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Fast sleep spindle density is associated with rs4680 (Val108/158Met) genotype of catechol-*O*-methyltransferase (*COMT*) FREE

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Abstract

Study Objectives

Sleep spindles are a hallmark of NREM stage 2 sleep. Fast sleep spindles correlate with cognitive functioning and are reduced in schizophrenia. Although spindles are highly genetically determined, distinct genetic mechanisms influencing sleep spindle activity have not been identified so far. Spindles are generated within a thalamocortical network. Dopaminergic neurotransmission modulates activity within this network and importantly depends on activity of catechol-O-methyltransferase (COMT). We aimed at testing whether the common functional rs4680 (Val108/158Met) polymorphism of *COMT* modulates fast spindle activity in healthy participants.

Methods

In 150 healthy participants (93 women, 57 men; mean age 30.9 ± 11.6 years) sleep spindle density was analyzed during the second of two nights of polysomnography. We investigated the effect of the *COMT* Val108/158Met genotype on fast spindle density in whole-night NREM sleep stages N2 and N3.

Results

As predicted, higher Val allele dose correlates with reduced fast spindle density. Additional exploratory analysis of the effect of *COMT* genotype revealed that slow spindle density in heterozygote participants was lower than that of both homozygote groups. Morphological characteristics of fast and slow spindles did not show significant differences between genotypes. *COMT* genotype had also no significant effect on measures of general sleep quality.

Conclusions

This is the first report of a distinct gene effect on sleep spindle density in humans. As variation in the *COMT* Val108/158Met polymorphism is associated with differential expression of fast spindles in healthy participants, genetically determined dopaminergic neurotransmission may modulate spindle oscillations during NREM sleep.

Clinical Trial registration

DRKS00008902

sleep spindles, sleep/wake cognition, sleep/wake mechanisms, gene polymorphisms, biomarkers, genetics, catechol-o-methyltransferase, dopamine, schizophrenia

Statement of Significance

This study provides the first report of a specific genetic marker contributing to the expression of sleep spindles in healthy humans. The association of the common functional Val108/158Met genotype of catechol-O-methyltransferase (*COMT*) with fast spindle activity links specific sleep processes relevant for cognition to genetically determined variance in dopamine transmission. Elucidating the genetic background of sleep spindles fosters the characterization of the neurobiological processes underlying spindle activity, its modulation, and its functional correlates. As fast spindles are reduced in schizophrenia and the Val/Val genotype of *COMT* is implicated in genetic risk constellations for schizophrenia, this finding also contributes to the understanding of pathomechanisms in neuropsychiatric disorders. Given the high heritability of sleep spindles, genome-wide association studies will be promising.

Introduction

Sleep spindles are brief bursts of 12–15 Hz oscillatory electroencephalographic (EEG) activity occurring in non-rapid eye movement (NREM) sleep and are a defining feature of stage 2 sleep [1, 2]. Studies investigating the heritability of sleep spindle activity point to a strong genetic background [3–5]. Furthermore, studies of the spectral composition of the human sleep EEG revealed trait-like individual characteristics [5, 6]. Indeed, the heritability of the EEG frequency band containing sleep spindle activity in non-REM sleep has been estimated up to 96% [3]. However, the genetic variants which contribute to the heritability of human sleep microarchitecture remain largely unknown.

The neuroanatomical substrate underlying sleep spindle generation is the thalamocortical network. Spindle rhythms are generated in the reticular nucleus of the thalamus, which sends gamma-amino-butyric acidergic afferents to the thalamic relay nuclei [7]. Spindles are then expressed in a network of reciprocal glutamatergic thalamocortical connections [8]. There is evidence that neocortical mechanisms may trigger spindle expression [9, 10]. A recent study using bipolar depth recordings in humans revealed that the neocortex controls thalamic spindling by inducing downstates in the thalamus triggering the generation of spindles which are then projected back to the cortex [11]. Two types of sleep spindles can be distinguished based on their frequency (12–15 Hz fast spindles, 9–12 Hz slow spindles), their topographic distribution, and the recruitment of partially segregated cortical networks [1, 12, 13]. Recent evidence suggests that both types may also be differentially generated or modulated [14, 15].

