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ORIGINAL ARTICLE

Genetic polymorphisms of *DAT1* and *COMT* differentially associate with actigraphy-derived sleep–wake cycles in young adults

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Accumulating evidence suggests that dopamine plays a key role in sleep–wake regulation. Cerebral dopamine levels are regulated primarily by the dopamine transporter (DAT) in the striatum and by catechol-O-methyl-transferase (COMT) in the prefrontal cortex. We hypothesized that the variable-number-tandem-repeat (VNTR) polymorphism in the 3′-untranslated region of the gene encoding DAT (*DAT1, SLC6A3*; rs28363170) and the Val158Met polymorphism of *COMT* (rs4680) differently affect actigraphy-derived rest-activity cycles and sleep estimates in healthy adults (65 men; 45 women; age range: 19–35 years). Daytime sleepiness, continuous rest-actigraphy and sleep diary data during roughly 4-weeks were analyzed. Nine-repeat (9R) allele carriers of *DAT1* ($n = 48$) more often reported elevated sleepiness (Epworth sleepiness score ≥ 10) than 10-repeat (10R) allele homozygotes ($n = 62$, $p < 0.02$). Moreover, male 9R allele carriers showed higher wrist activity, whereas this difference was not present in women ("*DAT1 genotype*" × "*gender*" interaction: $p < 0.005$). Rest-activity patterns did not differ among *COMT* genotypes. Nevertheless, a significant "*COMT genotype*" × "*type of day*" (workdays *vs.* rest days) interaction for sleep duration was observed ($p = 0.04$). The Val/Val ($n = 36$) and Met/Met ($n = 24$) homozygotes habitually prolonged sleep on rest days compared to workdays by more than 30 min, while Val/Met heterozygotes ($n = 50$) did not significantly extend their sleep (mean difference: 7 min). Moreover, whereas the proportion of women among the genotype groups did not differ, *COMT* genotype affected body-mass-index (BMI), such that Val/Met individuals had lower BMI than the homozygous genotypes ($p < 0.04$). While awaiting independent replication and confirmation, our data support an association of genetically-determined differences in cerebral dopaminergic neurotransmission with daytime sleepiness and individual rest-activity profiles, as well as other sleep-associated health characteristics such as the regulation of BMI. The differential associations of *DAT1* and *COMT* polymorphisms may reflect the distinct local expression of the encoded proteins in the brain.

Keywords: Body-mass-index, circadian, daytime sleepiness, dopamine, *SLC6A3*

INTRODUCTION

The brain levels of dopamine are regulated in the striatum primarily by dopamine transporter (DAT), which removes dopamine from the synaptic cleft, and in the prefrontal cortex primarily by catechol-O-methyl-transferase (COMT), which degrades dopamine to 3-methoxy-tyramine. Accumulating evidence suggests that dopamine is a prominent regulator of wakefulness and sleep (Monti & Monti, 2007), which are controlled by the intricate interplay of the endogenous circadian clock and a sleep–wake-dependent, homeostatic process (Borbely, 1982). Pronounced diurnal fluctuations of extracellular brain dopamine levels across 24-h rest-activity and sleep–wake cycles are well established (Rye & Freeman, 2011). Furthermore, disease states with altered dopaminergic neurotransmission, such as Parkinson's disease (PD) and attention deficit hyperactivity disorder (ADHD), are often associated with disturbed rest-activity profiles and sleep problems (Van Veen et al., 2010; Whitehead et al., 2008).

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Apart from influencing the circadian clock, dopamine may also play a key role in regulating the homeostatic facet of the sleep–wake cycle. Studies in animal models identified wake-active dopaminergic neurons innervating sleep-promoting regions such as the ventro-lateral pre-optic area (Lu et al., 2006; Ueno et al., 2012), and also pharmacologic and clinical observations suggest an important contribution of dopamine to sleep–wake regulation. For example, stimulants like methamphetamine and agonists of dopamine receptors promote wakefulness and motor activity in mice and humans (Wise & Bozarth, 1987; Wisor et al., 2001). Dopamine D_2 receptor knock-out mice exhibit prolonged sleep time when compared to wild-type animals (Qu et al., 2010), while genetically modified mice and flies without functional dopamine transporter (DAT) have increased wakefulness (Giros et al., 1996; Kume et al., 2005). Finally, patients with PD often suffer from rapid-eye-movement (REM) sleep behavior disorder and excessive daytime sleepiness (Comella, 2008; Rye & Jankovic, 2002). Increased motor activity to counteract elevated sleepiness due to reduced prefrontal dopaminergic ''tone'' may also be present in patients with ADHD (Cohen-Zion & Ancoli-Israel, 2004; Cortese et al., 2009). Such a pathophysiology may explain why hyperactivity in ADHD can be improved with medications that increase dopamine release (Minzenberg, 2012).

