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CHAPTER 4

Genetic determination of sleep EEG profiles in healthy humans

Hans-Peter Landolt[†,‡,*]

[†] *Institute of Pharmacology & Toxicology, University of Zürich, Zürich, Switzerland*
[‡] *Zürich Center for Integrative Human Physiology (ZIHP), University of Zürich, Zürich, Switzerland*

Abstract: The contribution of slow brain oscillations including delta, theta, alpha, and sigma frequencies (0.5–16 Hz) to the sleep electroencephalography (EEG) is finely regulated by circadian and homeostatic influences, and reflects functional aspects of wakefulness and sleep. Accumulating evidence demonstrates that individual sleep EEG patterns in non-rapid-eye-movement (NREM) sleep and rapid-eye-movement (REM) sleep are heritable traits. More specifically, multiple recordings in the same individuals, as well as studies in monozygotic and dizygotic twins suggest that a very high percentage of the robust interindividual variation and the high intraindividual stability of sleep EEG profiles can be explained by genetic factors (>90% in distinct frequency bands). Still little is known about which genes contribute to different sleep EEG phenotypes in healthy humans. The genetic variations that have been identified to date include functional polymorphisms of the clock gene *PER3* and of genes contributing to signal transduction pathways involving adenosine (*ADA*, *ADORA2A*), brain-derived neurotrophic factor (*BDNF*), dopamine (*COMT*), and prion protein (*PRNP*). Some of these polymorphisms profoundly modulate sleep EEG profiles; their effects are reviewed here. It is concluded that the search for genetic contributions to slow sleep EEG oscillations constitutes a promising avenue to identify molecular mechanisms underlying sleep–wake regulation in humans.

Keywords: trait; heritability; twins; PERIOD3 (PER3); adenosine deaminase; adenosine A2A receptor; brain-derived neurotrophic factor; catechol-*O*-methyltransferase; prion protein.

Introduction

The presence or absence of slow brain oscillations in the electroencephalography (EEG), together with information obtained from an electrooculogram (EOG) and an electromyogram (EMG),

*Corresponding author.
Tel.: +41-44-635-59-53; Fax: +41-44-635-57-07
E-mail: landolt@pharma.uzh.ch

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underlies the polygraphic discrimination among the three basic vigilance/sleep states wakefulness, non-rapid-eye-movement (NREM) sleep, and rapid-eye-movement (REM) sleep (Iber et al., 2007). A powerful tool to quantify amplitude and prevalence of EEG oscillations with distinct frequencies is power spectral analysis based on the fast-Fourier transform (FFT; Borbély et al., 1981). This method faithfully reveals the EEG characteristics of wakefulness, NREM sleep, and REM sleep. Rested wakefulness with closed eyes is characterized in many individuals by regular alpha (~9–12 Hz) activity. Decreasing alpha activity and increasing prevalence of theta (~5–9 Hz) oscillations, together with slow eye movements, herald the transition into NREM sleep (stage N1). The EEG in more superficial sleep (stage N2) is characterized by phasic events representing sleep spindles (~12–16 Hz, sigma frequency range) and K-complexes. In deep slow-wave sleep (stage N3), high-amplitude, slow waves in the low delta frequency range (0.5–2 Hz) are most prevalent. The amplitude and prevalence of delta oscillations are highest shortly after sleep onset and decrease during sleep, in parallel with decreasing sleep depth. The decline of EEG delta activity during sleep is not monotonous but is interrupted by the periodic occurrence of REM sleep (stage R). This state is identified by low-amplitude EEG activity characterized by theta and higher frequency oscillations, rapid eye movements, and atonia in antigravity muscles.

