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BDNF Val66Met polymorphism moderates the association between sleep spindles and overnight visual recognition

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Highlights

- Interaction of *BDNF* genotype and sleep spindles largely unstudied
- Val66Met polymorphism did not impact picture recognition accuracy
- Frontal spindles related with better recognition accuracy in Val homozygotes only

- Val66Met moderated significantly the association regarding frontal fast spindles
- Sleep spindles may not associate with learning equally across individuals

Abstract

A common single nucleotide polymorphism (SNP) of the brain-derived neurotrophic factor (*BDNF*) gene, Val66Met, has been reported to impair BDNF secretion and memory function. However, few studies have investigated the interaction of *BDNF* genotype and sleep characteristics, such as sleep spindles, that promote long-term potentiation during sleep. In this study we compared overnight visual memory between the carriers of *BDNF* Met and non-carriers (Val homozygotes), and examined how sleep spindle density associated with memory performance.

The sample constituted of 151 adolescents (mean age 16.9 years; 69% Val homozygotes, 31% Met carriers). The learning task contained high and low arousal pictures from Interactive Affective Picture System. The learning task and all-night polysomnography were conducted at the homes of the adolescents. Slow (10–13 Hz) and fast (13–16 Hz) spindles were detected with automated algorithm.

Neither post-sleep recognition accuracy nor spindle density differed between Val homozygotes and Met carriers. While frontal slow and fast spindle densities associated with better recognition accuracy in the entire sample, examining the allelic groups separately indicated paralleling associations in Val homozygotes only. Interaction analyses revealed a significant genotype-moderated difference in the associations between frontal fast sleep spindles and high arousal pictures.

In sum, sleep spindles promote or indicate visual learning in Val homozygote adolescents but not in Met carriers. The result suggests that the role of sleep spindles in visual recognition memory is not equal across individuals but moderated by a common gene variant.

Keywords: LTP, plasticity, sleep spindle, Val66Met, visual memory

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a growth hormone mediating neuronal survival and differentiation [1, 2]. BDNF also promotes synaptic plasticity [3] such as hippocampal long-term potentiation (LTP) [1, 2, 4-7], important in memory and learning [8]. Regarding memory function specifically, a single nucleotide polymorphism (SNP) of the human *BDNF* gene is rs6265, or Val66Met, has drawn interest. This methionine (Met) substitution for valine (Val) at codon 66 has been observed to alter intracellular packaging of pro-BDNF, its axonal transport while also reducing the activity-dependent dendritic secretion of BDNF [9, 10]. Evidence in rodents suggests that Val66Met polymorphism impairs hippocampal synaptic plasticity [11]. However, human studies examining memory function between Met carriers and non-carriers (Val homozygotes) have provided contrasting observations of hippocampal activation [12-14] and memory performance [15-19], leaving the impact of Val66Met polymorphism on human memory performance unestablished [20].

Sleep is a powerful memory enhancer [21-23]. Given that BDNF facilitates late-phase LTP (i.e. memory lasting longer than 1-2 hours) [24, 25], studies involving *BDNF* variants in post-encoding sleep deserve focus. In some studies differences in memory performance emerged only after night's sleep, even when reporting equal short-delay recall between the genotypes [26, 27]. In overnight studies the memory performance of Val homozygotes has been reported equal [15] or better [19, 26, 27] compared to Met carriers. A study associating sleep characteristics with overnight learning found that the improved face picture recognition of Val homozygotes related to the increase of slow oscillation (SO) power between baseline and test night, suggesting a more profound impact of pre-sleep learning on sleep power dynamics [26]. Sleep spindles, bursts of thalamocortical sigma-band oscillations (~10–16 Hz) mostly seen in stage 2 (N2) sleep [28], did not affect the learning outcome in the study. However, sleep was only analyzed in the first quartile of

the first non-rapid eye movement sleep (NREM) episode [26], hardly entirely representing the role of spindles in overnight learning.

Comprehensive evidence links sleep spindles with enhanced memory performance [29-37]. Yet, there is a lack of studies investigating sleep spindles together with BDNF, despite existing basis to assume interaction in memory function. Sleep spindles are involved in memory replay during sleep [21, 38-42] and considered a mechanism of LTP [43]. Triggered by N-Methyl-D-aspartate receptor (NMDAR) activation, strong Ca^{2+} influx during sleep spindles activates postsynaptic signaling cascades underlying LTP [44]. BDNF, on the other hand, promotes NMDAR function [45, 46]. In addition, recognizing the role of sleep spindles on hippocampal memory formation and neocortical information transfer [47-49], observations of Val66Met-related alterations in the hippocampal activation [12, 50], connectivity [13, 51, 52] and synchronization with neocortical processing [50] gain interest.