Sleep spindles play a role in the stabilization of sleep, as they protect the cortex from incoming sensory stimuli [16]. In addition, they have been shown to correlate positively with cognitive abilities [17–21], neuroplasticity [22], and sleep-dependent memory consolidation [23]. Most of these studies focused on fast spindles. Further, a marked fast sleep spindle deficit has repeatedly been reported in schizophrenia [24], reviewed in the study by Gardner et al. 25, as well as in healthy first-degree relatives of patients with schizophrenia [26, 27] and has been associated with deficient sleep-dependent consolidation of procedural and declarative memory in schizophrenia [28, 29] and impaired cognitive functioning in first-degree relatives [26]. Slow spindles seem to be spared from the spindle deficit observed in schizophrenia and first-degree relatives [26]. Whether fast and slow spindles are involved in different aspects of brain function is still unknown.

Dopamine neurotransmission is of central importance for cognitive processes in healthy participants [30] as well as in schizophrenia [31–34]. Further, dopamine has a marked impact on sleep regulation [35]. For example, manipulating dopamine levels in mice enhances or decreases NREM and rapid eye movement sleep [35, 36]. Dopaminergic neurotransmission also modulates activity within the thalamocortical network underlying sleep spindle activity [37]. Thus, variation in dopaminergic tone in healthy participants and in schizophrenia may affect spindle activity.

Cortical dopamine levels importantly depend on the activity of the dopamine degrading enzyme catechol-O-methyltransferase (COMT), which by methylation converts dopamine to inactive 3-methoxytyramine [38]. The common functional Val108/158Met polymorphism of COMT influences the activity of COMT and thus the availability of dopamine in the prefrontal cortex with the Met allele being associated with less active COMT and thus higher cortical dopamine levels [39, 40].

In view of the crucial role of COMT in the metabolism of cortical dopamine and the established role of dopamine in the regulation of sleep and arousal [35, 36], it was suggested that its polymorphism Val108/158Met impacts on sleep-wake regulation in healthy participants [41] and in schizophrenia [42]. Recent studies of sleep and sleep-wake rhythm reported *COMT* genotype-dependent differences in rest-activity profiles [43], in the individual response to partial sleep deprivation [44] and in sleep continuity of children with attention-deficit hyperactivity disorder, with Val allele carriers having poorer sleep continuity than Met homozygotes [45]. Interestingly, the Val108/158Met polymorphism of *COMT* has been found to influence the power spectrum of NREM sleep EEG activity within the upper alpha range partly overlapping with the spindle frequency band, with the Met/Met genotype being associated with higher alpha power than the Val/Val genotype [46].

Furthermore, the *COMT* Val108/158Met polymorphism strongly affects cognitive functioning related to the prefrontal cortex [30], and the *COMT* Val/Val genotype is implicated in genetic risk constellations for schizophrenia [31, 34].

The present study investigated whether the common Val108/158Met polymorphism of *COMT* modulates sleep spindle activity in healthy participants and, thus, links specific sleep processes relevant for cognition to dopamine transmission. We hypothesized that the presence of more Met alleles would predict higher fast spindle density, i.e. the Val/Val risk genotype for schizophrenia would be associated with reduced fast spindle density. We also carried out additional exploratory analyses looking into slow spindle density and morphological characteristics in both spindle types.

Methods

Procedures

The study was approved by the ethics committee of the Medical Faculty Mannheim, University of Heidelberg (2011-315N-MA), conformed to the Declaration of Helsinki [47] and was registered at German Clinical Trials Register (DRKS00008902). All participants provided their informed written consent before the study.

Participants underwent two consecutive nights of polysomnography (PSG) in the sleep laboratory of the Central Institute of Mental Health. Bedtimes were standardized from 11:00 am to 06:30 am. The first night was considered an adaptation night and was used for exclusion of previously undiagnosed sleep disorders. The data from the second night were included in the analysis. Whole blood samples were drawn for genotyping after the first sleep laboratory night in the morning. Sleep staging and spindle analysis were performed without knowledge of the genotype.

Study participants

The healthy males and females were recruited at the Sleep laboratory of the Central Institute of Mental Health in Mannheim, Germany. Inclusion criteria comprised age between 18 and 60 years; absence of any prediagnosed sleep disorder; good self-reported sleep quality; absence of sleep curtailment before the study; absence of neurological or psychiatric disorders; no severe other health problems; no history of substance abuse; no current medication intake; and no circadian abnormalities including shift work, recent travels across time zones, or advanced or delayed sleep-wake rhythms. All participants received monetary compensation for their participation in the study.