Sleep–wake regulation

Salient features of nocturnal sleep in humans include a declining trend in EEG delta/theta activity, an increase in the frequency range of sleep spindles, and a decrease in the ratio between NREM sleep and REM sleep in the course of the night. These characteristics reflect the influence of three basic processes assumed to underlie physiological sleep–wake regulation (Borbély and Achermann, 2005): (1) a circadian process as the output of an oscillator with an endogenous period of roughly to 24 h (lat. "circadian" = ~1 day) that determines the daily phases of high and low propensity for sleep, REM sleep, and wakefulness; (2) a homeostatic process keeping track of "sleep propensity" or "sleep need," which accumulates during wakefulness and dissipates during sleep; and (3) an ultradian process underlying the cyclic occurrence of NREM and REM sleep across the sleep episode.

According to the two-process model of sleep regulation (Borbély, 1982), the interaction between the sleep–wake independent, circadian process C and the sleep–wake dependent, homeostatic process S regulates variations in sleep propensity, the alternation between waking and sleep episodes, NREM sleep structure and intensity, and the timing of REM sleep. Thus, sleep is an active process, which is finely and reliably regulated. Recovery sleep after sleep deprivation occurs with reduced latency, and is prolonged and more intense than baseline sleep. The duration of slow-wave sleep and initial low-frequency (delta/theta) activity rise as a function of time awake, while spindle frequency activity is typically reduced after sleep loss (Borbély and Achermann, 2005; Borbély et al., 1981).

Taken together, the EEG in NREM sleep undergoes highly predictable changes reflecting physiological sleep–wake regulation. Nevertheless, abundant evidence exists that also strong genetic influences contribute to major characteristics of sleep and the sleep EEG, as well as of the waking EEG.

Heritability of waking EEG

Classic twin studies have long suggested that additive genetic factors (referred to as heritability) clearly outweigh the environmental influences on the waking EEG. More specifically, EEG profiles show much higher resemblance between monozygotic twins than between dizygotic twins and

unrelated persons (Lennox et al., 1945; Vogel, 1958). Later studies revealed high test–retest correlations in spontaneous waking EEG activity and confirmed that genetic influences importantly contribute to the pronounced interindividual differences observed in the waking EEG (Stassen et al., 1987; van Beijsterveldt et al., 1996). Boomsma and coworkers estimated that delta (1.5–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–12.5 Hz), and beta (13.0–25.0 Hz) frequencies show heritabilities of 76%, 89%, 89%, and 86%, respectively (van Beijsterveldt et al., 1996). Similarly, the heritability of the peak frequency in the alpha range equals roughly 80% (van Beijsterveldt and van Baal, 2002). Bodenmann et al. (2009a) recently reported that the functional Val158Met polymorphism of the gene encoding catechol-*O*-methyltransferase (COMT) predicts a difference of 1.4 Hz in alpha peak frequency between homozygous Val and Met allele carriers of *COMT*.

Trait-like nature of sleep and sleep EEG characteristics

Sleep architecture

Not only the waking EEG but also self-reported and polysomnographically recorded sleep characteristics such as interindividual variation in diurnal preference, sleep duration, sleep structure, and the EEG in NREM sleep and REM sleep have all been shown to be under strong genetic control (Landolt and Dijk, 2010). Already the first sleep studies in monozygotic twins revealed almost complete concordance in the temporal sequence of sleep stages (Zung and Wilson, 1966). Later work demonstrated that, in particular, those sleep variables that most reliably reflect homeostatically regulated sleep propensity are under tight genetic control. Apart from total sleep time, they include the duration of NREM sleep stages, especially slow-wave sleep, and the density of rapid eye movements in REM sleep. Linkowski (1999) estimated that REM density shows heritability of 95%.

To quantify the stability, robustness, and magnitude of interindividual variation in sleep variables, Tucker et al. (2007) completed in 21 young adults 8 all-night polysomnographic recordings interspersed with three 36-h periods of extended wakefulness. They found that almost all sleep variables that define sleep structure exhibit stable and robust—that is, trait-like—interindividual differences characterized by intraclass correlation coefficients (ICC) of 36–89%. The ICC estimates the intraindividual stability of a variable across different conditions (e.g., baseline sleep vs. recovery sleep after prolonged wakefulness) and equals for slow-wave sleep 73%. This high value reflects substantial stability across equivalent nights (baseline and recovery nights) and substantial robustness against external influences such as sleep deprivation (Tucker et al., 2007). Not only for slow-wave sleep but also for stage 2 (N2) and REM sleep, the robust interindividual differences are considerably larger in magnitude than the effect of prolonged wakefulness.

