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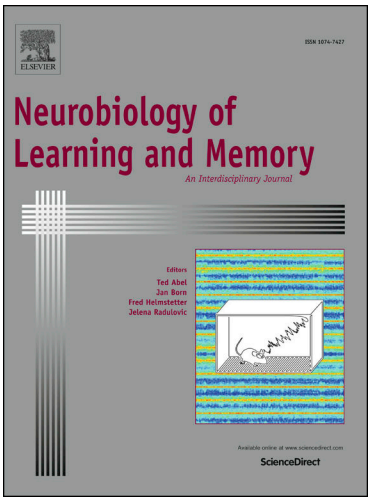

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The association between sleep-wake ratio and overnight picture recognition is moderated by *BDNF* genotype

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ABSTRACT

A wealth of studies supports the role of sleep in memory performance. Experimentally controlled studies indicate that prolonged wake after memory encoding is detrimental for memory outcome whereas sleep protects from wake-time interference and promotes memory consolidation. We examined how the natural distribution of wake and sleep between encoding and retrieval associated with overnight picture recognition accuracy among 161 adolescents following their typical sleep schedule with an in-home polysomnography. The memorized pictures varied in their level of arousal (calm to exciting) and valence (negative to positive). Suspecting genotypic influence on the sensitivity for sleep/wake dynamics, we also assessed if these associations were affected by known gene polymorphisms involved in neural plasticity and sleep homeostasis: brain-derived neurotrophic factor (*BDNF*) Val66Met and Catechol-O-methyltransferase (*COMT*) Val158Met. In the whole sample, overnight recognition accuracy was associated with the levels of arousal and valence of the pictures, but not with sleep percentage (i.e. the percentage of time spent asleep between memory encoding and retrieval). While the allelic status of *BDNF* or *COMT* did not have any main effect on recognition accuracy, a significant moderation by *BDNF* Val66Met was found ($p = .004$): the subgroup homozygous for valine allele showed positive association between sleep percentage and recognition accuracy. This was underlain by detrimental influence of wake, rather than by any memory benefit of sleep. Our results complement the mounting evidence that the relation between sleep and memory performance is moderated by *BDNF* Val66Met. Further studies are needed to clarify the specific mechanisms.

Keywords: sleep electroencephalography, rs6265, rs4680, overnight learning, sleep pressure

1. INTRODUCTION

The role of sleep in memory formation is central. Better learning is observed after a time period including sleep compared to equal time awake (Baran, Pace-Schott, Ericson, & Spencer, 2012; Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Maurer et al., 2015; Potkin & Bunney, 2012; Rasch & Born, 2013; Sheth, Nguyen, & Janvelyan, 2009), and even a short duration of sleep after encoding suffices to benefit learning (Lahl, Wispel, Willigens, & Pietrowsky, 2008; Tucker & Fishbein, 2009). Remaining awake builds up sleep pressure, decreases the signal-to-noise ratio of potentiated synapses (Tononi & Cirelli, 2014) and exposes new memory traces to interference (Wixted, 2004). Accordingly, short, relative to long, delays between learning and sleep has yielded greater performance benefits (Gais, Lucas, & Born, 2006; Talamini, Nieuwenhuis, Takashima, & Jensen, 2008; Ullrich Wagner, Kashyap, Diekelmann, & Born, 2007). Sleep itself is known to promote memory formation by strengthening recently potentiated synaptic connections (Klinzing, Niethard, & Born, 2019) and by reducing the net synaptic strength (Tononi & Cirelli, 2014).

Sleep preserves emotional information over neutral, whereas such preference is not perceived over wake conditions (Ashton, Harrington, Guttesen, Smith, & Cairney, 2019; Baran et al., 2012; Hu, Stylos-Allan, & Walker, 2006; Nishida, Pearsall, Buckner, & Walker, 2009; Payne, Chambers, & Kensinger, 2012; Payne, Stickgold, Swanberg, & Kensinger, 2008; U. Wagner, Hallschmid, Rasch, & Born, 2006). This selective consolidation is associated with elevated post-sleep amygdala activity and connectivity among emotional network (Lewis, Cairney, Manning, & Critchley, 2011; Payne & Kensinger, 2011). Whereas the role of slow-wave sleep (SWS) on memory consolidation is acknowledged (Ackermann & Rasch, 2014), especially rapid eye-movement (REM) sleep is implicated with the reactivation of emotional content (Bennion, Payne, & Kensinger, 2015). However, according to a recent meta-analysis, evidence for sleep's selective enhancement for valenced memories over neutral ones is far from uniform and suspect to methodological variation (Lipinska, Stuart, Thomas, Baldwin, & Bolinger, 2019). Emotionality is conventionally defined by two dimensions, arousal (calm to exciting) and valence (negative to positive), but their separate influence on memory over sleep is rarely scrutinized. Besides this, inter-individual factors modulating emotional memory consolidation over sleep are scarcely studied. Of particular interest are genes that regulate neural plasticity, emotional responsiveness and sleep

homeostasis, as these might explain some of the variation in individual consolidation processes and preferences.