The gene encoding DAT (*DAT1*, *SLC6A3*) exists in different variants in the healthy population. More specifically, it contains a 40-base pair (bp) variable-number-tandem-repeat (VNTR) polymorphism in its 3′-untranslated region (SNP-ID: rs28363170), expressing 3 to 11 repeats, with the presence of 9 and 10 repeats as the most common isoforms (Kang et al., 1999; Vandenbergh et al., 1992). Although VNTRs in general (Nakamura et al., 1998) and the VNTR domain of *DAT1* in particular (Michelhaugh et al., 2001) can influence transcriptional and translational processes, the consequences of this polymorphism on DAT availability in the human striatum are slightly controversial (Heinz et al., 2000; Jacobsen et al., 2000; van de Giessen et al., 2009; van Dyck et al., 2005). Nevertheless, more recent brain imaging studies in young adults consistently suggest that the presence of the 9-repeat (9R) allele of *DAT1* increases striatal DAT availability compared to 10-repeat (10R) allele homozygotes (Costa et al., 2011; Spencer et al., 2013). This polymorphism affects the rebound in deep slow wave sleep after prolonged waking in healthy volunteers (Holst et al., 2014), and the 9R allele has been associated with ADHD in adult patients (Barkley et al., 2006; Franke et al., 2010; Spencer et al., 2013) who typically exhibit increased DAT expression when compared to matched controls (Cheon et al., 2003; Dougherty et al., 1999; Dresel et al., 2000; Krause et al., 2006; Spencer et al., 2005, 2013). We, thus, hypothesized that 9R carriers of *DAT1* may differ from 10R homozygotes and show elevated sleepiness and increased wrist activity across wakefulness and sleep, similar to patients with ADHD in comparison to healthy controls (Boonstra et al., 2007; Surman et al., 2009).

In contrast to the effect of the *DAT1* VNTR, the functional impact of the Val158Met polymorphism (SNP-ID: rs4680) in the gene encoding COMT is well established. It leads to a Val-to-Met amino acid substitution in the COMT protein, which reduces thermo-stability of the enzyme and drastically decreases enzymatic activity in Met-allele carriers (Akil et al., 2003; Chen et al., 2004). This polymorphism has been associated with various psychiatric disorders (Hosak, 2007), as well as individual differences in daytime sleepiness and efficacy of modafinil in narcoleptic patients (Dauvilliers et al., 2001, 2002). Furthermore, it modulates individual responses to modafinil in healthy adults after sleep deprivation (Bodenmann & Landolt, 2010; Bodenmann et al., 2009) and to methylphenidate in children with ADHD (Kereszturi et al., 2008). In ADHD children, preliminary actigraphic data indicated that Val-allele carriers have poorer sleep continuity when compared to children with the Met/Met genotype (Gruber et al., 2006). We predicted that the Val158Met polymorphism of *COMT* also affects rest-activity patterns in healthy adults and investigated long-term actigraphy-derived habitual rest-activity profiles in young men and women. Additionally, because previous studies reported an association between individual sleep–wake habits and BMI (Lazar et al., 2012) and between *COMT* genotype and food intake (Annerbrink et al., 2008; Galvao et al., 2012; Tworoger et al., 2004), we hypothesized that this polymorphism would also affect BMI in our study sample. The BMI provides an important sleep-associated health outcome measure that differs widely even among healthy individuals (Spiegel et al., 2009).

MATERIALS AND METHODS

Study participants

One-hundred twenty-nine young healthy males and females were recruited with flyers and on the Internet for participation in sleep studies at the Universities of Zürich and Basel. The study protocols, screening questionnaires, and consent forms were approved by the local ethics committees and conformed to the Declaration of Helsinki (Portaluppi et al., 2010).

A general entrance questionnaire was used to gather demographic information including age, gender, weight (in kg) and height (in m) to calculate BMI, level of education and to screen for medical diseases. The inclusion criteria consisted of young age (19–35 years), normal BMI (17–29 kg/m^2), good subjective sleep quality, absence of neurological or psychiatric disorders, no history of drug abuse, no current medication intake, no excessive consumption of alcohol, no shift work or crossing of more than two time zones within the last 3 months, and no extreme chronotype as assessed with the Munich ChronoType Questionnaire

(Roenneberg et al., 2003). Subjective sleepiness was assessed with the Epworth Sleepiness Scale (Johns, 1991). All subjects received monetary compensation for their participation.

Actimetry

All participants completed 3- to 4-week rest-activity recordings at home, including at least two weekends, without scheduled restrictions to their sleep–wake behavior. During the recording period, they continuously wore an Actiwatch® (Cambridge Neurotechnology, Cambridge, UK) on their non-dominant arm, and filled-in a sleep–wake diary twice per day. On average, 19.5 ± 4.4 workdays and 7.7 ± 2.1 rest days (i.e. weekend days) worth of actigraphic data per study participant were recorded. The validity of actigraphic recordings for sleep–wake estimation in healthy volunteers and patients is widely accepted (Morgenthaler et al., 2007; Sadeh, 2011).

The non-parametric circadian rhythm analysis (NPCRA) developed by Van Someren et al. (1999) was used to determine circadian rhythm characteristics. The analyzed outcome variables included inter-daily stability (IS) (i.e. degree of resemblance across activity patterns of individual days for a given subject), intra-daily variability (IV) (i.e. fragmentation of periods of activity and rest), activity during the 5-least-active-hours (L5), activity during the 10-most-active-hours (M10) and relative amplitude (RA) (ratio between M10 and L5). L5 and M10 were determined from the 24-h average curve indicating the mean activity counts of nadir and peak of the day, as well as their time of onset.