The EEG in NREM sleep and REM sleep

Due to the prevalence of slow waves, the EEG in NREM sleep is characterized by highest power in the delta range and decreasing activity with increasing frequencies. Reflecting sleep spindles, a secondary prominent peak in the power spectrum is also present in the 11–16 Hz range. Even in a homogenous sample of young men adhering to stringently controlled sleep–wake patterns prior to laboratory sleep recordings (Bodenmann et al., 2009a), the EEG in NREM sleep shows pronounced interindividual variation (Fig. 1a). To investigate whether such differences are stable and reflect individual traits, interindividual variation and intraindividual stability in sleep and the sleep EEG characteristics were studied in eight male

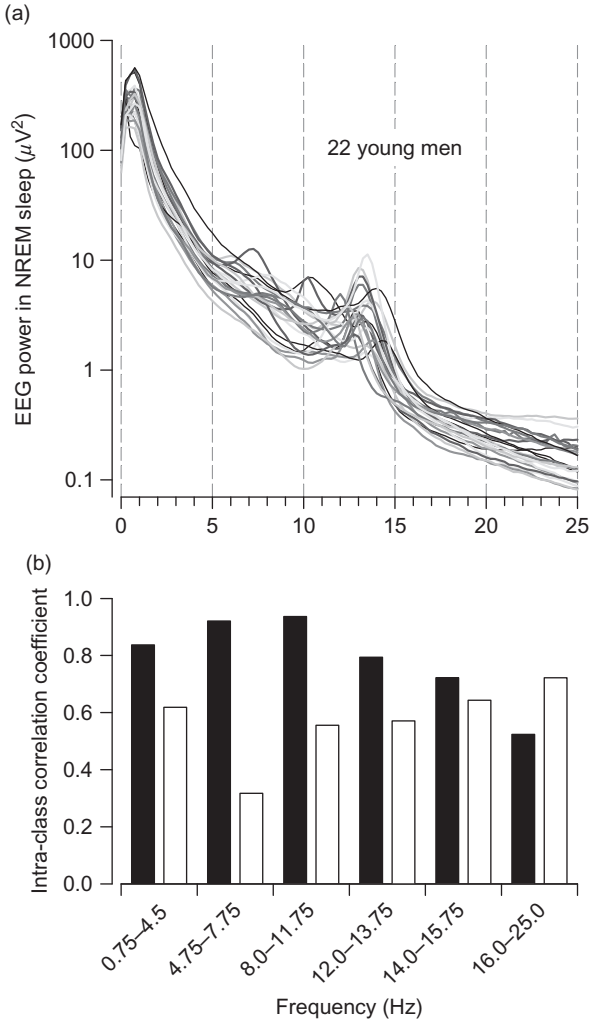

Fig. 1. Healthy adults have highly variable sleep EEG profiles that are genetically determined. (a) All-night EEG power spectra in NREM sleep (stages 1–4) in 22 male volunteers (23.4 ± 0.5 years) in baseline (mean of two baseline sleep recordings). Data from Bodenmann et al. (2009a). (b) Group differences in within-pair similarity as quantified by intraclass correlation coefficients (ICC) in distinct EEG frequency bands between monozygotic (black bars) and dizygotic (white bars) twin pairs. Thirty-five pairs of monozygotic twins (17 male pairs, 18 female pairs) and 14 pairs of dizygotic twins (7 male pairs, 7 female pairs). The ICC values were replotted from published data (Ambrosius et al., 2008).