A polymorphism of the gene encoding brain-derived neurotrophic factor (BDNF), a protein involved in synaptic plasticity (Lu, Nagappan, & Lu, 2014), substitutes valine (Val) to methionine (Met) in the codon 66 (Val66Met). This results in impaired intracellular trafficking and reduced activity-dependent secretion of BDNF (Z.-Y. Chen et al., 2004). In humans, Val66Met polymorphism is perceived to implicate neuroanatomical and functional alterations in fronto-hippocampal network (Pezawas et al., 2004; Schofield et al., 2009) and amygdala (Molendijk et al., 2012; Montag, Weber, Fliessbach, Elger, & Reuter, 2009). Evidence links *BDNF* valine homozygosity with better memory performance (Toh, Ng, Tan, Tan, & Chan, 2018), including overnight learning (Cathomas, Vogler, Euler-Sigmund, de Quervain, & Papassotiropoulos, 2010; Mascetti et al., 2013), and with elevated dependence on consolidated sleep in next-day memory performance (Gosselin et al., 2016). As possible markers of sleep-related memory processing, only Val_{BDNF} homozygotes have shown early-night slow-oscillation power (Mascetti et al., 2013) and fast sleep spindles (Halonen et al., 2019) to associate with better visual recognition. On the other hand, Met_{BDNF} carriers exhibit post-sleep recollection benefit for emotional pictures over neutral ones (Harrington et al., 2019). Val66met affects sleep homeostasis. After sleep onset, slow-wave activity builds up steeper in Val_{BDNF} homozygotes, reflecting elevated sleep pressure (Bachmann et al., 2012). It also dissipates fast to equal the level of Met_{BDNF} carriers after the first episode of non-rapid eye movement (NREM) sleep (Bachmann et al., 2012).

Catechol-O-methyltransferase (COMT), encoded by *COMT* gene, participates in the degradation of dopamine in the brain (J. Chen et al., 2004). A substitution of valine to methionine at codon 158 (Val158Met) lowers the enzymatic activity, leading to higher extracellular dopamine level in prefrontal cortex. Conversely, the existence of a Val_{COMT} allele is relatively detrimental for prefrontally guided executive functions (Wishart et al., 2011). In non-sleep studies on declarative memory, Val_{COMT} allele is shown to be associated with less activation of hippocampal formation during encoding and retrieval (Bertolino et al., 2006; Krach et al., 2010) and with declined performance (Bertolino et al., 2006; de Frias et al., 2004; Krach et al., 2010). Notably, while Met_{COMT} allele relates with increased prefrontal and limbic activation when processing emotionally aversive content (Drabant et al., 2006; Herrmann et al., 2009; Smolka et al., 2005), emotional material benefits Val_{COMT} carriers performance-wise (Gibbs, Bautista, Mowlem, Naudts, & Duka, 2014; Naudts, Azevedo, David, van Heeringen, & Gibbs, 2012). Sleep-deprived Val_{COMT} carriers show impairments in adaptive decision making (Satterfield et al., 2018) and slower dissipation of

sleep pressure (Goel, Banks, Lin, Mignot, & Dinges, 2011). However, the lack of overnight learning studies on Val158Met is obvious.

Adolescence is a period of neural maturation (Gogtay et al., 2004) and elevated affective responsivity (Guyer, Silk, & Nelson, 2016). Sleep is essential for learning in adolescence (Kopasz et al., 2010; Potkin & Bunney, 2012), although overnight learning of emotional items is scarcely studied within that age group. Moreover, neuroanatomical research suggests that both *BDNF* (Jasińska et al., 2017; Pezawas et al., 2004) and *COMT* (Meyer et al., 2016; Raznahan et al., 2011) affect neurodevelopmental trajectories between childhood and adulthood. Yet, studies clarifying the influence of these genes on long-term memory during adolescence are nonexistent.

With in-home polysomnography (PSG) on a large adolescent sample following their everyday rhythm, we investigated how *naturally* occurring variation in the durations of sleep and wake between memory encoding and retrieval affected overnight picture recognition. The pictures were categorized by their intensity (low and high arousal) and affective tone (negative, moderate and positive) to study the interaction of these dimensions (Mickley Steinmetz, Addis, & Kensinger, 2010) over sleep. Expecting sleep to interact with plasticity-related genes, we also examined how different variants of *BDNF* and *COMT* moderate the association between sleep, wake, and learning. We assumed a higher proportion of sleep relative to wake to associate positively with recognition accuracy in all subjects, and that this relation would be accentuated in the carriers of gene variants previously associated with improved memory in adult studies (i.e. Val_{BDNF} homozygotes and Met_{COMT} homozygotes).

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 (Strandberg, Jarvenpaa, Vanhanen, & McKeigue, 2001). Detailed descriptions of the cohort and follow-up participation are found elsewhere (Pesonen et al., 2014). 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 consented for further contact, were recruited by phone and were offered a monetary compensation (50 €) for their effort. In total 196 adolescents participated in the follow-up. Technically valid polysomnography (PSG) measurements were obtained from 183 participants. Out of those, 163 had been genotyped at an earlier follow-up. Memory test data was missing for two participants. The final analytical sample consisted of 161 adolescents. None were excluded based on the background data.

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 in the evening (mean 6:16 p.m., SD = 27 min) with a questionnaire about factors possibly affecting testing, e.g. handedness, native language and potential handicaps. Then a trained research nurse administered a cognitive assessment and the encoding phase of the visual memory task. The mean time of encoding was 7:28 p.m. (SD = 30 min) The polysomnography (PSG) device was then attached, and the subjects were instructed to follow their typical routines and sleep schedule. The next morning, as was agreed, the research nurse detached the PSG wiring and administered the retrieval phase of the memory task, the mean time being 8:41 a.m. (SD = 1 h 20 min) See Figure 1 for a schematic illustration of the study night procession.