The study sample consisted of 150 healthy participants of caucasian background, comprising 93 women and 57 men, with a mean age of 30.9 ± 11.6 years. Sex distribution did not differ significantly between COMT genotype groups (chi-square test; $\chi^2 = 3.3$; $p = .191$), but Val/Met heterozygotes were slightly older than both groups of homozygotes (analysis of variance [ANOVA] with Met allele dose as factor and age as dependent variable; $F = 3.7$; $p = .025$; Table 1).

Table 1.

Demographic Data and Sleep Parameters (Means ± SD)

	Val/Val (*n* = 39)	Val/Met (*n* = 72)	Met/Met (*n* = 39)	*F*(2,143), *p*
Demographics				
Age	28.9 ± 10.0	33.5 ± 12.6	28.0 ± 10.0	
Gender (M/F)	18/21	22/50	17/22	
Sleep parameters				
Sleep latency (minutes)	19.8 ± 17.3	19.7 ± 15.2	19.1 ± 15.5	0.2, .811
TST (minutes)	394.1 ± 38.3	386.8 ± 47.4	402.7 ± 28.3	1.7, .184
SPT (minutes)	430.9 ± 29.3	423.2 ± 39.4	429.7 ± 23.5	0.7, .504
Sleep efficiency (%)	86.3 ± 7.9	86.4 ± 8.9	89.4 ± 5.1	2.1, .132
WASO (minutes)	36.8 ± 30.5	36.3 ± 33.1	27.0 ± 18.7	1.3, .283
Stage 1 sleep (minutes)	39.4 ± 23.0	41.3 ± 22.1	40.8 ± 23.1	0.2, .844
Stage 1 sleep (%)	9.1 ± 5.1	9.8 ± 5.4	9.5 ± 5.3	0.2, .832
Stage 2 sleep (minutes)	220.9 ± 46.7	226.4 ± 44.1	220.4 ± 33.3	0.0, .961
Stage 2 sleep (%)	51.3 ± 10.6	53.5 ± 9.3	51.3 ± 7.4	0.0, .978
SWS (minutes)	59.9 ± 35.2	54.6 ± 45.8	72.3 ± 36.7	1.3, .265
SWS (%)	14.0 ± 8.2	13.1 ± 11.2	16.9 ± 8.9	1.1, .321
REM sleep (minutes)	73.6 ± 25.5	64.2 ± 21.5	68.9 ± 24.9	1.5, .234
REM sleep (%)	17.0 ± 5.8	15.0 ± 4.7	15.9 ± 5.4	1.4, .258
REM sleep latency (minutes)	98.9 ± 61.5	97.9 ± 59.3	90.2 ± 41.1	0.3, .774
REM density	18.3 ± 7.3	17.4 ± 7.2	18.0 ± 8.3	0.0, .960
Arousal-index (n/h TST)	7.6 ± 6.1	7.1 ± 4.2	6.6 ± 4.2	0.5, .599
PLM-index (n/h SPT)	2.4 ± 4.4	2.5 ± 3.9	2.3 ± 5.2	0.0, .957

TST = total sleep time; SPT = sleep period time; WASO = Wake after sleep onset; SWS = slow wave sleep; REM = rapid eye movement; PLMS = periodic limb movements; ANCOVA = controlling for age and sex.

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Genotyping

Genotyping was performed after the sleep recordings. DNA was extracted from whole blood, and rs4680 was genotyped using TaqMan assay-on-demand (ID C_25746809_50). Genotyping revealed 39 Val/Val homozygotes, 39 Met/Met homozygotes, and 72 heterozygotes. Distribution of genotypes was in Hardy-Weinberg equilibrium (p = .624, Pearson test; https://ihg.gsf.de/cgi-bin/hw/hwa2.pl?mytext=rs4680,39,72,39&submit=1; accessed January 11, 2018).