To illuminate the effect of individual genotype on memory functioning, we investigated how Val homozygotes and Met carriers differ in visual overnight learning outcome, and how sleep spindles moderate the associations in a community-based sample of 151 late adolescents in a natural overnight in-home setting. We hypothesize that Val homozygotes would display better overnight picture recognition performance and positive association between recognition performance and spindle density during N2 and N3 sleep.

2. Experimental Procedure

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 [53]. Detailed descriptions of the cohort and follow-up participation are found elsewhere [54, 55]. 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 a monetary compensation (50 €) for their effort. In total 196 adolescents participated of which 173 had been genotyped at an earlier follow-up. 22 participants had to be excluded from the sleep spindle analyses due to poor impedance levels or other measurement problems, and visual memory task data was missing from three participants due to technical problems. The final analytical sample consisted of 151 Caucasian adolescents (56 % girls; mean age 16.9 y, SD=0.1, range 16.6–17.2). We did not exclude any participants, as there were no current neurodevelopmental disorders reported. Two cases reported having had learning difficulties during elementary school.

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. Experiment flow

The in-home assessment started between 6–7 p.m. with a short questionnaire about possible factors affecting testing, e.g. handedness, native language and possible sensory or motor handicaps. After that a trained research nurse administered a cognitive assessment and the encoding phase of the recognition accuracy task. The polysomnography (PSG) device was then attached, and the subjects were instructed to follow their own sleep schedule. The next morning the research nurse detached the PSG wiring and administered the recognition phase of the recognition accuracy task.

2.3. Picture Recognition Task

The stimuli consisted of two sets of 100 pictures from the International Affective Picture System [56]. The sets were differentiated by their arousal (calm–exciting dimension) ratings: the mean normative arousal of the high and low arousal picture sets were 5.68 (5.00–7.35) and 3.47 (2.28–3.99), respectively (statistically significant difference, $p<.001$). The mean valence ratings were parallelized between the sets (mean valence of high and low arousal pictures were 5.75 and 5.84, respectively; $p = .63$). In the learning phase the participants were instructed to memorize 100 target pictures (50 low and 50 high arousal), viewed on a 14" laptop screen. The following morning, in the recognition phase, the 100 target pictures were mixed with 100 unseen sham pictures and displayed to the participants in random order. If they recognized the picture, the participants were instructed to press a key (space bar) while the picture was visible. In both learning and recognition phases the pictures lasted for 1000 ms on the screen, followed by blank black screen, lasting 1500 ms. The research nurse monitored that participants focused on the task. Recognition accuracy scores (*d'*, separately for high and low arousal) were calculated as the difference between the hit rate (standardized proportion of correctly recognized target pictures of all target pictures) and the false alarm rate (standardized proportion of incorrectly recognized sham pictures of all sham pictures) to correct for response bias. Due to false alarm rates of 0, we applied loglinear approach [57].

2.4. PSG protocol and spindle detection

All recordings were done using SOMNOscreen plus (SOMNOmedics GmbH, Germany). A trained research nurse attached gold cup electrodes at 6 electroencephalography (EEG) locations (frontal (F) hemispheres: F3, F4; central (C) hemispheres: C3, C4; occipital (O) hemispheres: O1, O2) and two for the mastoids (A1, A2) accordingly. 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. In addition, an

online reference Cz and a ground electrode in the middle of 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 and REM according to AASM guidelines (The AASM Manual for the Scoring of Sleep and Associated Events). Percentages of each stage were calculated based on total sleep time. All signals were digitally offline filtered with pass band of 0.5-35 Hz (Hamming windowed sinc zero-phase FIR filter, cut-off (-6dB) 0.25 Hz and 39.3 Hz respectively) and re-referenced to the average signal of A1 and A2 electrodes.

The manually scored PSG signals were converted to EDF format in DOMINO software and then further analyzed by using functions of EEGlab 14.1.2b (Delorme and Makeig 2004) running on Matlab R2018a (The Mathworks Inc., USA). All signals were digitally offline filtered with pass band of 0.5–35 Hz (Hamming windowed sinc zero-phase FIR filter, cut-off (-6dB) 0.25 Hz and 39.3 Hz respectively) and re-referenced to the average signal of A1 and A2 electrodes. Electrodes located at F3, F4, C3, C4 were included in the analysis. Only epochs with with electrode-scalp and both mastoids impedance equal or lower than 10 kΩ were included in the analyses.