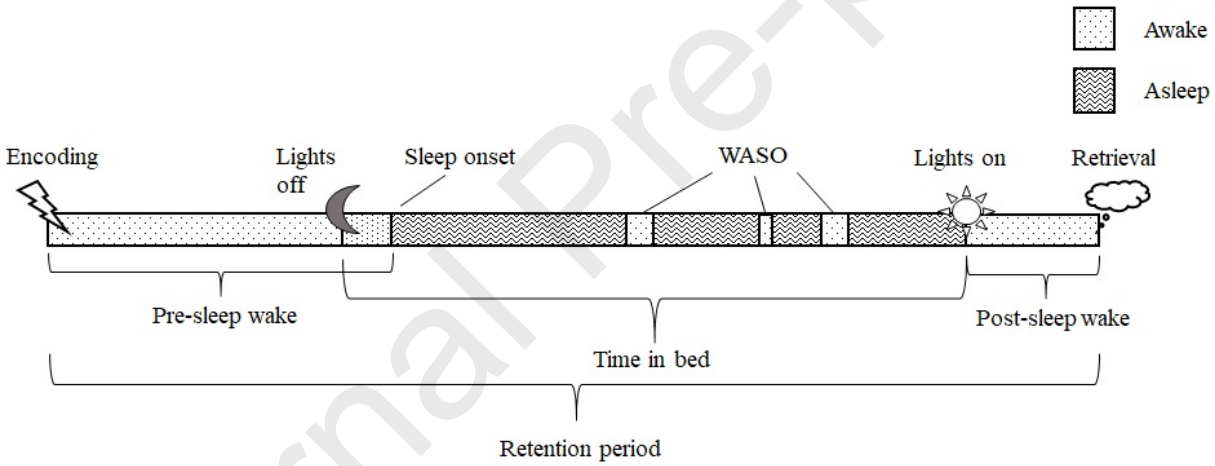

Figure 1. Schematic illustration of the study night procedure. The timing of bedtime and awakening followed the daily schedule of the participants. The mean times of encoding and retrieval were 7:28 p.m (SD = 30 min) and 8:41 a.m. (SD = 1 h 20 min), respectively. WASO = wake after sleep onset.

2.3. Recognition Task

The stimuli consisted of pictures from the International Affective Picture System, that are rated on nine-point scales for emotional arousal (1 = calm, 9 = exciting) and valence (1 = negative, 5 = neutral, 9 = positive) (Lang, Bradley, & Cuthbert, 2005). In the present study, 200 pictures were divided into 100 target and 100 sham pictures. These pictures were differentiated into categories by their normative arousal and valence ratings (Lang et al., 2005) into two levels of arousal (low / high; LA / HA, respectively) and three levels of valence (negative / moderate / positive; NV / MV /

PV, respectively). The mean normative arousal was 3.47 (SD = 0.43) in the LA category and 5.68 (SD = 0.55) in HA category (one-way ANOVA $p < .001$). The mean normative valence values in NV, MV and PV were 4.18 (SD = 0.56), 5.98 (SD = 0.52) and 7.23 (SD = 0.37), respectively (one-way ANOVA $p < .001$). Arousal values were balanced between the valence categories (one-way ANOVA $p = .629$), and valence values were balanced between the arousal categories (one-way ANOVA $p = .902$). The mean arousal and valence ratings were balanced between target and sham pictures (one-way ANOVAs $p = .744$ and $p = .675$, respectively).

In the learning phase, the participants were instructed to memorize 100 target pictures (17 HA-NV; 16 HA-MV; 17 HA-PV; 17 LA-NV; 16 LA-MV; 17 LA-PV) viewed on a 14" laptop screen. Pictures were displayed for 1000 ms, followed by blank black screen lasting 1500 ms. The following morning, in the recognition phase, the 100 target pictures, mixed with 100 unseen sham pictures (distributed equally between arousal and valence categories), were displayed to the participants in a random order. 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. The research nurse monitored that participants focused on the task.

Recognition accuracy (*d'*) was separately calculated for all picture categories. The measures of *d'* 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 (Stanislaw & Todorov, 1999). Because of false alarm rates of 0, we applied loglinear approach (Hautus, 1995).

2.4. PSG protocol and sleep/wake variables

All recordings were performed using SOMNOscreen plus (SOMNOmedics 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 (SWS), REM and wake,

according to AASM guidelines (The AASM Manual for the Scoring of Sleep and Associated Events).

Sleep onset was defined as the start of at least 10 minutes of consecutive sleep. Based on the scoring, we defined the total sleep time (TST), durations of N1–3 and REM sleep stages, wake after sleep onset (WASO) and sleep efficiency (the percentage of TST between lights off and lights on). Sleep percentage (Sleep%) was calculated by dividing TST with retention period length (i.e. the time elapsed between encoding and retrieval). Total wake time (TWT) was the accumulated time spent awake during the retention period. In addition, we calculated the time spent awake between encoding and sleep onset (pre-sleep wake) as well as between awakening and retrieval (post-sleep wake).

2.5. Genotyping

DNA of the final sample was extracted from blood (4.3%) and saliva samples (95.7%) 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.

2.6. Defining additional covariates

We specified variables that were examined as potential confounders:

1. The length of the retention period (i.e. time between encoding and retrieval) controlled because of likely impact on Sleep%.
2. General cognitive ability was obtained from all participants with a shortened version of the Wechsler Adult Intelligence Scale III (WAIS-III) (Wechsler, 1997). 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. We regarded FSIQ as a potential confounder, due to the association between intelligence and learning (Alexander & Smales, 1997).
3. The habitual bedtime was measured with actigraphy. Participants were instructed to wear actigraphy for 10 consecutive days. Bedtime values containing at least 5 valid measurement nights (N = 154) were averaged to represent the habitual bedtime. This confounder was addressed to control for any possible impacts caused by circadian mismatch on sleep, and subsequently, memory.