Polysomnographic sleep analysis

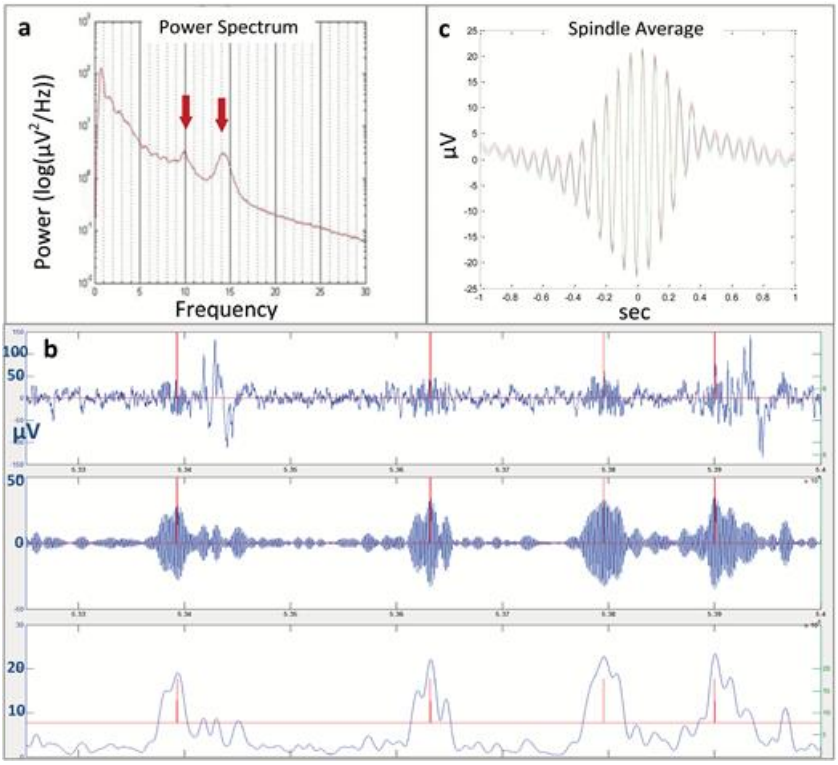
PSG was performed with a Schwarzer Comlab 32 polysomnograph (Schwarzer GmbH, Munich, Germany) using standard montage according to the criteria of the American Academy of Sleep Medicine [2]. This included electroencephalography (EEG) in six derivations (F4–A1, C4–A1, O2–A1, F3–A2, C3–A2, and O1–A2), bilateral electrooculography, chin electromyography, surface electromyography of both tibialis anterior muscles, electrocardiogram (ECG) recording, and recording of respiratory variables. Bed times of the sleep recordings were 11:00 pm (lights off) and 06:30 am

(lights on). Intake of caffeine or alcohol as well as smoking was not allowed in the evening prior or during the sleep recordings. The EEG sampling rate was 256 Hz. Sleep stage scoring and detection of arousals were performed visually according to American Academy of Sleep Medicine criteria [2].

Sleep spindle detection

Sleep spindles were identified during NREM sleep stages N2 and N3 using the C3-A2 derivation. Only 30-second sleep epochs free of artefacts and arousals were included. Detection of artefacts and arousals was performed by visual inspection. Discrete spindle events were detected automatically using a custom-made software tool (SpindleToolbox, version 3) using MATLAB R2009b (The MathWorks, Natick, MA) based on an algorithm adopted from previous studies [48, 49]. In brief, power spectra of each participant were calculated, enabling the user to visually determine the peak frequency of each individual's fast and slow spindle activity (Figure 1a). In accordance with literature findings applying this method [14], visual inspection of spindle peaks justified a distinction between fast and slow spindles at a cutoff frequency of 12 Hz. If no slow spindle peak was visually detectable in the power spectrum, the participant's data were excluded from the slow spindle analysis. The signal was bandpass filtered in the range ±1.5 Hz around the detected spindle peak, and the root mean square (RMS) was calculated for each 200-ms interval of the filtered signal. A spindle was detected if the RMS signal exceeded a threshold of 1.5 standard deviations of the filtered signal for the duration of 0.5 to 3 seconds (Figure 1b). Spindle density was defined as the number of spindles detected per 30-second epoch of all artefact-free NREM 2 and 3 sleep epochs and used as primary quantitative measure of spindle activity. Morphological characteristics of individual spindle events (amplitude, duration, and peak frequency) were additionally analyzed in an exploratory way. Spindle duration was calculated as the interval between the threshold crossing points of a spindle. Spindle amplitude was defined as the maximal spindle voltage following bandpass filtering.

Figure 1.