volunteers across four separate recordings (two pairs of baseline nights 4 weeks apart; Buckelmüller et al., 2006). It was found that the EEG not only in NREM sleep but also in REM sleep differed largely among all individuals. The absolute power values and the shape of each subject's spectra, however, were impressively constant. Hierarchical cluster analyses of Euclidean distances based on feature vectors of EEG spectral values demonstrated that all nights of each individual segregated into the same single cluster (Buckelmüller et al., 2006). In other words, each participant of that study could be separated from the other members of the sample, only based on the EEG power spectra in NREM sleep and REM sleep. The distribution of similarity coefficients of EEG feature vectors confirmed high between-subject variation and high within-subject stability. This was true, even when the EEG in NREM sleep was separately analyzed for the first and second halves of the nights. Thus, within-subject stability of the NREM sleep EEG is independent of homeostatic sleep pressure. By contrast, within-subject similarity between the first and second halves of each night is as low as between-subject similarity. This finding reflects the systematic EEG changes in NREM sleep associated with the dissipation of sleep propensity in the course of the night.

Another research group used an alternative approach to examine the internight reliability in quantitative sleep EEG measures. First, Tan et al. (2000) reported remarkably high Pearson correlation coefficients ($r \approx 0.9$) in delta (0.3–3 Hz), sigma (12–15 Hz), and beta (15–23 Hz) frequencies in NREM sleep in 16 young adults (10 men, 6 women; age range: 19–26 years) who underwent 5 consecutive baseline night recordings. Because this high internight reliability was not dependent on EEG amplitude, which could reflect unspecific or extracerebral factors such as scull thickness, it was concluded that

electrical brain activity in NREM sleep is reliable. To corroborate this conclusion, the same authors conducted a second study of 4 nonconsecutive nights in 19 young (10 men, 9 women; age range: 20–25 years) and 19 elderly (8 men, 11 women; age range: 65–82 years) volunteers (Tan et al., 2001). They extended their analyses to 26 distinct frequency bands in NREM and REM sleep and found that the spectral values in both age groups differed significantly among individuals, yet were highly consistent within subjects. The internight reliability coefficients (r) equaled between 0.8 and 0.95 for all frequency bands. Notably, the sleep EEG spectra in the elderly appeared to be as highly reliable as those in the young adults.

Taken together, accumulating data strongly suggest that individual EEG profiles in NREM and REM sleep are genetically determined.

Heritability of sleep EEG

This notion is further supported by the recent publication of two twin studies of the sleep EEG. Ambrosius et al. (2008) quantified the EEG profiles in NREM sleep in 35 pairs of monozygotic twins (17 male pairs, 18 female pairs; age range: 17–43 years) and 14 pairs of dizygotic twins (7 male pairs, 7 female pairs; age range: 18–26 years). Genetic variance analysis identified substantial genetic influences on spectral power in 2–13 Hz oscillations. The ICC reflecting within-pair similarity was higher in monozygotic twins (ICC$\approx$0.8) than in dizygotic twins (ICC$\approx$0.6). The differences between monozygotic and dizygotic twins included the EEG frequency bands capturing delta waves (0.75–4.5 Hz) and sleep spindles (12–13.75 Hz), yet appeared most pronounced in theta and alpha (4.75–11.75 Hz) frequencies (Fig. 1b).

De Gennaro et al. (2008) tested the hypothesis that the EEG in NREM sleep provides an individual "fingerprint," which is genetically determined. They recorded baseline and recovery sleep after sleep deprivation in 40 healthy subjects (mean age: 24.6$\pm$2.4 years), consisting of 10 pairs of monozygotic (5 male pairs, 5 female pairs) and 10 pairs of dizygotic (5 male pairs, 5 female pairs) twins. They observed highest variability in the 8–16 Hz range and restricted their analyses to this frequency band. Group similarity as quantified by an ICC procedure was consistently higher in monozygotic twin pairs (ICC$=$0.934; 95% confidence intervals: 0.911–0.965) than in dizygotic twin pairs (ICC$=$0.459; 95% confidence intervals: 0.371–0.546). In fact, the similarity values in the monozygotic twins were comparable to the mean correlation coefficient ($r=0.958\pm0.026$) in this frequency range across six different experimental nights of single individuals (De Gennaro et al., 2005). The authors estimated that the heritability of the 8–16 Hz range in NREM sleep is as high as 95.9% and independent of sleep propensity (De Gennaro et al., 2008). This finding suggests that the sleep EEG qualifies as the most heritable trait known so far, matched only by heritabilities for brain architecture such as the distribution of gray matter in the cerebral cortex (Andretic et al., 2008). Considering the facts that functional brain connectivity and rhythmic brain oscillations are determined by common genetic factors (Posthuma et al., 2005) and that the frequency-specific, regional distribution of EEG power in NREM sleep is highly stable (De Gennaro et al., 2005; Finelli et al., 2001), it is possible that these two traits are interrelated.