4. The duration of sleep in the night preceding the study night, as well as wakeup time in the morning of the study night, were measured with actigraphy. These measures were obtained from 115 participants. Lack of sleep may affect subsequent memory encoding (Yoo, Hu, Gujar, Jolesz, & Walker, 2007).

2.7. Statistical analyses

One-way analysis of variance (ANOVA) was used to test for differences in age, wake and sleep measures and in general cognitive ability (FSIQ) between the *BDNF* and *COMT* allelic subgroups. No covariates were used in these comparisons. Sex ratio between genotypic subgroups was tested with Chi-squared test.

First, mixed ANOVA was applied to test how recognition accuracy *d'* (dependent variable) was affected by picture category (within-subject variables; 2 levels of arousal, 3 levels of valence). Second, we examined the effect of sleep/wake variables (continuous independent variables) on recognition accuracy in the whole sample as well as their interaction with picture category. We run four separate models for 1) Sleep%; 2) TWT and TST; 3) N3 and REM; 4) Pre- and post sleep wake. Third, genotypic main effects and 'genotype x picture category' interaction were then tested (without sleep/wake variables) including either *BDNF* Val66Met or *COMT* Val158Met as between-subjects variable (two-levels for both *BDNF* and *COMT*, i.e. Val_{BDNF} homozygotes and Met_{BDNF} carriers; and Met_{COMT} homozygotes and Val_{COMT} carriers, respectively). Finally, the interaction between genotype and Sleep%, TWT and TST were tested one-by-one, including the interaction term along with the main effects in to the model. In the follow-up analyses we used either within-subject ANOVAs (for picture category effects on *d'*) or regression analyses with the averaged *d'* (across picture categories) as the dependent variable.

Sex was controlled for in all mixed ANOVA and regression analyses, because of its effect on cognitive functioning within the age-group (Pesonen, Ujma, Halonen, Räikkönen, & Kuula, 2019). To address for the common variance in sleep/wake measures, we controlled for TWT when testing the sleep variables (TST, N3 or REM), and for TST when testing the wake variables (TWT, pre- and post-sleep wake). The effects of potential confounders (Ch. 2.6) were separately tested by including them as covariates in the mixed ANOVA model.

The nominal level of statistical significance was set at $p < 0.05$. When testing the impact of picture category on recognition accuracy, we run Bonferroni corrections. When applicable, we run Levene's test for variance homogeneity, Mauchly's test for sphericity as well as collinearity

diagnostics. All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

3. RESULTS

3.1. Genotyping

BDNF Val66Met 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 108 (67 %), 45 (28 %), and 8 (5 %) of GG (Val/Val), GA (Val/Met), AA (Met/Met) genotypes. For analyses, Val/Met and Met/Met groups were combined, resulting into subgroups of 108 Val_{BDNF} homozygotes and 53 Met_{BDNF} carriers. Differences in the sample characteristics (Table 1) between *BDNF* Val/Met and Met/Met groups were examined with one-way ANOVA, but no significant differences were detected (p-values ≥ .297, data not shown).

COMT Val158Met showed genotyping success rate ≥95%, minor allele frequency of 0.41, and was in Hardy–Weinberg equilibrium (p-value > 0.05). In the analytic sample, there were 28 (17 %), 76 (47 %), and 57 (35 %) of GG (Val/Val), GA (Val/Met), AA (Met/Met) genotypes. For analyses, Val/Val and Val/Met groups were combined, resulting into subgroups of 104 Val_{COMT} carriers and 57 Met_{COMT} homozygotes. No differences in the sample characteristics (Table 1) between *COMT* Val/Val and Val/Met groups were detected (p-values ≥ .098, data not shown).

3.2. Sample Characteristics

Table 1 presents the age, wake and sleep measures and the general cognitive ability of the sample (N = 161, 90 female subjects / 56 %). No significant differences were found between either *BDNF* or *COMT* subgroups (p-values ≥ 0.130). Sex ratio did not differ between *BDNF* ($p_{\chi 2}$ = .423) nor *COMT* ($p_{\chi 2}$ = .478) subgroups.

Table 1. Sample characteristics, compared between the genotypic subgroups.

	ALL N = 161			*BDNF* (VH/MC) N = 108/53	*COMT* (MH/VC) N = 57/104
	Mean	SD	Range	p	p
Age	16.89	0.12	16.64 – 17.26	.50	.30
Sleep percentage %	57.81	8.26	23.63 – 76.57	.66	.99
Time awake total (hh:mm)	5:36	1:20	2:18 – 10:23	.94	.90
Before sleep onset	4:20	1:15	1:23 – 9:00	.97	.56
WASO	0:16	0:20	0:01 – 3:20	.39	.86

After awakening	1:01	0:36	0:20 – 3:23	.68	.12
TST (hh:mm)	7:37	1:08	3:09 – 10:45	.31	.96
N1	0.50	0:22	0:13 – 2:05	.55	.86
N2	3:08	0:41	1:00 – 5:24	.56	.75
N3	2:03	0:28	0:53 – 3:20	.66	.23
REM	1:36	0:30	0:16 – 2:50	.19	.28
Sleep efficiency %	92.72	6.82	58.55 – 98.86	.49	.70
Retention length (hh:mm)	13.23	1.12	9:50 – 17:23	.30	.85
FSIQ (raw score mean)	31.02	4.25	15.40 – 40.20	.27	.09

VH = Val homozygote. MC = Met carrier. MH = Met homozygote. VC = Val carrier. SD = standard deviation. p: p-value of the genotypic difference. WASO = wake after sleep onset. TST = Total sleep time. N1–3: Non-rapid eye movement sleep stages 1–3. REM = rapid eye movement sleep. Retention length = The time between picture encoding and retrieval. FSIQ = Full-scale intelligence quotient.