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Sleep spindle detection. (a) Power spectrum (whole night NREM sleep at electrode C3) with typical spindle peaks of 12–15 Hz (fast spindles) and 9–12 Hz (slow spindles) (red arrows); (b) (upper trace) raw EEG signal of 30-second duration during NREM sleep (here sleep stage N2), (middle trace) bandpass-filtered EEG signal, and *(lower trace)* RMS signal with four detected spindle events (red lines); (c) spindles and their SEMs of one individual averaged over the whole night's NREM sleep.

Statistical analysis

Sociodemographic parameters in genotype groups were analyzed using ANOVAs for age and chi-square test for gender distribution. Analysis of the effect of Met allele dose on fast spindle density was done by linear regression with Met allele dose as independent variable and spindle density as dependent variable. Age and sex as possible confounders were included in the regression analysis. Post hoc testing using two-way analyses of

covariance (ANCOVAs) controlling for age and sex further analyzed differences in fast spindle density between pairs of genotype groups (Met/Met vs. Val/Val, Met/Met vs. Val/Met, Val/Met vs. Val/Val). Because of the directed hypothesis regarding fast spindle density we used one-tailed tests. Values of fast spindle density were normally distributed (Shapiro-Wilk test 0.988; $p = .235$).

In exploratory analyses, we then also studied the impact of Met allele dose on slow spindle density as well as on morphological spindle parameters (spindle amplitude, length, and peak frequency) of both spindle types. In the absence of any specific hypothesis regarding these parameters, we used two-way ANCOVAs (two-tailed tests) with genotype and sex as independent variables and age as a covariate. Values of slow spindle density were nearly normally distributed (Shapiro-Wilk test 0.976; $p = .014$). We also analyzed the effect of genotype on polysomnographic sleep parameters (again using two-way ANCOVAs with genotype and sex as independent variables and age as covariate). The significance level for all analyses was set at $\alpha = 0.05$.

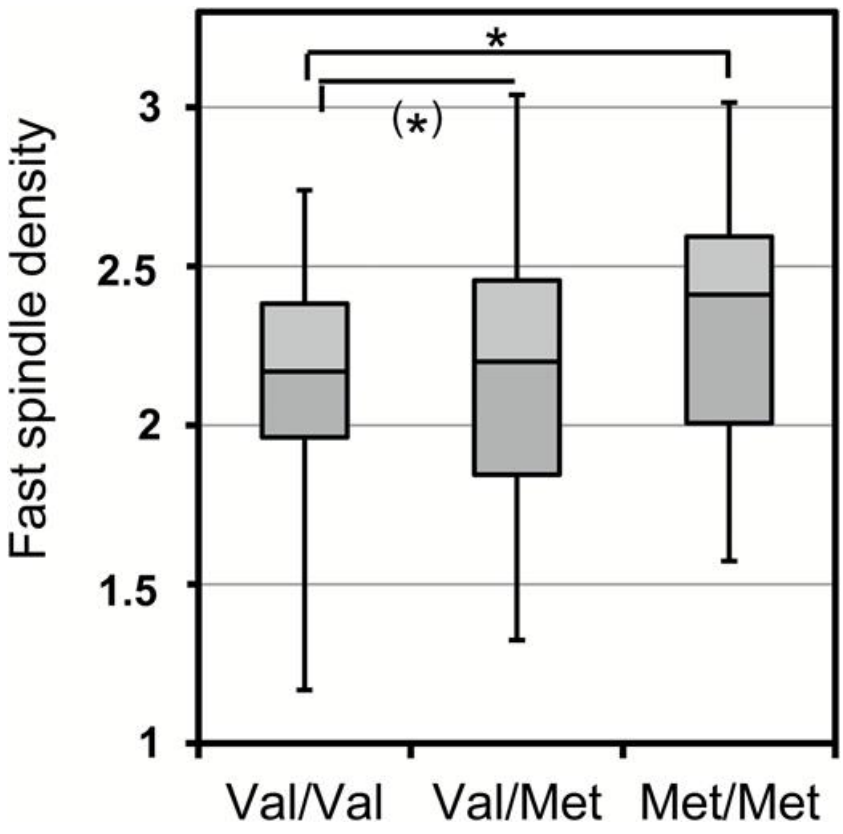
To obtain an a priori estimate of sample size, we computed the effect size of previously published data on COMT genetic variability on EEG spectral activity in the spindle frequency range [46]. The effect size was very high ($d = 3.124$) and, therefore, given that effect size even a sample size of $n = 10$ would have been sufficient for the comparison of two homozygous groups assuming an alpha level of 0.05 and a beta power of 0.8. Even for a medium effect size ($\eta^2 = 0.13$) and given our sample size of $n = 150$ and an alpha level of 0.05 (one-sided) the beta power would be 0.997.