Spindles were computationally extracted separately in N2 and N3 sleep with a method based on an automated detection algorithm described by Ferrarelli [58]. The spindle analysis was conducted in valid N2 and N3 epochs in two different frequency bands (slow: 10–13 Hz, and fast: 13–16 Hz) in order to differentiate between slow and fast spindles, which are likely to serve different functions in overnight learning [49, 59, 60]. Before applying the spindle thresholding method, the pre-processed EEG data were further filtered using the above-mentioned frequency bands separately, using high-order filter (13,200) to minimize overlap between the frequency bands [61]. The threshold values for finding spindle peak amplitude in each channel were defined by the mean of the channel amplitude (μV) multiplied with 5 (higher) including all valid epochs (impedance in the target channel and both mastoids ≤ 10 kΩ). The higher threshold (5) was iterated

by visual inspection of EEG data to provide best detection of spindle events. The spindle's amplitude was required to stay over the mean channel amplitude multiplied by 2 (lower) for 250 ms in both directions from the peak maximum, resulting in minimum spindle duration of 0.5 seconds [62]. Thus, we used channel-wise threshold definitions, taking into account that signals may vary across the channels. The maximum cut-off for spindle length was set 3.0 seconds [28] and maximum peak amplitude was set to 200 μV. Also, between spindles the signal amplitude 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, in order to prevent false alarms. Spindle-like bursts detected during arousals were excluded. Fast and slow spindle densities (number of spindles per minute) in each EEG locations were used as measures of spindle activity. Spindle densities were calculated only if the amount of valid minutes in N2 or N3 equaled or exceeded 10.

2.5. 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. We assessed the frequencies of GG (Val/Val), GA (Val/Met) and AA (Met/Met) genotypes. For data analysis Val/Met and Met/Met were grouped as Met carriers.

2.6. Statistics

All statistical analyses were done using IBM SPSS Statistics version 25.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Significance was set at $p<0.05$. Baseline differences between the genotype groups were analyzed using one-way analysis of variance (ANOVA).

Mixed ANOVAs were used in assessing recognition accuracy and the interaction of arousal level and genotype, with arousal level (low, high) as within-subjects factor and genotype (Val homozygotes, Met carriers) as between-subjects factor.

To examine the effect of sleep spindles on learning we first averaged the densities of frontal (F3, F4) and central (C3, C4) slow and fast spindles, resulting in four variables: central slow density, central fast density, frontal slow density and frontal fast density. Linear regression analysis was used to test the significance of each spindle variable (independent) on learning task score (dependent) for the whole sample and separately for the allelic groups. To test if the associations between each spindle variable and recognition task score differed between the genotypes, General Linear Model (GLM) two-way ANOVA was used to compare the regression slopes with an interaction term of 'spindle density variable x genotype'.

The analyses were run with two models including different covariates. As covariates in Model 1 we used only sex. In model 2 we used added full-scale intelligence quotient (FSIQ), total sleep time (TST) and the time awake between the encoding and recognition phase of the memory task (before and after night's sleep). To control for the impact of general cognitive ability on learning performance, we assessed intellectual ability with a shortened version of the Wechsler Adult Intelligence Scale III (WAIS-III) [63]. The assessment included five WAIS-III subtests in the following order: Vocabulary, Block Design, Similarities, Matrix Reasoning and Digit Span. Full-Scale IQ (FSIQ) was calculated by averaging the Z scores of the subtests. TST was included in the covariates to control for differences in sleep duration, which may affect overnight learning performance [64]. As we chose not to directly affect the bedtime or awakening of the participants, the time the participants spent awake between the encoding phase and sleep onset and between awakening and recognition phase were used as a single covariate. Timing of the encoding and recollection phases in overnight learning paradigms may affect results [65].

3. Results

3.1. Genotyping

rs6265 showed genotyping success rate ≥95%, minor allele frequency of 0.16, and was in Hardy–Weinberg equilibrium (p-value > 0.05). In the analytic sample, there were 103 (68 %), 42 (27 %), and 6 (4 %) of GG (Val/Val), GA (Val/Met), AA (Met/Met) genotypes. For analyses, Val/Met and Met/Met groups were combined (31 % in any Met carrier group). Possible differences in sample characteristics variables between Val/Met and Met/Met groups were examined with one-way ANOVA, but no significant differences were detected (p values > .08, data not shown).

