found in those that underwent stress-induction before memory encoding, suggesting that high stress can impair the memory benefits by SO-spindle coupling. The exact contribution of SO-spindle synchrony on emotional memory consolidation is a compelling subject for further research. It is of note that the contrast between negative and neutral pictures was not statistically significant in our study, and perhaps REM sleep properties would better reflect negative memory processing [60, 61].

4.1. Strengths and limitations

High ecological validity was reached by having a sizable, community-based sample undergoing a study setting where the participants were allowed to adhere to their typical sleep routines. By examining two genetic polymorphisms, we contribute to the mounting understanding that there is inter-individual variability in how overnight memory outcome is reflected by acknowledged mechanisms of sleep-dependent memory consolidation.

There are important limitations to consider. First, the generalizability of the results is limited because the sample consisted of 17y old adolescents. Although the synchrony between SOs and spindles has previously been shown consequential for memory retention within that age group [7], adolescence may confound the effects of especially

Val158Met on the studied variables [58,59]. Second, all the results are correlational. Making causal deductions require experimentally controlled verification studies. Third, the memory task lacked a short-delay testing, obscuring whether the found associations between SO-spindle coupling and recognition accuracy reflected memory consolidation or rather a trait or a pre-sleep process. Moreover, we did not segregate between familiarity and recollection responses, possibly diluting interactions between genotype and emotion in our results [47, 62,63].

4.2. Conclusions

This study provides further evidence that the synchrony between SOs and fast spindles associates with overnight memory. The tendency (relative measure) and the amount (absolute measure) of fast spindles peaking close to the positive SO peak associated positively with overnight recognition accuracy in the whole sample. This association was moderated by *BDNF* Val66Met, as the frequent occurrence of SO-upstate-coupled fast spindles predicted memory outcome only in Val_{BDNF} homozygotes. Such interaction was not observed regarding Val158Met, implying that especially BDNF may modulate the significance of sleep-dependent consolidation mechanisms.

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CRediT authorship contribution statement

Risto Halonen: Conceptualization, Methodology, Writing – original draft, Formal analysis, Investigation, Visualization. **Liisa Kuula:** Conceptualization, Writing – review & editing. **Jari Lahti:** Data curation, Writing – review & editing. **Katri Räikkönen:** Data curation, Writing – review & editing. **Anu-Katriina Pesonen**: Conceptualization, Writing – review & editing, Supervision, Project administration.

Declarations of interest

None.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2022.113889.

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