Results

COMT genotype and fast spindle density

Spindle density significantly depended on the Met allele dose of the *COMT* Val108/158Met genotype in the sense that one or two Met alleles predicted higher spindle density (linear regression controlling for age and gender; $\beta = 0.160$; $t = 2.1$; $p = .037$; Figure 2). Post hoc tests showed that Val homozygotes had significantly lower spindle density than Met homozygotes (ANCOVA controlling for age and sex; $\eta^2 = 0.054$; $F(1, 73) = 4.2$; $p = .023$, one-tailed) and a marginally significant lower spindle density than carriers of the Val/Met genotype ($\eta^2 = 0.021$; $F(1, 106) = 2.3$; $p = .066$, one-tailed; Figure 2). The difference between Val/Met and Met/Met carriers was not significant ($\eta^2 = 0.005$; $F(1, 106) = 0.5$; $p = .231$).

Figure 2.



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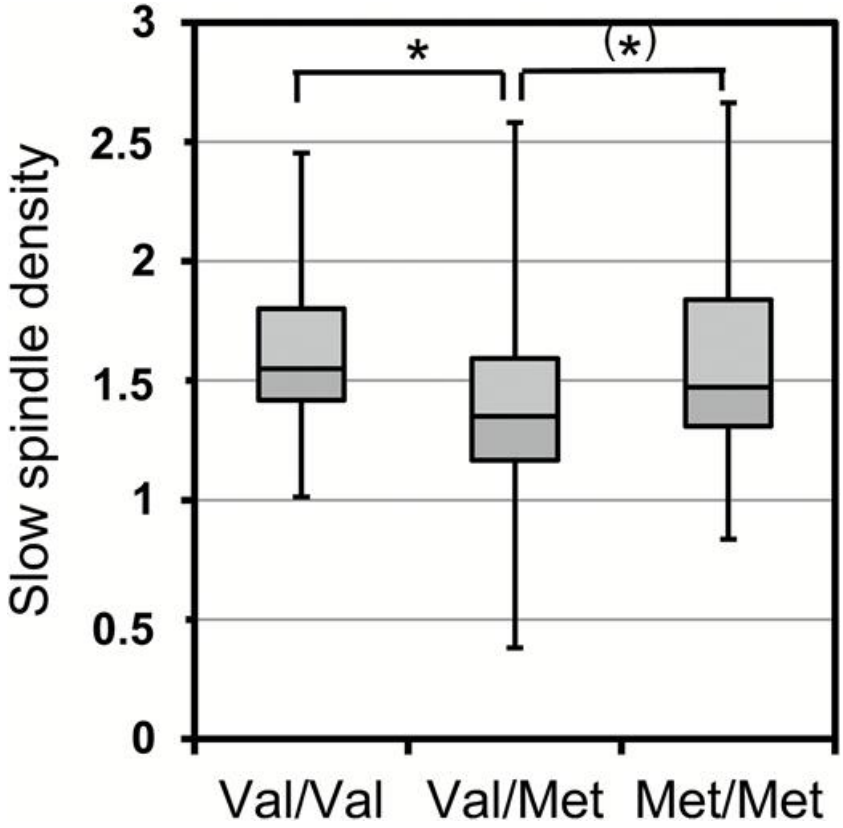
Fast spindle density (number of spindles/30-second sleep epoch) dependent on the COMT Val108/158Met genotype; upper and lower limit of the boxes represent the 75th and 25th quartile, the whiskers indicate the maximum and the minimum values. Linear regression

controlling for age and sex. Asterisks indicate significant differences in post hoc group comparisons (* $p < .05$; $^{(*)}p < .10$).

COMT genotype and slow spindle density

Exploratory analysis revealed a significant effect of the *COMT* Val108/158Met genotype on slow spindle density (two-way ANCOVA controlling for age and sex; $\eta^2 = 0.055$; $F(2, 133) = 3.9$; $p = .023$). Post hoc tests revealed that Val homozygotes had significantly higher slow spindle density than Val/Met heterozygotes ($\eta^2 = 0.070$; $F(1, 97) = 7.3$; $p = .008$; two-tailed) and Met homozygotes had marginally significant higher spindle density than Val/Met heterozygotes ($\eta^2 = 0.031$; $F(1, 100) = 3.2$; $p = .074$, two-tailed). The homozygote groups did not differ regarding slow spindle density ($\eta^2 = 0.003$; $F = 0.4$ (72, 67); $p = .529$; Figure 3).