In conclusion, strong evidence suggests that the sleep EEG is a highly heritable trait. Nevertheless, the underlying genetic determinants are largely unknown. Only a few studies are currently available in humans, which investigated the effects of known allelic variants of candidate genes on the sleep EEG. The findings demonstrate that single genes can profoundly modulate sleep and sleep EEG phenotypes. They are summarized in Table 1 and will be briefly discussed in the following paragraphs.

Table 1. Genes contributing to genotype-dependent differences in NREM and REM sleep EEG profiles in healthy adults

Gene	NCBI SNP-ID (major/minor alleles)	Amino acid substitution	NREM sleep		REM sleep		Frequency range
			Baseline	Recovery	Baseline	Recovery	
PER3	rs57875989	del(1011–1028 aa)	1.0–2.0				Delta
	del(3031–3084 nt)				7.0–10.0	7.75–8.0	Theta
ADA	rs73598374	Asp8Asn	0.25–5.5	1.0–1.25	2.0–2.25,		Delta
	(G/A)		0.5–1.25		3.5–4.75		
			6.75–10.0	7.75–10.0			Theta
ADORA2A	rs5751876	n/a	7.25–9.0		6.5–9.25		Theta
	(T/C)						
BDNF	rs6265	Val66Met	1.5–3.0	0–0.75,	8.25–8.75	0.5–0.75	Delta
	(G/A)			2.0–2.75			
			6.0–8.25	5.75–8.0			Theta
				12.5–13.0		16.25–16.5	Sigma
COMT	rs4680	Val158Met	10.25–12.0		10.5–14.0		Alpha
	(G/A)						
PRNP	rs1799990	Met129Val	0.5–4.0				Delta
	(A/G)		12.5–16.0				Sigma

Gene: National Center for Biotechnology Information (NCBI) gene symbol. NCBI SNP-ID number: single nucleotide polymorphism reference number. n/a: no amino acid substitution (silent polymorphism). Frequency bands within delta (<5 Hz), theta (~5–9 Hz), alpha (~9–12 Hz), and sigma (~12–16 Hz) ranges refer to significant differences between genotypes in baseline and/or recovery nights after sleep deprivation. Note the virtual independence from elevated sleep propensity of the genotype-dependent differences in NREM sleep.

Genetic polymorphisms affecting sleep and sleep EEG

Variable-number-tandem-repeat polymorphism of PERIOD3 gene

A 54-nucleotide sequence in the coding region of the clock gene *PER3* located on human chromosome 1 is either repeated in four or five units (SNP-ID number: rs57875989). The repeated segments are translated into numerous potential phosphorylation sites and may alter posttranslational modification and stability of PER3 protein (Dijk and Archer, 2010). Viola et al. (2007) observed that homozygous carriers of the long-repeat genotype (six men, four women; mean age: 25.2 years) fell asleep more rapidly and showed more slow-wave sleep than homozygous four-repeat individuals (eight men, six women; mean age: 24.8 years). In addition, in recovery sleep after sleep deprivation, REM sleep was reduced in $PER3^{5/5}$ individuals compared to $PER3^{4/4}$ homozygotes.