3.2. Sample Characteristics

3.3. Recognition accuracy

A two x two mixed ANOVA analyzed the influence of *BDNF* genotype group and image arousal on overnight recognition performance. We run analyses separately for Model 1 and Model 2. With recognition performance (*d'*) as the dependent variable (Fig. 1), the analyses showed no significant main effects of picture arousal (Model 1: $F_{1, 148} = 0.101$, p = 0.751, $\eta_p^2 = 0.001$; Model 2: $F_{1, 145} = 0.240$, p = 0.625, $\eta_p^2 = 0.002$) nor of the *BDNF* genotype ($F_{1, 148} = 1.820$, p = 0.179, $\eta_p^2 = 0.012$; Model 2: $F_{1, 145} = 0.903$, p = 0.344, $\eta_p^2 = 0.006$). The interaction of genotype and arousal was not significant ($F_{1, 148} = 0.014$, p = 0.906, $\eta_p^2 < 0.001$; Model 2: $F_{1, 145} = 0.029$, p = 0.865, $\eta_p^2 < 0.001$).

3.4. Sleep Spindles in Post-Sleep Recognition Accuracy

To assess how N2 slow and fast spindle densities associated with post-sleep recognition accuracy in high and low arousal pictures, the whole sample underwent regression analyses. In all subjects we observed recognition accuracy for high arousal (high *d'*) pictures to associate with N2 frontal slow spindles when controlling for sex only (Model 1: B = 0.092, t = 2.205, p = .029. Also,

high *d'* associated significantly with frontal fast spindles in both models in the entire sample (Model 1: B = 0.079, t = 2.258, p = .025; Model 2: B = 0.091, t = 2.386, p = .018). In addition, recognition performance of low arousal pictures (low *d'*) related significantly with frontal slow spindles (Model 1: B = 0.124, t = 2.626, p = .010); Model 2: B = 0.097, t = 2.106, p = .037). No associations were found regarding N3 spindles (see Supplementary Material 2).

Examining the allelic groups separately revealed significant associations in the Val homozygote group. Better recognition of high arousal pictures associated with frontal slow spindle density (Model 1: B = 0.114, t = 2.569, p = .012; Model 2: B = 0.098, t = 2.193, p = .031) and frontal fast spindle density (Model 1: B = 0.122, t = 2.977, p = .004; Model 2: B = 0.124, t = 3.080, p = .003). Regarding low arousal pictures, analogous relationships were found between low *d'* and frontal slow spindle density (Model 1: B = 0.147, t = 2.695, p = .008; Model 2: B = 0.114, t = 2.160, p = .033) and frontal fast spindle density (Model 2: B = 0.104, t = 2.155, p = .034). No associations were found regarding N3 spindles (see Supplementary Material 2).

To examine if the relationship between N2 sleep spindle density and recognition accuracy differed according to genotype, we ran two-way ANOVA interaction tests with the interaction term 'genotype x spindle density' (Table 2). After controlling for the covariate(s) and main effects, the interaction of N2 frontal fast spindles and genotype showed significance in high *d'* (Model 1: $F_{1,146}$ = 3.891, p = 0.050, ηp^2 = 0.026; Model 2: $F_{1, 143}$ = 4.662, p = 0.033, ηp^2 = 0.032), indicating divergence in the associations between the genotypes. No differences were found regarding N3 spindles (see Supplementary Material 2).

Residual plots for the extracted coefficients of determination (R^2) in Fig. 2 illustrate the genotype-moderated associations between frontal fast spindle density and high *d'* separately for Val homozygotes and Met carriers. In the Val/Val group frontal fast spindle density explains 8.9 % of the variability of high *d'* scores and 0.1 % in Met carriers.

4. Discussion

Our study found that carriers of common *BDNF* alleles (Val/Val, ie. Val homozygotes vs. Val/Met and Met/Met, ie. Met carriers) showed no diverging performance in overnight learning of pictures of low and high arousal in a large adolescent sample. Val homozygotes represented 69 % and Met carriers 31 % of the cohort, corresponding to allelic distribution in European populations [67, 68]. In the entire sample frontal spindle density associated with better post-sleep picture recognition, and when examining the allelic groups separately, this pattern recurred in Val homozygotes only. The genotype-moderated difference between spindle-recognition-relationship was significant regarding frontal fast spindle density and high arousal picture recognition.