Our preliminary analyses on the distributions of the dependent and independent variables revealed two major outliers regarding Sleep% (-4.1 SD) and in recognition accuracy averaged over the picture categories (+3.7 SD). We excluded these participants from further analyses.

3.3. Initial analysis: recognition accuracy related to arousal and valence

Both arousal (high/low) and valence (positive/moderate/negative) associated with recognition accuracy ($F = 11.176$, $p = .001$ and $F = 15.366$, $p < .001$, respectively). Recognition accuracy was higher for high arousal relative to low arousal pictures (Bonferroni-corrected $p = .001$). Positively and negatively valenced pictures were recognized more accurately than those with moderate valence (Bonferroni-corrected $p = .002$ and $p < .001$, respectively). In addition, the interaction between arousal and valence was significant ($F = 12.593$, $p < .001$). Follow-up within-subject ANOVAs (six levels of picture category) revealed that the pictures of HA-NV were more accurately recognized than the pictures from any other category (Bonferroni-corrected p-values $\leq .027$). Also, recognition accuracy for LA-PV pictures was higher than for MV pictures (Bonferroni-corrected $p < .001$). The estimated marginal means of recognition accuracy values are displayed in Figure 2.

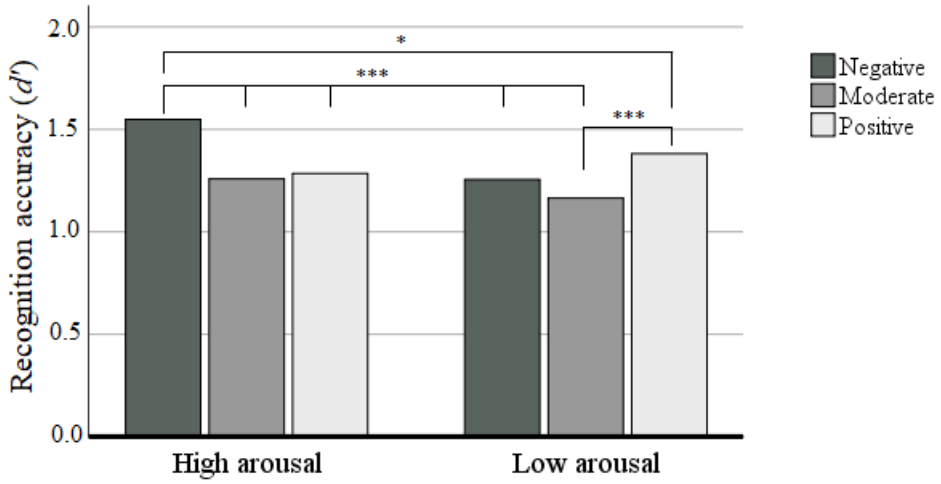

Figure 2. Recognition accuracy (*d'*) (estimated marginal means) in different picture categories. Highly arousing, negatively-valenced pictures had higher recognition accuracy than the pictures from any other category. Low-arousing positive pictures were better recognized than low-arousing moderate pictures. *** $p < .001$; * $p < .05$.

3.4. The association between sleep and wake and recognition accuracy

In the whole sample, we tested the impact of Sleep%, TWT and TST on recognition accuracy. No significant main effects on recognition accuracy were observed for Sleep% ($F = 3.447$, $p = .069$), TWA ($F = 2.092$, $p = .150$) or TST ($F = 0.194$, $p = .661$). For the F values of the main effects, see Table 2. The durations of sleep stages (N3, REM) or pre- and post-sleep wakefulness did not associate with recognition accuracy (p-values ≥ .265). Sleep/wake variables did not interact with picture arousal, valence or 'arousal x valence' (p-values ≥ .335).

3.5. The association between *BDNF* Val66Met and recognition accuracy

No main effect was found for the association between *BDNF* Val66Met and recognition accuracy ($F = 2.602$ $p = .109$), suggesting that there was not difference in recognition accuracy between the Val_{BDNF} homozygotes and Met_{BDNF} carriers. *BDNF* Val66Met did not interact with picture arousal ($F = 0.266$, $p = .607$), valence ($F = 2.597$, $p = .076$) nor with 'arousal x valence' ($F = 0.348$, $p = .706$).

Next, we examined if *BDNF* Val66Met interacted with sleep/wake variables on picture recognition accuracy. A significant interaction was found regarding Sleep% ($F = 8.754$, $p = 0.004$, $\eta^2 = .054$). The interaction '*BDNF* genotype x TWT' was significant when controlling for the main effect of TST ($F = 7.229$, $p = .008$, $\eta^2 = .045$). Instead, '*BDNF* genotype x TST' was not significant with TWT as a covariate ($F = 3.344$, $p = .069$). The significant interaction regarding TWT prompted us to control for the interaction instead of main effect only. Including 'genotype x

TWT' as well as 'genotype x TST' into the same model resulted in significant interaction regarding TWT ($F = 4.093$, $p = .045$, $\eta^2 = .026$) but not TST ($F = 0.308$, $p = .580$). For the F values of the interactions, see Table 2.