For the activity analyses, raw activity counts were exported from the ''Sleep and Activity Analysis 7.23 V software'' (version 5.42; Cambridge Neurotechnology Ltd, Cambridge, UK). The data of consecutive 30-min bins were averaged over 24 h in each individual. For the nighttime sleep analysis, the ''Sleep Scoring Algorithm'' module of the same software allowed the investigation of several objective, sleep-related variables, including time in bed (i.e. difference between bed time and rise time), bed time and rise time, estimated sleep duration (i.e. difference between sleep time and wake time), sleep latency (i.e. time between bedtime and sleep onset), sleep efficiency (i.e. estimated sleep duration divided by the time in bed), and wakefulness after sleep onset (WASO; i.e. time spent awake between sleep onset and sleep offset). The bed times and rise times (i.e. times of lights-off and lights-on) were identified and manually set by the same experienced person (AV) in all nights and subjects, whereas the sleep onset and wake offset times were calculated with the sleep–wake scoring algorithm. The wake/sensitivity threshold was set to ''low'', showing an optimal agreement between actigraphy and polysomnography (PSG) in a young healthy study population (Tonetti et al., 2008). The actimetric recordings were combined with the information contained in the sleep–wake diaries, including bed times, rise times, caffeine consumption, occurrence of naps, use of alarm clock, etc. The majority of study participants (89%) reported no medication use during the recording period. Only four participants reported regular (≥4 times a week) medication intake of a non-steroidal anti-inflammatory drug, an anti-histamine, or a synthesized retinoic acid derivative.

Genotyping

Genomic DNA was isolated from 3 ml fresh EDTA-blood ($n = 83$) (Wizard® Genomic DNA Purification Kit, Promega, Madison, WI) or from saliva ($n = 46$) (NucleoSpin® Blood Kit, Macherey-Nagel AG, Oensingen, Switzerland). The genotypes of both *DAT1* and *COMT* could be reliably established in 115 study participants.

The *DAT1* genotypes were determined by PCR on an MJ Research PTC-225 thermal cycler (MJ Research/Bio-Rad, Reno, NV). The following primers were used: forward primer, 5′-tgtggtgtagggaacggcctga-3′ and reverse primer 5′-cttcctggaggtcacggctcaa-3′ (annealing temperature of 67 °C with HOT FIREPol® DNA Polymerase; Solis Biodyne, Tartu, Estonia). The 430–480 bp PCR products were then analyzed by agarose gel electrophoresis. COMT genotypes were determined using a Taqman® SNP Genotyping Assay (Life Technologies Europe B.V., Zug, Switzerland) and allelic discrimination analysis was performed using the software SDS v2.2.2 (Applied Biosystems, Foster City, CA). All analyses were replicated at least once for independent confirmation of results.

Five volunteers had rare *DAT1* genotypes (one 10R/7R, two 9R/8R, two 10R/11R) and were excluded from the analyses. Seven subjects were homozygous for the 9R allele. They were combined with the 9R/10R genotypes and referred to as 9R carriers. The allelic distributions of *DAT1* ($p = 0.25$) and *COMT* ($p = 0.27$) genotypes were in the Hardy–Weinberg equilibrium (software freely available online: Genepop version 4.0.10) (Rousset, 2008).

Statistical analyses

All statistical analyses were performed with SAS 9.1.3 software (SAS® Institute, Cary, NC). Fisher's exact tests were used to evaluate differences in frequencies and distributions. Demographic data and sleep–wake variables were analyzed with 1-, 2- and 3-way mixed-model analyses of variance (ANOVA; SAS® PROC MIXED, autoregressive type 1 as covariance structure) with the between-subjects factors ''*gender*'' (male, female), ''*DAT1 genotype*'' (9R, 10R/10R), ''*COMT genotype*'' (Val/Val, Val/Met, Met/Met) and the within-subjects factors ''*time*'' (forty-eight 30-min bins across 24 h) and ''*type of day*'' (workdays, rest days). Because age had a significant effect on level of education and BMI, and because BMI differed among *COMT* genotypes (Table 1), ''*age*'' and ''*BMI*'' were used as covariates in all statistical analyses. Respective ANOVA models are indicated in text and legends to tables and figures; *p* values were

TABLE 1. Demographic characteristics of study participants.

	10R/10R			9R carriers			"*gender*"		"*DAT1* genotype"		"*COMT* genotype"		"*DAT1*" x "*COMT*"		"*age*"	
	Val/Val	Val/Met	Met/Met	Val/Val	Val/Met	Met/Met	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
N	21	27	14	15	23	10										
Sex ratio (% Female)	43	44	21	40	48	40										
Education (years)	13.0 ± 2.0	13.4 ± 1.8	13.2 ± 1.7	13.1 ± 2.8	13.3 ± 2.0	14.0 ± 2.4	$F_{1,95} = 0.24$	0.62	$F_{1,95} = 1.44$	0.23	$F_{2,95} = 0.50$	0.61	$F_{2,95} = 1.41$	0.25	$\mathbf{F_{1,95} = 16.1}$	**0.0001**
Age (years)	25.2 ± 3.9	24.9 ± 3.9	26.5 ± 4.0	25.3 ± 3.7	25.0 ± 3.7	24.3 ± 3.8	$F_{1,99} = 0.01$	0.91	$F_{1,99} = 0.03$	0.86	$F_{2,99} = 0.05$	0.95	$F_{2,99} = 0.44$	0.64		
Chronotype (MCTQ)	4.5 ± 1.0	4.2 ± 1.2	4.4 ± 1.0	4.5 ± 1.1	4.4 ± 1.0	4.1 ± 1.1	$F_{1,98} = 0.53$	0.47	$F_{1,98} = 0.06$	0.80	$F_{2,98} = 0.52$	0.60	$F_{2,98} = 0.23$	0.80	$F_{1,98} = 1.63$	0.20
Daytime sleepiness (ESS)	5.2 ± 2.5	5.3 ± 2.4	5.7 ± 3.2	6.5 ± 2.8	6.4 ± 3.4	6.5 ± 2.7	$F_{1,96} = 0.00$	0.99	$F_{1,96} = 2.43$	0.12	$F_{2,96} = 0.19$	0.82	$F_{2,96} = 0.15$	0.86	$F_{1,96} = 0.5$	0.48
Body Mass Index (kg/m^2)	23.3 ± 2.4	21.4 ± 2.2	23.4 ± 2.3	22.2 ± 2.2	21.6 ± 2.4	22.0 ± 1.4	$F_{1,99} = 0.31$	0.58	$F_{1,99} = 2.17$	0.14	$\mathbf{F_{2,99} = 3.36}$	**0.04**	$F_{2,99} = 1.10$	0.34	$\mathbf{F_{1,99} = 5.57}$	**0.02**
Actimetry recording (days)	29.2 ± 4.9	26.0 ± 7.5	27.1 ± 5.9	27.3 ± 4.9	27.7 ± 5.0	26.0 ± 6.9	$F_{1,98} = 0.98$	0.32	$F_{1,98} = 0.78$	0.38	$F_{2,98} = 0.98$	0.38	$F_{2,98} = 1.89$	0.16	$F_{1,98} = 0.54$	0.47