The null finding in the difference in visual recognition performance between the genotypes contradicts an earlier overnight study reporting improved performance in Val homozygotes [26]. However, it aligns with another study's findings where the overall recall performance was similar between Val homozygotes and Met carriers [15]. Interestingly, the authors found that emotionally high picture valence (positive and negative) improved the performance in Met carriers compared to

neutral pictures. Similar impact was not detected regarding picture arousal (calm–exciting) in our study. According to neuroimaging studies, image valence, but not arousal, correlates with amygdala activity [69, 70]. Amygdala activity during encoding associates with enhanced memory consolidation [71], and Met carriers have been reported to show higher amygdala activity towards emotional stimuli than Val homozygotes [72, 73]. Based on our results, it appears that the perception and processing of arousal does not separate *BDNF* polymorphisms to the extent of valence. However, we could not divide recognition performance into 'recollection' and 'familiarity' responses [74, 75] as a recent study (not involving post-encoding sleep), showing that only 'familiarity' response accuracy differed between Val homozygotes and Met carriers [76].

In our study, we also focused on the associations between sleep spindles and recognition accuracy. In the entire sample, frontal slow and fast spindle density in N2 sleep associated with better post-sleep recognition of pictures. Considering that numerous reports associate (also) central spindle density with declarative learning [29, 34, 77, 78] the topographical dichotomy urges further scrutiny. Previously frontal spindle activity has been linked with the learning of word-pairs [29, 79, 80], with associating faces and names [30, 81, 82] and with contextual memory [83]. One study found both frontal and central spindle power to correlate with better neutral picture memory [84]. Considering that recognition memory is deemed to depend upon prefrontal cortex [85-89], medial temporal lobe structures and interconnecting white matter projections [76, 90], our results contribute to relatively scarcely studied matter.

Arguably slow and fast spindles serve diverging functions in learning. Especially fast spindles are implicated with offline memory consolidation as they associate with greater encoding-related hippocampal activation [82] and higher hippocampal-neocortical functional connectivity [91]. Fast spindles coincide with slow oscillations and hippocampal sharp wave ripples, consequently promoting memory transfer between hippocampus and neocortex [49, 92] Moreover, Mander et al. [82] found frontal fast spindles to restore next-day learning capacity. Slow spindles,

on the other hand, have been proposed to follow fast spindles and be involved in cortico-cortical information processing within prefrontal cortex [60], although rather limited evidence associates slow spindles with better learning in adults [33]. Notably, sleep spindles of varying frequency ranges [93-95] have been attributed with pre-sleep memory performance, a measure not examinable in our study. Such 'learning aptitude' does not equal, but overlaps with [96, 97], the construct of general cognitive ability. Introducing full-scale intelligence quotient – a contested correlate with sleep spindle characteristics [98] – as a covariate did not dispel the associations between recognition accuracy and slow or fast frontal spindle density in our data. This implies a learning component beyond general cognitive ability regarding frontal spindles. However, the exact contribution of each spindle type on the learning performance would require further investigation of e.g. inter-spindle dynamics and synchronization with other sleep oscillations.

Not all studies report associations between spindles and declarative learning (for example, see [99]). Given that sleep spindles reflect synchronized activity of inter-individually variable neuroanatomical structures [100], few studies have considered the influence of subject-specific factors beyond age and sex on the obtained results. Hence, we examined the interaction between Val66Met polymorphism and sleep spindles on overnight memory performance. Analyses run separately for Val homozygotes and Met carriers revealed that each of the significant association in the entire sample involved a strong, paralleling association confined to Val homozygotes only, whereas spindle density in recognition accuracy showed no significance in Met carrier group. The associations were significantly divergent regarding frontal fast spindles in high arousal picture recognition. The result proposes that frontal fast sleep spindles promote or indicate visual recognition memory formation differently between Val homozygotes and Met carriers.