Figure 3.



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Relation of slow spindle density (number of spindles/30-second sleep epoch) and the COMT Val108/158Met genotype; upper and lower limit of the boxes represent the 75th and 25th quartile, the whiskers indicate the maximum and the minimum values. Two-way ANCOVA with genotype and sex as independent variables, slow spindle density as dependent variable and covariate age. Asterisks indicate significant differences in post hoc group comparisons (* $p < .05$; $^{(*)}p < .10$).

Morphological spindle characteristics

Exploratory analysis of an effect of genotype on morphological characteristics of fast spindles did not show significant effects (two-way ANCOVAs controlling for age and sex). Fast spindle duration ($\eta^2 = 0.030$; $F(2, 143) = 2.2$; $p = .115$), fast spindle amplitude ($\eta^2 = 0.006$; $F(2, 143) = 0.4$; $p = .654$), and fast spindle peak frequency ($\eta^2 = 0.008$; $F(2, 143) = 0.6$; $p = .573$). However, the nonsignificant differences for amplitude and duration of fast spindles followed the same linear relationship as obtained for fast spindle density: more Met alleles implicate slightly higher spindle amplitude and spindle duration. Regarding slow spindles, genotype did not have any significant effect on morphological spindle characteristics (two-way ANCOVA controlling for age and sex): Slow spindle duration ($\eta^2 = 0.003$; $F(2, 133) = 0.2$; $p = 0.816$), slow spindle amplitude ($\eta^2 = 0.004$; $F(2, 133) = 0.3$; $p = .753$), and slow spindle peak frequency ($\eta^2 = 0.031$; $F(2, 133) = 2.1$; $p = .123$; Table 2).

Table 2.

Morphological Spindle Parameters (Means ± SD)

	Val/Val (*n* = 39)	Val/Met (*n* = 72)	Met/Met (*n* = 39)	*F*(2,143), *p*
Fast spindle characteristics				
Duration (seconds)	0.807 ± 0.047	0.818 ± 0.055	0.828 ± 0.054	2.2, .115
Amplitude (μv)	26.83 ± 6.30	27.48 ± 7.90	28.32 ± 6.62	0.4, .654
Peak frequency (Hz)	13.53 ± 0.68	13.46 ± 0.57	13.43 ± 0.45	0.6, .573
	Val/Val (*n* = 35)	Val/Met (*n* = 67)	Met/Met (*n* = 38)	*F*(2,133), *p*
Slow spindle characteristics				
Duration (seconds)	0.806 ± 0.048	0.793 ± 0.056	0.801 ± 0.049	0.2, .816
Amplitude (μv)	27.87 ± 5.56	28.89 ± 8.89	27.40 ± 5.64	0.3, .753
Peak frequency (Hz)	11.01 ± 0.79	10.67 ± 0.77	11.01 ± 0.77	2.1, .123

Two-way ANCOVAs with genotype and sex as independent variables and the covariate age.

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COMT genotype and polysomnographic sleep parameters

Polysomnographic sleep parameters are listed in Table 1. The three groups (Val/Val, Val/Met, and Met/Met) did not differ significantly regarding sleep architecture.