Values represent means ± STD. Information about education and daytime sleepiness was missing in 3 and 2 individuals, respectively. Chronotype derived from the Munich ChronoType Questionnaire (MCTQ; Roenneberg et al., 2003) indicates the mid-sleep time on leisure days, corrected for age, gender, and sleep debt accumulated during the week. The mean number of days of actimetry recording in each genotype used for analyses is also reported. *F* and *p* values refer to mixed-model ANOVA with the factors "*gender*", "*DAT1 genotype*", "*COMT genotype*" and the covariates "*age*" and "*BMI*". Significant ANOVA results in bold.

based on Kenward-Roger's corrected degrees of freedom. Contrasts were obtained from the LSMEANS statement, and the Tukey–Kramer method was used for *post-hoc* analyses. If not mentioned otherwise, means ± STD are presented and only significant effects ($\alpha < 0.05$) of factors and interactions are reported.

RESULTS

Demographics of study sample

The data of 110 young healthy individuals were analyzed (Table 1). The study sample consisted of 65 men (59%) and 45 women (41%), with a mean age of 25.2 ± 3.8 years, 13.3 ± 2 years of education and a normal BMI (22.2 ± 2.3 kg/m^2). Chronotype (Munich Chronotype Questionnaire: 4.4 ± 1 [corrected midpoint of sleep]) and subjective sleepiness (Epworth Sleepiness Scale: 5.8 ± 2.8) ratings were also in the normal range. No significant differences among *DAT1* and *COMT* genotype groups with respect to sex ratio, age, years of education, chronotype and daytime sleepiness were noted ($p_{all} > 0.05$; Fisher's exact tests). When split by either *DAT1* or *COMT* genotype, the distributions of genotype groups of the other gene did not differ ($p_{all} > 0.05$; Fisher's exact tests).

Rest-activity profiles

Typical of our study sample consisting primarily of University students (77%), NPCRA revealed high-amplitude, yet relatively irregular circadian rest-activity rhythms (Table 2). The latter was reflected in low IS scores due to large differences between workdays and rest days. The periods of lowest (L5) and highest (M10) activity began roughly 1 h after actimetry-derived sleep onset and 2.7 h after actimetry-derived sleep offset, respectively. The L5 initiated significantly earlier and revealed lower activity counts in women than in men (Table 2).

Time spent in bed (TIB) derived from the actimetry recordings correlated with self-reported TIB in the

TABLE 2. Non-parametric circadian rhythm analysis (NPCRA).

	Women $n = 45$	Men $n = 65$	"*gender*" $F_{1,106}$	"*gender*" *p*
IS	0.40 ± 0.10	0.38 ± 0.12	1.11	0.29
IV	0.85 ± 0.16	0.84 ± 0.17	0.05	0.82
Relative Amplitude	0.85 ± 0.08	0.81 ± 0.09	**4.89**	**0.03**
L5 onset	1.31 ± 0.92	1.77 ± 1.11	**5.09**	**0.03**
M10 onset	10.52 ± 1.52	10.93 ± 1.70	0.08	0.22
Amplitude	19 428 ± 7 393	18 627 ± 6 934	0.44	0.51
L5	1664 ± 1110	2161 ± 1427	**4.31**	**0.04**
M10	21 092 ± 7686	20 788 ± 7424	0.08	0.78

Values represent means ± STD in all participants split by gender. IS = inter-daily stability; IV = intra-daily variability; L5 = activity during the least 5 active hours; M10 = activity during the 10 most active hours. *F* and *p* values refer to mixed-model ANOVA with the factor "*gender*" and the covariate "*age*". Significant ANOVA results in bold.

TABLE 3. Sleep-wake diary- and actimetry-derived sleep variables.