Neural underpinnings behind the observed difference between Val homozygotes and Met carriers remain a matter of speculation. Volumetric analyses indicate Val homozygosity to associate with larger prefrontal [101-103] and hippocampal [9, 50, 101, 104, 105] gray matter volume in

comparison to Met carriers. Based on altered activation patterns and higher error rate in verbal learning task, Schofield et al. [50] suggested Met-allele-associated dysregulated activation of hippocampus and its prefrontal projections. Concordantly, functional connectivity between hippocampal and neocortical areas is reportedly higher in Val homozygotes than in Met carriers [13, 51, 52], which proposedly [106] derives from more efficient pruning of silent axons, a process modulated by BDNF [107, 108]. Indeed, whereas white matter (WM) integrity underlies the propagation [100, 109] and memory benefit [110] of sleep spindles, the relation between WM characteristics and cognition may be affected by Val66Met polymorphism, and appears discernible in Val homozygotes only [111, 112]. Acknowledging the methodological distance, this evidence encourages us to suggest that the addressed genotypic differences in fronto-hippocampal network and in connectivity dynamics contribute to the frontal emphasis in spindle-learning-relation in Val homozygotes in our sample. Furthermore, it is well-established that specifically fast spindles promote memory consolidation via inter-oscillation synchronization [113, 114], orchestrated by prefrontal cortex [92]. Higher connectivity enhances synchrony [115-117] and BDNF is involved in stabilizing even complex patterns of potential fluctuations [118]. While this theoretically parallels the accentuated genotypic moderation regarding fast spindles in our data, further studies investigating the exact impact of Val66Met polymorphism on phase-amplitude coupling characteristics are warranted.

Some issues should be underscored here. Met carriers fared equally with Val homozygotes in recognition accuracy in our study, although no other correlate with learning aside spindles was identified. Val66Met polymorphism affects the dynamics between sleep and learning in a complex manner, affecting also next-day cognition [119, 120], which necessitates more research with varying settings. In addition, our sample consisted of closely-aged adolescents, with ongoing neural reorganization of brain [121], increasing thalamocortical functional connectivity [122] and altering spindle characteristics [78, 123]. The narrow age-range may highlight subtle inter-group differences

in neural activity and cognitive functioning. Hence, these results can only be cautiously generalized to other age groups.

4.1. Strengths and Limitations

A key strength of our study was the large, community-based longitudinal sample with a high age coherence. This study adds to the increasing research literature on adolescents' spindles. Uniquely, our study is the first to assess how *BDNF* gene moderates the association between sleep spindles and overnight picture recognition.

There are also major shortcomings requiring attention. Firstly, the study setting enables only correlative scrutiny of the associations. That is, the singular morning picture recognition without a pre-sleep measurement makes the overnight change in recognition accuracy unexaminable. This undermines the deductibility of causal role of sleep spindles in learning. Further obscuring causation, having only one night with PSG recording prevented us from examining how learning affected sleep spindle characteristics, as well as from considering previous night's impact on learning [82, 119, 120]. Also, due to the lack of a waking control group we could not properly assess how, or whether, sleep affected the recognition accuracy scores. Within these limitations it is not inferable if the associations between frontal spindles and recognition accuracy derives from offline consolidation or from general learning capability. Controlling for FSIQ diminishes the effect of intelligence on learning performance, but hardly equals immediate learning ability. Secondly, 'recollection' and 'familiarity' responses, evidently representing divergent neural processes [124], were undifferentiated. Thus, we were unable to investigate these subtypes separately although their relevance regarding Val66Met polymorphism has recently been reported [76]. Thirdly, while we parallelized the mean valence ratings of the applied picture sets, the variance in valence was rather high, possibly introducing unassessed impact on recognition performance [15]. Finally, due to less

Met carriers than Val homozygotes, the analyses run separately on the groups are not fully comparable due to difference in statistical power. This calls for balanced groups in further studies.

4.2. Conclusions

The relation between sleep microstructure and memory formation may not be equal across all individuals. This study is the first to show that sleep spindle density associates with better visual post-sleep recognition accuracy only in Val homozygotes. In Met carriers, sleep spindles did not associate with learning. We suggest that the results reflect genotype-moderated functional differences in fronto-hippocampal network. The exact nature of the divergence requires further studies.