In order to examine the significant interactions, we ran follow-up regression analyses separately for Val_{BDNF} homozygotes and Met_{BDNF} carriers, the averaged recognition accuracy as the dependent variable. There was no multicollinearity problem (variance inflation factors, VIF, < 1.659). We found that the fractioned coefficient of determination (R^2) for Sleep% on recognition accuracy was 9.5 % in Val_{BDNF} homozygotes (significant positive association; $R^2 = 0.095$, $B = 2.204$, $t = 3.303$, $p = .001$; Met_{BDNF} carriers: $R^2 = 0.019$, $B = -0.735$, $t = -0.881$, $p = .383$). TWT explained 5.4 % on recognition accuracy in Val_{BDNF} homozygotes (Val_{BDNF} homozygotes: $R^2 = 0.054$, $B = -0.104$, $t = -2.428$, $p = .017$; Met_{BDNF} carriers: $R^2 = 0.011$, $B = 0.049$, $t = 0.741$, $p = .462$). No significant association was found regarding TST (Val_{BDNF} homozygotes: $B = 0.043$, $t = 0.759$, $p = .499$; Met_{BDNF} carriers: $B = 0.004$, $t = 0.059$, $p = .953$). The regression slopes are shown in Figure 3. Dividing to pre- and post-sleep wake revealed that wakefulness before sleep onset associated significantly with recognition accuracy ($B = -0.101$, $t = -2.090$, $p = .039$) in Val_{BDNF} homozygotes, whereas wakefulness after awakening did not ($B = -0.102$, $t = -1.252$, $p = .214$).

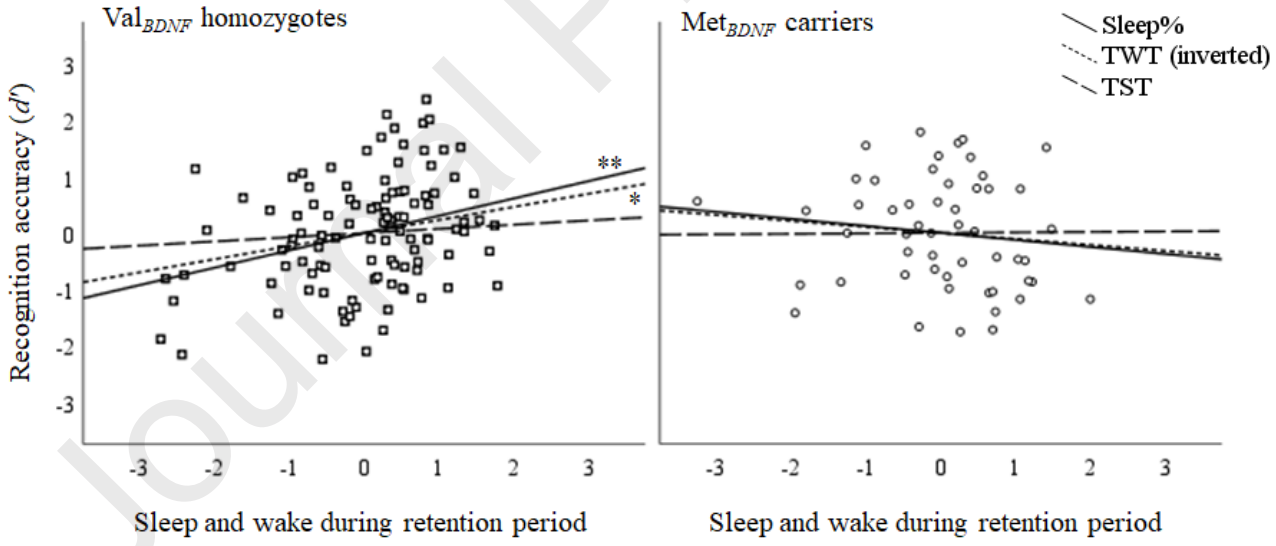

Figure 3. The associations between sleep/wake and recognition accuracy. Scatterplots in standardized residuals illustrate the regression slopes of Sleep percentage (Sleep%; continuous line; adhering to the markers), total wake time (TWT; dotted line; inverted for comparison) and total sleep time (TST; dashed line) on recognition accuracy, separately for Val_{BDNF} homozygotes and Met_{BDNF} carriers. In Val_{BDNF} homozygotes, Sleep% and TWT explained 9.5 % ($p = .001$) and 5.4 % ($p = .017$), respectively, of the variation of recognition accuracy. In Met_{BDNF} carriers, none of the sleep/wake regression slopes was significant. ** $p < .01$; *$p < .05$.

To assess the impact of potential confounders, we investigated how retention period length, general cognitive ability, deviation from habitual bedtime and last night's sleep affected the interaction between *BDNF* Val66Met and Sleep% on recognition accuracy. Additional adjustments for the confounders did not change the significant results. Please see Supplement 1.

3.6. The association between *COMT* Val158Met and recognition accuracy

COMT Val158Met was not associated with recognition accuracy (F = 0.425, p = .515), but a significant interaction between *COMT* Val158Met and picture arousal level was found (F = 6.706, p = .011, $\eta^2 = 0.041$). Within-subjects ANOVA, separately for Met_{COMT} homozygotes and Val_{COMT} carriers, showed higher recognition accuracy for pictures of high, than low, arousal level in Met_{COMT} homozygotes (F = 13.582, p < .001), whereas arousal level did not affect recognition accuracy in Val_{COMT} carriers (F = 1.852, p = .177) (Figure S1). Valence, or 'valence x arousal' did not interact with *COMT* Val158Met on recognition accuracy (F = 2.851, p = .063 and F = 1.543, p = .217, respectively).