	Women $n=45$	Men $n=65$	"gender" $F_{1,106}$	"gender" p	Work days $n=110$	Rest days $n=110$	"type of day" $F_{1,109}$	"type of day" p
N (days/person)	28.0 ± 5.3	26.8 ± 6.4	1.50	0.22	19.5 ± 4.4	7.7 ± 2.1		
Caffeine consumption (mg/day)	120 ± 85	99 ± 97	1.30	0.26	110 ± 97	104 ± 87	2.15	0.14
Alarm clock use (%)	60 ± 21	58 ± 21	0.32	0.57	64 ± 23	50 ± 29	**40.24**	**<0.0001**
Time in bed (h)	7.9 ± 0.6	7.7 ± 0.7	2.35	0.13	7.7 ± 0.7	8.0 ± 0.9	**18.50**	**<0.0001**
Bedtime (h:min ± min)	0:04 ± 47	0:38 ± 76	**7.17**	**<0.01**	0:07 ± 67	1:10 ± 81	**128.5**	**<0.0001**
Risetime (h:min ± min)	7:58 ± 46	8:22 ± 63	**4.05**	**0.05**	7:48 ± 62	9:12 ± 75	**144.3**	**<0.0001**
Sleep duration (h)	7.6 ± 0.6	7.4 ± 0.7	2.68	0.10	7.4 ± 0.7	7.8 ± 0.9	**20.34**	**<0.0001**
Sleep onset (h:min ± min)	0:16 ± 50	0:52 ± 76	**7.72**	**<0.01**	0:20 ± 68	1:21 ± 82	**122.9**	**<0.0001**
Wake onset (h:min ± min)	7:52 ± 46	8:17 ± 64	**4.44**	**0.04**	7:43 ± 63	9:06 ± 74	**143.9**	**<0.0001**
Midsleep time (h:min ± min)	3:53 ± 36	4:34 ± 66	**6.69**	**0.01**	4:04 ± 60	5:08 ± 73	**158.9**	**<0.0001**
WASO (min)	37 ± 22	35 ± 15	0.20	0.65	35 ± 18	38 ± 19	**8.99**	**<0.01**
Sleep efficiency (%)	88.5 ± 4.4	88.3 ± 3.9	0.04	0.84	88.4 ± 4.2	88.5 ± 4.4	0.31	0.58
Sleep latency (min)	12 ± 4	14 ± 7	3.10	0.08	13 ± 6	12 ± 6	**5.80**	**0.02**
Mean activity	27 ± 14	26 ± 12	0.10	0.75	26 ± 13	27 ± 14	**3.96**	**0.05**
Total activity	7220 ± 3838	7010 ± 2599	0.22	0.64	6945 ± 3177	7471 ± 3504	**8.91**	**<0.01**

Values represent means ± STD, split by gender and type of day. Reported caffeine consumption was estimated based on the following average caffeine contents per serving: Coffee: 100 mg; Black or green tea: 30 mg; Cola drink: 40 mg (2 dl); Energy drink: 80 mg (2 dl); Chocolate: 50 mg (100 g). Alarm clock use = number of days when an alarm clock was used, expressed as a percentage of total recording days. WASO = Wakefulness after sleep onset. *F* and *p* values refer to mixed-model ANOVAs with the between-subjects factor "*gender*" and the within-subjects factor "*type of day*", and the covariates "*age*" and "*BMI*". Significant ANOVA results in bold.

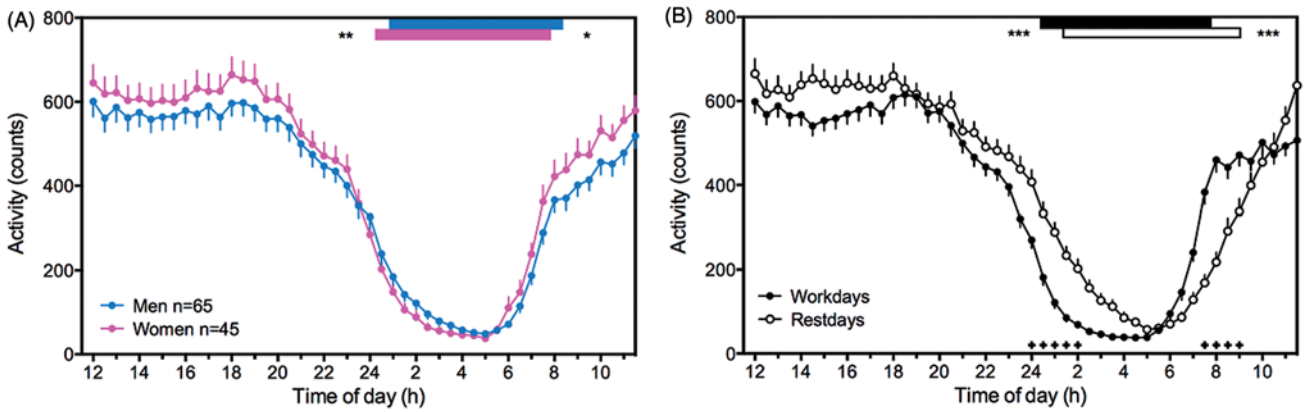

FIGURE 1. Rest-activity rhythms and sleep are affected by gender and type of day. (A) 24-h rest-activity profiles in men ($n=65$) and women ($n=45$). Means ± SEM are represented. Mixed-model ANOVA with the between-subject factor "*gender*", the within-subject factor "*time*" (30-min bins), and the covariates "*age*" and "*BMI*" revealed a significant effect of "*time*" ($F_{48,5113}=20.2$, $p<0.0001$). Horizontal bars reflect the actigraphy-derived sleep episodes in women (magenta) and in men (blue). Sleep onset: $p<0.01$ (**); sleep offset: $p<0.05$ (*) (Table 3). (B) 24-h rest-activity profiles on workdays and rest days. Means ± SEM are represented. Horizontal bars reflect the actigraphy-derived sleep episodes on workdays (black) and on rest days (white). Sleep onset and sleep offset: $p_{all}<0.0001$ (***) (Table 3). Crosses at the bottom of the panel indicate significant differences between workdays and rest days ($p<0.05$; Tukey–Kramer *post-hoc* tests).