Discussion

In agreement with our hypothesis, we found that indeed the Met allele dose significantly predicts higher fast sleep spindle density in healthy participants. Further exploratory analyses of morphological spindle characteristics revealed no additional significant effects of genotype, even though small effects with more Met alleles associated with higher values for amplitude and duration were found. Our results demonstrate that genetic variation in COMT activity is associated with differential expression of fast spindles in healthy participants. Two small studies reported genetic effects in spectral NREM EEG power in the sigma frequency range containing the spindle frequency band, which is a proxy of spindle activity, one in patients with Costello syndrome arising from a mutation in the HRas Proto-Oncogene (*HRAS*) [50] and in a kindred of fatal familial insomnia (effect of the codon 129 polymorphism of the prion protein gene (*PRNP*) in unaffected participants) [51]. However, these studies did not determine individual spindles, and the Costello syndrome study may have been biased by the disturbed sleep patterns found in these patients. Thus, our study provides, to our knowledge, the first report of a genetic marker being associated with the expression of sleep spindles in healthy humans. Our data suggest that genetically determined variation in dopaminergic neurotransmission may modulate fast spindle generation during NREM sleep in healthy humans. COMT is abundantly expressed in the prefrontal cortex, whereas striatal dopamine levels are primarily regulated by dopamine transporter [52, 53]. Thus, the Val108/158Met *COMT* polymorphism may exert its impact on thalamocortical network activity underlying spindles primarily on cortical compared to thalamic level by modulating the availability of cortical dopamine levels. As we did not directly measure dopaminergic neurotransmission, this potential molecular pathway should be addressed in further studies. Although spindles arise primarily thalamically [7, 54], their generation clearly also involves the cortex [55]. Recently it has been shown that cortical downstates, i.e. cyclic periods of hyperpolarization during cortical slow wave activity in NREM sleep, are the primary event in a sequence of cortico-thalamo-cortical events implicated in the expression of spindles [11].

Most previous studies on sleep spindle activity focused on fast spindles. Aiming to investigate whether the effect of *COMT* genetic variability on spindle activity was specific to fast spindles, we performed an exploratory analysis of slow sleep spindle activity. Although slow spindle density also differed dependent on *COMT* genotype, the pattern was different from that observed in fast spindles. In contrast to the linear relationship between Met allele dose and spindle activity in fast spindles, slow spindle density was higher in both types of homozygotes as compared to heterozygotes. Thus, the observation of different patterns is in line with the assumption that fast and slow spindles may be differentially generated or modulated [14, 15].

Given the important function of sleep spindles in sleep-dependent memory consolidation [23] and our present evidence for the impact of the *COMT*

polymorphism on spindle expression, it would be interesting to investigate whether there are genetic effects on memory consolidation mediated by spindle activity.

A recent study in 4625 healthy participants genotyped for *COMT* Val108/158Met revealed no impact of genetic COMT variability on 7-day actigraphy assessment as an indirect measure for general sleep quality [56]. This is in accordance with our present data indicating no correlation of genetic COMT variability with polysomnographic measures of sleep.

Effect sizes of genetic *COMT* variability on spindle activity in our study were small to medium and thus lower than the effect size reported by Bodenmann and coworkers who did spectral EEG analyses [46]. The difference might be explained by the different methodological approach, i.e. the frequency band of the Bodenmann study might include much more than actual spindles. In addition, the small sample size might have contributed to an overestimation of the effect (selection bias). Bodenmann and coworkers reported an impact of genetic COMT variability on the spectral EEG composition in all sleep and wake stages [46]. As spindles, however, are specific to NREM sleep, at least partially different mechanisms probably underly the findings by Bodenmann *et al.* compared to our results.

As the *COMT* Val/Val genotype is implicated in genetic risk constellations for schizophrenia [31, 34], our present data suggest that genetically determined reduction in cortical dopaminergic modulation of thalamocortical network activity may contribute to the impairment of spindle activity, which is frequently found in schizophrenia and discussed as a potential endophenotype [26, 27].

Genetic variance in *COMT* may explain interindividual differences in spindle density and differential effects of dopaminergic interventions on spindle activity. In this context, it would be interesting to investigate whether tolcapone, a selective reversible COMT inhibitor, enhances spindle activity.

In conclusion, variation in the *COMT* Val108/158Met genotype is associated with differential expression of fast sleep spindles in healthy participants but not with polysomnographic sleep parameters, suggesting that genetically determined variation in dopaminergic neurotransmission may modulate spindle oscillations during NREM sleep. Furthermore, our finding corroborates the notion of reduced spindle activity as a genetically determined endophenotype of schizophrenia. Future studies should extend the investigation of the genetic background of spindle activity to more genes, preferably genome-wide association studies. Elucidating the genetic background of sleep spindle activity may (1) help to understand the neurobiological processes underlying spindle activity, (2) shed light on possible pathomechanisms underlying neuropsychiatric disorders associated with deficient spindle activity such as schizophrenia, (3) help to understand potential interindividual heterogeneity in pharmacological effects on spindle activity, and (4) promote the discovery of new avenues for pharmacological modulation of spindle activity, aiming at the improvement of cognitive deficits in schizophrenia.

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Notes

Conflict of interest statement. None declared.

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