Testing the interactions between *COMT* Val158Met and Sleep%, TWT and TST did not reveal significant interactions on recognition accuracy (Sleep%: F = 0.299, p = .586; TWT: F = 0.015, p = .903; TST: F = 2.241, p = .136) (Table 2).

Table 2. The impact of Sleep%, TWT and TST on recognition accuracy in the whole sample, and their interaction with *BDNF* Val66Met and *COMT* Val158Met.

	All		*BDNF*		*COMT*	
	F	p	F	p	F	p
Sleep%	3.447	.069	8.754**	.004	0.299	.586
TWT	2.092	.150	4.093*	.045	0.015	.904
TST	0.194	.661	0.308	.580	2.241	.136

BDNF/*COMT* = The interaction between *BDNF*/*COMT* genotype and sleep/wake variables on recognition accuracy (*d'*). Sleep% = The percentage of sleep during retention period. TWT = The total time spent awake during the retention period. TST = The total time spent asleep during the retention period. * = $p \leq .05$; ** = $p \leq .01$.

1. DISCUSSION

In a sizable cohort of 161 adolescents adhering to their typical sleep schedules, we examined how the temporal distribution of sleep and wake between memory encoding and retrieval affected overnight picture recognition accuracy. While *BDNF* Val66Met did not associate with recognition accuracy, we found it to moderate the association between sleep percentage during the

retention period and recognition accuracy. Specifically, an increased time spent awake after encoding deteriorated recognition accuracy in Val_{BDNF} homozygotes only. *COMT* Val158Met did not affect memory outcome.

The study contributed to the understanding of the complex interplay between *BDNF* Val66Met, sleep and memory. While no genotypic difference in recognition accuracy *per se* was found, higher sleep percentage between encoding and retrieval improved the accuracy in Val_{BDNF} homozygotes but not in Met_{BDNF} carriers. The found association was not explained by general cognitive ability or factors possibly affecting sleep pressure or percentage on the test night, as indicated by the analyses of potential confounders. Noteworthy, the association between sleep percentage and recognition accuracy appeared to be drawn by the performance impairment along prolonged wake, rather than any benefit by the time spent asleep.

Potential mechanisms can only be speculated at this stage. One explanation involves the accumulation of sleep pressure, which has been suggested to be greater in Val_{BDNF} homozygotes relative to Met_{BDNF} carriers, reflected in higher slow-wave activity (Bachmann et al., 2012). More time spent awake after encoding increases sleep pressure which in turn potentially impairs LTP maintenance (Prince & Abel, 2013) and reduces signal-to-noise ratios of memories (Tononi & Cirelli, 2014). During the subsequent sleep, global downscaling of synaptic weights (Tononi & Cirelli, 2014) could erase memories with weakened relative strength. Tentative support came from the finding that accumulated wake before sleep onset related with poorer performance in Val_{BDNF} homozygotes. No similar association was observed regarding the wake after awakening, although comparison without a controlled setting is not feasible.

Interestingly, wake was more influential than sleep for picture recognition in Val_{BDNF} homozygotes. Previous studies on *BDNF* Val66Met and sleep EEG markers of memory consolidation provide basis to expect that specifically sleep would appear significant. For example, memory outcome in Val_{BDNF} homozygotes is related to slow oscillation power (Mascetti et al., 2013) and fast sleep spindles (Halonen et al., 2019). However, it should be bore in mind that the sleep measures of interest in this study (i.e. the *durations* of sleep, N3 and REM sleep) do not readily capture possible sleep-driven consolidation mechanisms. Additionally, we cannot rule out if these mechanisms were affected by the duration of pre-sleep wake. Further experimental studies with control conditions on sleep pressure, *BDNF* Val66Met and learning are warranted.

As mentioned, the overall recognition accuracy was not affected by *BDNF* Val66Met, the result equal to the previous report within the same cohort (Halonen et al., 2019). The literature

on the subject is controversial. Better overnight memory performance in Val_{BDNF} homozygotes relative to Met_{BDNF} carriers have been reported regarding positive words (Cathomas et al., 2010) and neutral faces (Mascetti et al., 2013). However, our result converges with an earlier study deploying pictures of varying emotionality (Harrington et al., 2019), where a Met_{BDNF}-only 'emotional enhancement' in post-sleep recollection. This implies that including affective material among the memorized items attenuates any possible memory advantage of Val_{BDNF} homozygotes.

This is the first study to examine *COMT* Val158Met in overnight learning. We did not find any genotypic main effect, largely conforming to previous observations from non-sleep studies on recognition memory (Bertolino et al., 2006; de Frias et al., 2004; Krach et al., 2010). Additionally, our study contributes to the existing research by showing that Val158Met does not interact with modest variation of sleep/wake on picture recognition memory. Previous studies that have investigated executive function as the outcome measure indicate detriments after total (Satterfield et al., 2018), but not partial (Goel et al., 2011), sleep deprivation in the carriers of Val_{COMT} allele. Our study did not include induced sleep deprivation, which would likely elicit more robust effects.