sleep–wake diaries ($R^2=0.51$, $p<0.001$, $n=109$; Pearson's product moment correlation). On average, the study participants slept 7.5 h ± 36 min, with actigraphy-derived sleep onset at 00:36 ± 66 min and sleep offset at 08:06 ± 60 min. Sleep onset and offset (i.e. wake onset) were affected by "*gender*" and "*type of day*" (Table 3). These values were roughly 25–35 min earlier in women than in men (Figure 1A), and approximately 60–75 min earlier on workdays than on rest days (Figure 1B). Sleep duration was not affected by "*gender*". By contrast, sleep was shorter on workdays than on rest days (Table 3). The average difference was 22 ± 51 min, and similar in women and in men (ANOVA factor "*gender*": $F_{1,106}=1.0$, $p>0.3$). Yet, it was highly variable among all individuals studied (range: −89 to 173 min).

Two-way mixed-model ANOVA revealed significant effects of "*type of day*" ($F_{1,461}=6.6$, $p=0.01$), "*time*" ($F_{48,4988}=23.5$, $p<0.0001$), and a significant "*time*" × "*type of day*" interaction ($F_{48,5185}=4.8$, $p<0.0001$) (Figure 1B). More specifically, the actigraphy-derived sleep episode occurred later and lasted longer on rest days than on workdays (Table 3). When compared to workdays, wrist activity values on rest days were higher between 00:00 and 02:00 and lower between 06:30 and 09:00 (Figure 1B).

The rs28363170 polymorphism of *DAT1*, individual subjective sleepiness and wrist activity

Although the statistical analyses revealed no significant main effect of *DAT1* genotype on subjective

sleepiness (Table 1), focusing on those individuals with clinically-defined elevated daytime sleepiness (Epworth sleepiness score higher than 10) (Johns, 2000) demonstrated that *DAT1* 9R (8/47 = 17.0%) carriers were more often present in this subgroup than 10R homozygotes (2/61 = 3.3%) (Figure 2).

The 24-h activity profiles in the entire study sample did not differ between men and women (Figure 1A). By contrast, male 9R carriers showed generally higher wrist activity than male 10R homozygotes (Figure 3A). Such a difference was absent in women (Figure 3B). Thus, mixed-model ANOVA with the between-subjects factors ''*gender*'', ''*DAT1 genotype*'', ''*COMT genotype*'' and the within-subjects factor ''*time*'' yielded significant effects of ''*time*'' ($F_{48,4731} = 17.4$, $p < 0.0001$) and a significant ''*DAT1 genotype*'' × ''*gender*'' interaction ($F_{1,199} = 8.5$, $p < 0.005$). The interaction between ''*DAT1 genotype*'' and ''*gender*'' was further corroborated when workdays ($F_{1,255} = 11.5$, $p < 0.001$) and rest days ($F_{1,249} = 11.6$, $p < 0.001$) were separately considered, and when the NPCRA outcome variables ''mean activity during sleep'' ($F_{1,98} = 7.8$, $p < 0.007$) and L5 ($F_{1,98} = 6.2$, $p = 0.01$) were analyzed. In summary, the *DAT1* VNTR associates with gender-specific differences in wrist activity throughout the circadian sleep–wake cycle.

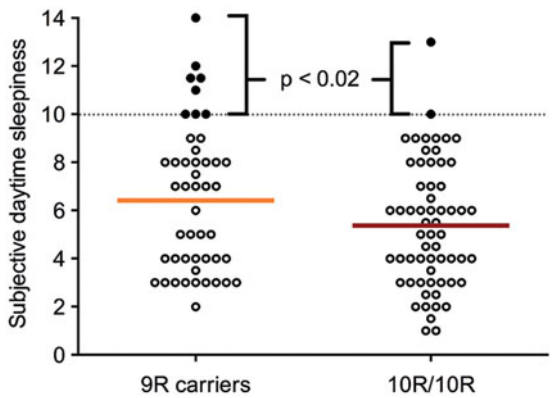

FIGURE 2. *DAT1* genotype affects subjective daytime sleepiness. Data reflect individual scores on the Epworth Sleepiness Scale ($n = 108$). Black (ESS score ≥ 10) and white (ESS score < 10) circles represent all individual data points. *DAT1* 9R carriers are more often present in the subgroup with elevated daytime sleepiness when compared to 10R homozygotes ($p < 0.02$; Fisher's exact test). Colored horizontal bars represent the mean values in 9R ($n = 47$) and 10R/10R ($n = 61$) carriers.

The rs4680 polymorphism of *COMT*, sleep–wake patterns and body weight regulation

The Val158Met polymorphism of *COMT* had no effect on subjective sleepiness and circadian rhythm variables. By contrast, *COMT* genotype associated with a different increase in sleep duration ($F_{2,98} = 3.2$, $p = 0.04$) between workdays and rest days. The Val/Val and Met/Met homozygotes prolonged their sleep on rest days relative to workdays by 37 ± 58 and 31 ± 54 min. The increase equaled only 7 ± 41 min in Val/Met individuals. A statistical analysis of sleep duration with ''*COMT genotype*'' as between-subjects factor and ''*type of day*'' as within-subjects factor confirmed the genotype-dependent difference (Figure 4A). Importantly, mean sleep duration across workdays and rest days was similar in the three genotypes, and did not significantly differ between genotypes, neither on workdays nor on rest days ($p_{all} > 0.1$).