Not only sleep architecture but also sleep EEG profiles were affected by this polymorphism. More specifically, the carriers of the $PER3^{5/5}$ genotype had higher EEG activity in the delta range (1–2 Hz) in NREM sleep and in the theta/alpha range (7–10 Hz) in REM sleep when compared to the $PER3^{4/4}$ genotype (Viola et al., 2007). Moreover, the findings of another group suggested that the increase in slow-wave energy after acute sleep restriction was slightly elevated in adults carrying the $PER3^{5/5}$ ($n=14$) genotype when compared to $PER3^{4/5}$ ($n=63$) and $PER3^{4/4}$ ($n=52$) allele carriers (aged 22–45 years; Goel et al., 2009). Slow-wave energy refers to EEG power within 0.5–4.5 Hz accumulated over all epochs of stage 2–4 sleep in the first two NREM sleep episodes.

22G>A polymorphism of adenosine deaminase gene

Convergent pharmacologic and genetic evidence strongly suggests that the adenosine neuromodulator/neurotransmitter system is importantly involved in the homeostatic regulation of sleep (Landolt, 2008). The enzyme adenosine deaminase (ADA) catalyzes the irreversible degradation of adenosine to inosine and contributes to the regulation of extracellular adenosine levels. The human *ADA* gene is located on chromosome 20q13.11 and encodes two electrophoretic variants of ADA, referred to as ADA*1 and ADA*2 (SNP-ID number: rs73598374). The ADA*2 variant results from a guanine-to-adenine transition at nucleotide 22, which is translated into an asparagine-to-aspartic acid substitution at codon 8. The heterozygous ADA*1-2 (G/A) genotype shows reduced catalytic activity of ADA compared to homozygous individuals carrying the ADA*1 (G/G genotype) variant (Riksen et al., 2008). Rétey et al. (2005) found that healthy adults with the G/A genotype (five men, two women; mean age: 26.4 years) had roughly 30 min more slow-wave sleep in an 8-h baseline sleep episode than individually matched subjects with the G/G genotype (five men, two women; mean age: 26.1 years). This difference is similar in magnitude to the effect on recovery sleep of one night of total sleep deprivation. All other sleep variables were comparable in both genotypes.

The 22G>A polymorphism of *ADA* also affects the spectral composition of the sleep EEG. Thus, EEG activity was higher within the delta range in the G/A genotype compared to the G/G genotype in NREM sleep (0.25–5.5 Hz), as well as in REM sleep (2.0–2.25 and 3.5–4.75 Hz; Rétey et al., 2005). Consistent with these findings in humans, genetic studies in inbred mice revealed that a genomic region including *Ada* modifies the rate at which NREM sleep need accumulates during wakefulness (Franken et al., 2001). Moreover, local pharmacological inhibition of ADA in rats increased extracellular adenosine concentration and the duration of deep NREM sleep (Okada et al., 2003). Bachmann et al. (2011a) investigated whether G/A and G/G genotypes of *ADA* respond differently to prolonged wakefulness. Consistent with the previous data, these researchers found that slow-wave sleep and low-frequency delta (0.75–1.5 Hz) activity in NREM sleep were elevated in G/A compared to G/G genotype. The difference was invariably present in baseline and recovery nights. In addition, *ADA* genotype-dependent alterations in the EEG profile were not restricted to the low delta range in NREM sleep, but also included a pronounced increase in theta/alpha frequencies (~6–12 Hz) in NREM sleep, REM sleep, and wakefulness (Bachmann et al., 2011a).

1976T>C polymorphism of adenosine A_{2A} receptor gene

The cellular effects of adenosine are mediated via four different subtypes of G-protein-coupled adenosine receptors: A_1, A_{2A}, A_{2B}, and A_3 receptors. For the effects on sleep and the sleep EEG, however, the A_1 and A_{2A} receptors may be primarily important (Landolt, 2008). A common synonymous 1976T>C variation (SNP-ID number: rs5751876) on chromosome 22q11.2 is located in the coding region of the adenosine A_{2A} receptor (*ADORA2A*) gene. This polymorphism is linked to a 2592C>T_{ins} polymorphism in the 3′-UTR of *ADORA2A* and may modulate receptor protein expression (Alsene et al., 2003). Rétey and coworkers observed that the 1976T>C polymorphism not only contributed to individual sensitivity to the effects of caffeine on sleep (Rétey et al., 2007) but also affected EEG activity in all sleep/vigilance states. In a case–control study, spectral power in the ~7–10 Hz range was shown to be invariably higher in subjects with the C/C genotype than in subjects with the T/T genotype (Rétey et al., 2005). Because the C allele of *ADORA2A* is thought to facilitate A_{2A} receptor function when