Emotion associated with memory performance in the whole sample. Merging rather consistently with previous research (Atienza & Cantero, 2008; Baran et al., 2012; Bennion, Mickley Steinmetz, Kensinger, & Payne, 2013; Harrington, Nedberge, & Durrant, 2018; Hu et al., 2006; B. J. Jones, Schultz, Adams, Baran, & Spencer, 2016; Morgenthaler et al., 2014; Payne, Chambers, et al., 2012), recognition accuracy was higher for exciting over calm pictures, and for negative and positive over moderately valenced pictures. Essentially, the interaction of arousal and valence was seen as increased accuracy in highly arousing negative pictures, in accordance to numerous studies (Baran et al., 2012; Bennion et al., 2013; B. J. Jones et al., 2016; Payne & Kensinger, 2011), but also in calm positive pictures. Behavioral studies on sleep and memory performance have thus far left the latter combination largely unexamined. However, calm positive pictures evoke similar amygdala connectivity than aversive content (Mickley Steinmetz et al., 2010), perchance mirrored by our pattern of recognition accuracy.

Considering genotype, we did not find picture category to interact with *BDNF* Val66Met. While this contrasts an earlier study (Harrington et al., 2019), some methodological differences are obvious: the categorization of pictures between these studies was different, and we avoided using overly aversive pictures due to the adolescent sample. Additionally, we did not separate between 'familiarity' and 'recollection' responses, which possibly attenuated genotypic differences regarding hippocampal contribution (Yonelinas, Aly, Wang, & Koen, 2010). *COMT*

Val158Met, on the other hand, interacted with arousal to improve accuracy for high arousal (over calm) pictures in Met_{COMT} homozygotes. This diverges from previous behavioral outcomes on adult males, where memory (benefit) for high arousal items is impaired in Met_{COMT} homozygotes (Gibbs et al., 2014; Naudts et al., 2012). Age may partially explain the discrepancy between these findings. During adolescence, Met_{COMT} allele associates dose-dependently with prefrontal dopamine levels (Wahlstrom, White, & Luciana, 2010), higher cortical thickness (Raznahan et al., 2011) and default mode network connectivity (Meyer et al., 2016), but these associations are inverted by adulthood. We assume that this maturational shift could moderate the role of limbic response in mnemonic tasks.

Against our expectations, we did not find sleep percentage during the retention period to affect recognition accuracy in the whole sample, which appears to contradict previous studies reporting detrimental effect of prolonged post-encoding wake on picture recognition (Payne, Tucker, et al., 2012; Ullrich Wagner et al., 2007). However, the performance in our simple recognition task may have been less susceptible for reduced sleep, compared to a more complex task (Kopasz et al., 2010). Also, the wake-to-sleep ratio in our sample approximated the habitual sleep patterns of the adolescents, and did not include total sleep deprivation. Given that even short duration of sleep may benefit learning (Lahl et al., 2008; Tucker & Fishbein, 2009), such benefits may have been achieved across our sample.

1.1. Strengths and limitations

Our key strength was the natural in-home setting with a wide, non-manipulated variation in wakefulness and sleep. As we did not impose sleep schedules, we preserved natural homeostatic process of the participants, thus obtaining high ecological validity. Also, this study adds to the unfoundedly scarce data of how plasticity-related variants of *BDNF* and *COMT* genes affect overnight learning during adolescence. The moderation by Val66Met, found within the limits of typical variation in wake-to-sleep dynamics over one night, highlights the sensitivity of this phenomenon. However, further studies are needed to clarify the generalizability of these results to adults.

There are also limitations to our study. The study is correlational, precluding any causality. This is emphasized by including only one post-sleep retrieval test without pre-sleep assessment. Hence, we were unable to examine the change of recognition performance over wake or sleep. Despite exploring the influence of several potential confounders, there might be additional factors that remained unstudied. Second, the lack of a waking control group disabled us from

inspecting if total sleep deprivation would inflict qualitatively distinct implications on learning. It is also possible that sleep improves memory retention during the subsequent wake (Talamini et al., 2008). Third, in the retrieval phase we did not make distinction between 'recollection' and 'familiarity' answers. There is grounds to assume that this would have yielded more precise observations regarding how the degree of emotion interacts with both Val66Met (Harrington et al., 2019; R. Jones, Craig, & Bhattacharya, 2019) and Val158Met (Naudts et al., 2012) on recognition accuracy. Finally, the number of pictures in the different emotion categories was low. Besides applying Bonferroni corrections on the perceived differences, we carefully inspected the distribution and variance metrics of the derived recognition parameters.

1.2. Conclusion

The ratio between sleep and wake within the span of one night associates differently with overnight recognition accuracy depending on the *BDNF*, but not *COMT*, genotype. High proportion of sleep during the retention period emerges beneficial Val_{BDNF} homozygotes only. This relation appears to stem from detrimental influence of increased wake, rather than from the benefit of sleep. Genotypic differences in sleep pressure accumulation may underlie this phenomenon. As a consequence of our results, the proximity of sleep relative to memory task can affect performance, which should be considered in future studies.

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DECLARATIONS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Risto Halonen: Conceptualization, Methodology, Writing – Original draft preparation, Formal analysis, Investigation, Visualization.

Liisa Kuula: Conceptualization, Writing – Review & Editing.

Jari Lahti: Data Curation, Writing – Review & Editing.

Katri Räikkönen: Data Curation, Writing – Review & Editing.

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HIGHLIGHTS

- We examined overnight picture recognition accuracy (*d'*) in adolescents
- No main effects of *BDNF* Val66Met or *COMT* Val158Met on recognition accuracy
- Val66Met moderated the association of sleep percentage and recognition accuracy
- Negative association between wake duration and *d'* in Val_{BDNF} homozygotes only

Risto Halonen: Conceptualization, Methodology, Writing – Original draft preparation, Formal analysis, Investigation, Visualization.

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