A genotype-dependent association between sleep–wake timing as estimated by the midpoint of sleep (early, intermediate, late) on workdays and rest days and BMI was recently suggested for a *PER3* polymorphism (Lazar et al., 2012). We, therefore, examined whether the Val158Met polymorphism of *COMT* affects BMI in our study sample. Indeed, ANOVA confirmed a significant main effect of ''*COMT genotype*'' (Table 1 and Figure 4B). Specifically, BMI was lower in Val/Met heterozygotes when compared to Val/Val homozygotes and tended to be lower in Val/Met heterozygotes when compared to Met/Met homozygotes ($p = 0.09$).

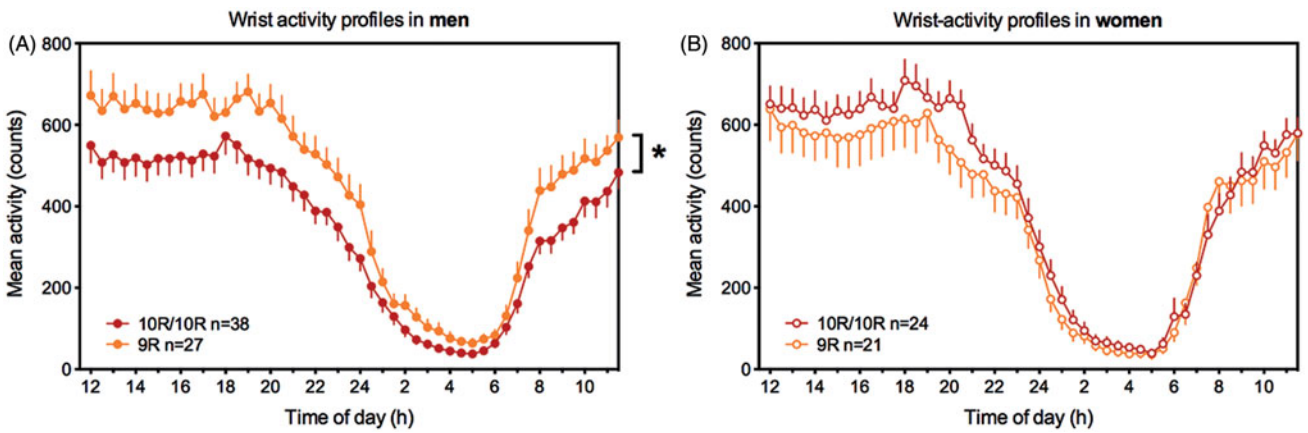

FIGURE 3. *DAT1* polymorphism associates in a gender-dependent manner with differential wrist activity profiles across the daily rest-activity cycle. 24-h rest-activity profiles in 9R and 10R/10R genotypes of *DAT1* in men (A) and women (B). Means ± SEM are represented. Male 9R carriers had higher activity levels throughout day and night when compared to 10R/10R homozygotes ($p = 0.02$, Tukey–Kramer *post-hoc* test) (*). Female study participants did not show this difference ($p = 0.6$).

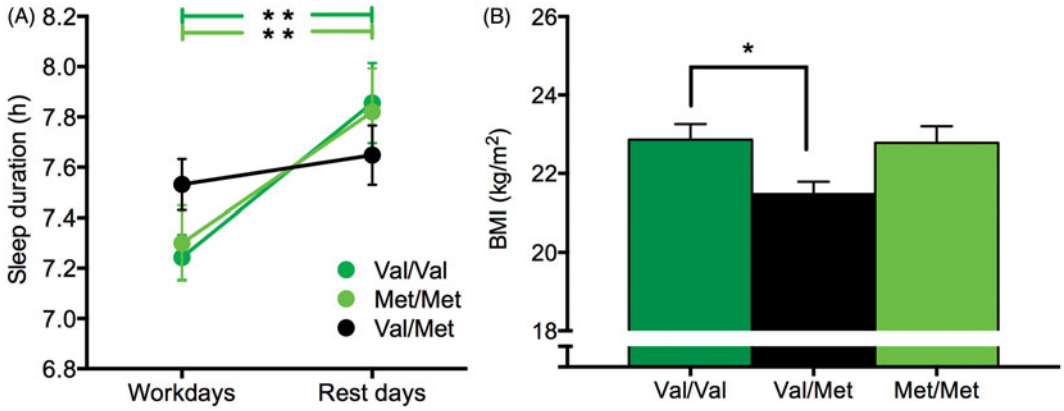

FIGURE 4. *COMT* genotype modulates the sleep rebound from workdays to rest days and affects BMI. Mean values ± SEM are represented. (A) Sleep duration on workdays and rest days in the three *COMT* genotypes. Mixed-model ANOVA with the between-subjects factor ''*COMT genotype*'', the within-subjects factor ''*type of day*'', and the covariates ''*age*'' *and* ''*BMI*'' yielded a significant main effect of ''*type of day*'' ($F_{1,107} = 26.6$, $p < 0.001$) and a significant ''*type of day*'' × ''*COMT genotype*'' interaction ($F_{2,107} = 3.8$, $p < 0.03$). Thus, in contrast to Val/Val (dark green) and Met/Met (light green) homozygotes, Val/Met allele carriers (black) did not increase their sleep duration on rest days when compared to workdays. $^{**}p < 0.01$, Tukey–Kramer *post-hoc* test. (B) Mean BMI in Val/Val, Val/Met and Met/Met genotypes of *COMT*. Mixed-model ANOVA with the between-subjects factors ''*DAT1 genotype*'', ''*COMT genotype*'' and ''*gender*'', and the covariate ''*age*'' yielded a significant main effect of ''*COMT genotype*'' ($F_{2,99} = 3.36$, $p < 0.04$). $^{*}p < 0.05$, Tukey–Kramer *post-hoc* test.