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Figure1

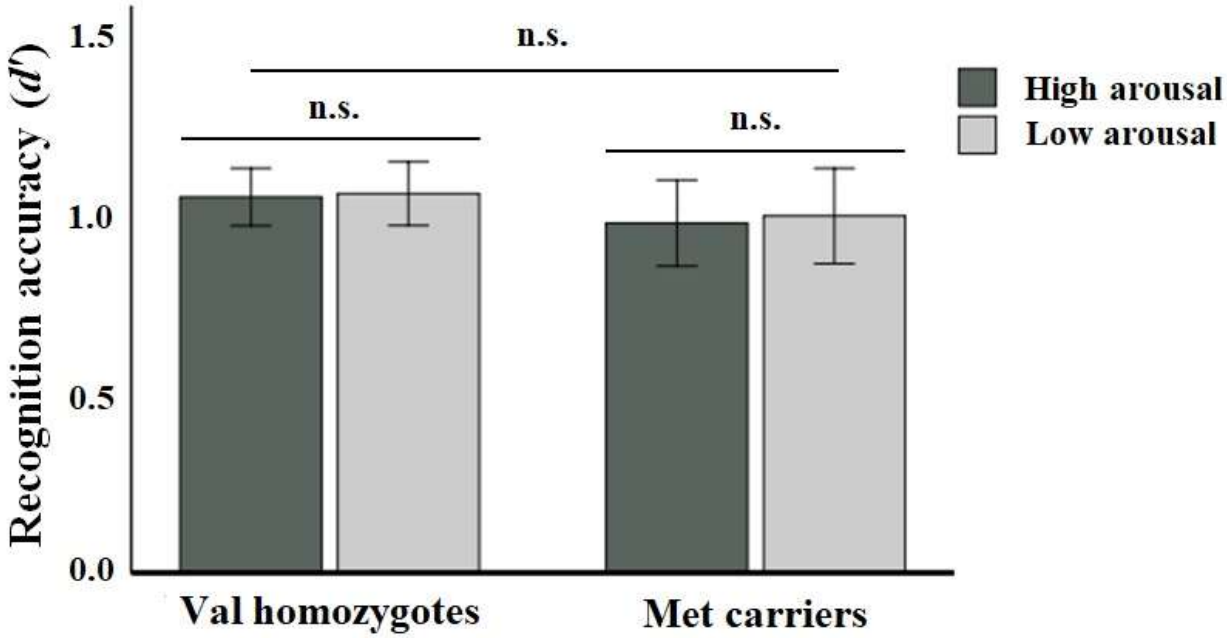

Figure2

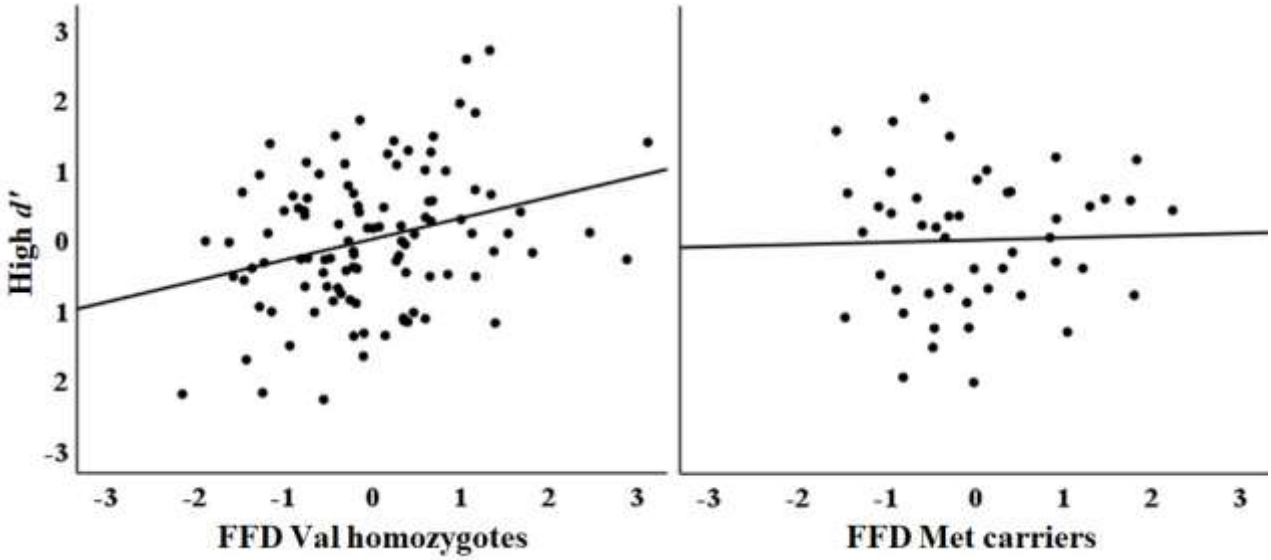

Table 1 presents the age, pubertal development, FSIQ, sleep measures and spindle densities. No differences in the variables emerged between the genotype groups (Val homozygotes and Met carriers). Furthermore, spindle duration, amplitude and frequency showed no significant differences between the genotypes in N2 and N3 spindles. (all p values ≥ .11; see Supplementary Material 1).