compared to the T allele, these data may suggest that genetically increased A_{2A} receptor-mediated signal transduction enhances EEG theta/alpha activity in vigilance/sleep state-unspecific manner.

196G>A polymorphism of brain-derived neurotrophic factor gene

Another region in the mouse genome affecting the accumulation of sleep propensity during wakefulness includes the gene encoding the neurotrophic receptor, tyrosine kinase B (TrkB; Franken et al., 2001). This genetic locus explains almost 50% of the variance in the rebound in delta activity after sleep deprivation. It may, thus, contain a major gene contributing to sleep–wake regulation. TrkB is the high-affinity receptor for brain-derived neurotrophic factor (BDNF; Luikart and Parada, 2006), and recent findings in rats suggest that BDNF secretion is causally related to sleep homeostasis (Faraguna et al., 2008; Huber et al., 2007).

In humans, BDNF is expressed throughout the brain, particularly in prefrontal cortex and hippocampus (Pezawas et al., 2004). This neurotrophin exerts long-term effects on neuronal survival, migration, and dendritic/axonal growth. The *BDNF* gene is located on chromosome 11p13 and composed of five or more exons. One functional polymorphism of this gene occurs with high frequency in humans (SNP-ID number: rs6265). Specifically, a guanine-to-adenine transition at nucleotide 196 produces a valine-to-methionine amino acid substitution at codon 66 of the pro-BDNF sequence. *In vitro* studies suggest that the Met allele impacts activity-dependent secretion and intracellular trafficking of BDNF (Egan et al., 2003). Further, neuropsychological testing revealed that this polymorphism is typically associated with reduced performance on tasks, which are also impaired by sleep deprivation, including various types of memory, fine motor tasks, and executive functions (Egan et al., 2003; Pezawas et al., 2004).

To investigate whether the Val66Met polymorphism of *BDNF* affects the sleep EEG, 11 carriers of the variant allele (Val/Met genotype; 4 women, 7 men; 20–29 years) were prospectively matched on an individual basis with 11 Val/Val homozygotes (4 women, 7 men; 20–29 years). Sleep and sleep EEG were studied in baseline and recovery nights after 40-h prolonged wakefulness. In baseline and recovery conditions, slow-wave sleep was shorter in Val/Met than in Val/Val genotype (Bachmann et al., 2011b). Moreover, in both nights, EEG activity was lower in Met allele carriers than in Val/Val homozygotes, particularly in delta (baseline: 1.5–3 Hz; recovery: 0–0.75 and 2–2.75 Hz) and theta (baseline: 6–8.25 Hz; recovery: 5.75–8 Hz) frequencies in NREM sleep. In contrast to the previously discussed *ADA* and *ADORA2A* polymorphisms, the *BDNF* genotype-dependent differences in the theta range were NREM sleep specific and were not present in REM sleep and wakefulness. This finding indicates that genetic variation of adenosine and BDNF affect theta activity via different underlying mechanisms.