Table 1. Sample Characteristics.

	Val homozygotes			Met carriers			
	Mean	Range	SD	Mean	Range	SD	p
Age	16.9	16.6–17.2	0.1	16.9	16.7–17.2	0.1	.53
Pubertal development	3.2	2.4–3.8	0.4	3.3	2.2–3.8	0.4	.79
FSIQ	0.0	-1.4–1.5	0.6	-0.1	-2.5–0.9	0.7	.24
Sleep variables							
Total Sleep Time (hh:mm)	7:41	3:10–9:52	1:02	7:29	3:49–10:46	1:22	.33
N1 %	10.4	3.0–27.0	4.4	9.8	2.7–18.0	4.3	.47
N2 %	38.3	23.2–51.2	6.0	37.9	20.5–50.6	6.3	.76
N3 %	25.0	12.4–39.6	5.7	26.0	15.7–39.6	6.3	.36
REM %	19.7	4.4–30.9	5.1	18.7	4.3–28.4	4.9	.25
Sleep efficiency (%)	93.4	70.7–98.4	4.8	93.1	60.8–98.9	6.9	.34
N2 Spindle density (n/min)							
Central slow	3.4	2.3–4.6	0.6	3.6	2.2–4.6	0.7	.23
Frontal slow	4.4	1.6–6.3	0.8	4.5	2.9–6.2	0.7	.39
Central fast	3.6	1.8–6.2	0.9	3.5	2.1–5.7	0.9	.65
Frontal fast	2.9	0.9–5.7	0.9	3.0	1.6–4.8	0.8	.79
N3 spindle density (n/min)							
Central slow	2.4	0.6–3.8	0.6	2.5	1.1–3.2	0.8	.20
Frontal slow	3.3	1.0–5.5	0.9	3.3	1.5–6.3	1.0	.85
Central fast	3.6	1.5–5.9	0.9	3.5	1.7–5.1	0.8	.87
Frontal fast	2.5	1.0–5.6	0.8	2.5	1.3–5.1	0.9	.86

Pubertal development estimated using the Pubertal Development Scale (PDS) [66]. FSIQ = Full-Scale Intelligence Quotient. REM = Rapid Eye Movement sleep; N1-N3 = stages of non-REM sleep.

Table 2. Regression and interaction analyses between picture learning scores and N2 spindle densities.

Spindle density	All	VH	MZ	Genotype x spindle	All	VH	MZ	Genotype x spindle
High *d'*	B (SE)	B (SE)	B (SE)	F	B (SE)	B (SE)	B (SE)	F
Central slow	0.02 (.06)	0.07 (.07)	-0.04 (.11)	0.55	0.01 (.06)	0.05 (.07)	-0.04 (.11)	0.33
Frontal slow	0.09* (.04)	0.11* (.04)	0.07 (.10)	3.3	0.08 (.04)	0.10* (.05)	0.03 (.10)	1.03
Central fast	0.08 (.04)	0.07 (.05)	0.11 (.10)	1.83	0.07 (.04)	0.06 (.05)	0.11 (.10)	0.31
Frontal fast	0.09* (.04)	0.12** (.04)	0.01 (.09)	3.89*	0.09* (.04)	0.12** (.04)	0.02 (.09)	4.66*
Low *d'*	B	B	B	F	B	B	B	F
Central slow	0.06 (.07)	0.11 (.09)	0.00 (.11)	0.54	0.05 (.07)	0.06 (.08)	0.00 (.11)	0.23
Frontal slow	0.10** (.05)	0.15** (.06)	0.07 (.10)	0.72	0.10* (.05)	0.11* (.05)	0.03 (.10)	1.02
Central fast	0.07 (.05)	0.06 (.06)	0.07 (.10)	0.01	0.05 (.05)	0.05 (.05)	0.07 (.10)	0.00
Frontal fast	0.06 (.05)	0.10 (.05)	-0.07 (.09)	2.31	0.06 (.04)	0.10* (.05)	-0.05 (.09)	3.23

B = Regression analysis coefficient B for spindle density variables in the entire sample (All) and separately for Val homozygotes (VH) and Met Carriers (MC). SE = Standard Error. F = F-value of the interaction term 'genotype x spindle'. High d' = recognition accuracy as d' for high arousal pictures. Low d' = recognition accuracy as d' for low arousal pictures. Model 1 covariates: sex. Model 2 covariates: sex. FSIQ, total time awake and sleep duration.
* = p < .05, ** = p < .01.