544G>A polymorphism of COMT *gene*

The gene encoding COMT is located on human chromosome 22q11.2, and contains a common functional 544G>A variation altering the amino acid sequence of COMT protein at codon 158 from Val to Met (SNP-ID number: rs4680). Individuals homozygous for the Val allele show higher COMT activity and lower dopaminergic signaling in prefrontal cortex than Met/Met homozygotes (Akil et al., 2003). Sleep variables and the sleep EEG response to sleep deprivation did not differ between male carriers of Val/Val and Met/Met genotypes (Bodenmann and Landolt, 2010). By contrast, the variation of the *COMT* gene was associated with consistently lower EEG activity in the upper alpha (11–13 Hz) range in NREM sleep, REM sleep, and wakefulness (Bodenmann et al., 2009a). The difference in NREM sleep

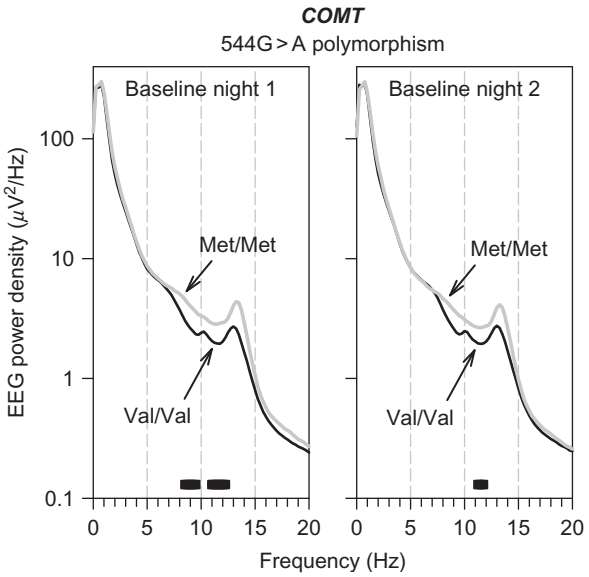

Fig. 2. The 544G>A (Val158Met) polymorphism of *COMT* modulates EEG alpha activity in NREM sleep (all-night power spectra of stages 1–4). Black bars at the bottom of the panels indicate frequency bins, which differed significantly between Val/Val ($n=10$, black lines) and Met/Met ($n=12$, gray lines) genotypes ($p<0.05$, unpaired, two-tailed t-tests). The two baseline nights were recorded 1 week apart. Data from Bodenmann et al. (2009a).

(Fig. 2) was present before and after sleep deprivation and persisted after administration of a moderate dose of the stimulant modafinil during prolonged wakefulness. By contrast, the polymorphism profoundly modulated the efficacy of modafinil to improve impaired well-being and cognitive functions after sleep deprivation (Bodenmann et al., 2009b).

385A > G polymorphism of prion protein gene

A point mutation at codon 178 (in rare cases, also a mutation at codon 200) of the prion protein (*PRNP*) gene causes fatal familial insomnia (FFI; Lugaresi et al., 1986). Healthy relatives of FFI patients appear to have normal sleep EEG (Ferrillo et al., 2001). By contrast, the polymorphic codon 129 of the *PRNP* gene (SNP-ID number: rs1799990) may influence EEG activity in NREM sleep (Plazzi et al., 2002). A preliminary analysis indicated that subjects with Met/Val genotype had lower slow-wave activity and higher spindle frequency activity than individuals with the Val/Val genotype.

Concluding remarks

Polymorphic variations in a number of genes (*PER3*, *ADA*, *ADORA2A*, *BDNF*, *COMT*, *PRNP*) have now been shown to affect distinct characteristics of sleep and sleep EEG in humans. Consistent with recent findings showing that EEG differences in NREM sleep between monozygotic and dizygotic twin pairs are independent of elevated sleep propensity, profound genotype-dependent differences are present in baseline and mostly persist in recovery sleep after sleep deprivation (Table 1). The consistent effects, particularly in the theta/alpha range, of these genes in NREM sleep, REM sleep, and wakefulness support the hypothesis that common neuronal mechanisms underlie the generation of major EEG oscillations. On the other hand, functional polymorphisms of *PER3*, *ADA*, and *BDNF* cause state- and frequency-specific differences within the slow-wave range (~0.5–3 Hz) in NREM sleep. These genes may contribute to the regulation of sleep homeostasis. Elucidating the signaling pathways that are affected by these genetic variations will aid our understanding of molecular mechanisms underlying sleep and may provide new targets for the pharmacological improvement of disturbed sleep in sleep disorders.

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