DISCUSSION

In an attempt to further specify the roles for dopamine in physiological sleep–wake regulation, we examined the effects of two functional polymorphisms in genes regulating cerebral dopamine levels on circadian rest-activity profiles and objective sleep estimates derived from actimetry. Consistent with our hypotheses, we found that a VNTR polymorphism of *DAT1* affects subjective sleepiness and modulates overall wrist activity counts throughout activity and rest in men. Moreover, heterozygous Val/Met allele carriers of the Val158Met polymorphism of *COMT* showed consistently lower values than Val/Val and Met/Met homozygotes in their sleep rebound on rest days compared to workdays, as well as in their BMI.

With respect to the rs28363170 polymorphism of *DAT1*, we found that elevated daytime sleepiness was more prevalent in 9R allele carriers than in 10R/10R allele homozygotes. Accumulating evidence in healthy adults demonstrates that the 9R allele is associated with higher DAT expression and lower dopamine availability than the 10R allele (Costa et al., 2011; Jacobsen et al., 2000; Miller & Madras, 2002; Spencer et al., 2013; van de Giessen et al., 2009; van Dyck et al., 2005). Our data may, thus, suggest a possible pathophysiological link between reduced dopaminergic tone and elevated sleepiness in humans.

This notion is further strengthened by the finding that male 9R carriers exhibited higher wrist activity throughout days and nights compared to 10R/10R individuals. Elevated sleepiness and increased activity may be reminiscent of patients suffering from adult ADHD. This disorder more often afflicts males than females, and patients typically present with excessive daytime sleepiness, superficial sleep, elevated daytime and nighttime motor activity, and increased DAT expression when compared to controls (Cheon et al., 2003; Dougherty et al., 1999; Dresel et al., 2000; Krause et al., 2006; Spencer et al., 2005, 2013).

The observed differential effects of the *DAT1* polymorphism on wrist activity in male and female study participants may reflect the known impact of sex hormones and the menstrual cycle on the dopaminergic system (Dreher et al., 2007; Munro et al., 2006). Because the recording period in our study covered roughly an entire menstrual cycle, it is unlikely that cycle-related changes in DAT expression account for the different impact of *DAT1* genotype in men and women. Nevertheless, future studies with a longer recording time and inclusion of hormone measurements may be needed to corroborate our finding.

With respect to the Val158Met polymorphism of *COMT*, we observed that Val/Met heterozygotes showed an attenuated increase in sleep duration on rest days when compared to workdays, and also had a lower BMI than homozygous genotypes. Investigating the possible impact of another genetic variant on sleep and sleep-related health outcomes, Lazar et al. (2012) examined the impact of a *PER3* polymorphism on sleep and BMI in 675 study participants. Similar to our results, they found that the group reporting the largest difference in time in bed between workdays and rest days (*PER3*$^{5/5}$ genotype) also showed the highest BMI. These observations are in accordance with a large-scale epidemiological study in 20 731 participants in which, based on a questionnaire, a positive association was found between BMI in overweight individuals (BMI $\geq$ 25) and ''social jetlag'' as quantified by the reported difference in mid-sleep time between workdays and free days (Roenneberg et al., 2012). While the number of participants in the present study is smaller

than in the other samples, our work not only relied on questionnaires but also quantified sleep–wake patterns objectively over several weeks. It adds to the accumulating evidence that circadian rhythm irregularities and sleep–wake cycle disruptions contribute to individual differences in body-weight regulation, even in a population with normal weight and in the absence of shortened sleep duration.

Increasing evidence supports a role for dopamine in regulating food intake and modulating food reward via a meso-limbic circuitry (Schwartz et al., 2000; Wang et al., 2001). COMT metabolizes catechol-estrogens in peripheral tissue to 2-methoxyestradiol, which influences fat regulation (Pico et al., 1998; Tworoger et al., 2004). Based on this background, a growing area of research has begun to explore potential associations between dopaminergic genes and obesity (Need et al., 2006; Wang et al., 2001). Indeed, an association between the Val158Met polymorphism of *COMT* and individual differences in food intake or BMI has been previously suggested (Annerbrink et al., 2008; Galvao et al., 2012; Tworoger et al., 2004). Nevertheless, while the available studies revealed an inconsistent picture, comparison to our work is difficult because different research questions were addressed and in different populations with respect to age, gender and health for example. Thus, further investigations of the effects of different *COMT* polymorphism on the relationships among sleep–wake habits, food intake and body mass regulation are warranted.

Our analyses disclosed no epistatic interactions between *DAT1* and *COMT* polymorphisms on rest-activity cycles, subjective sleepiness or actimetry-derived sleep timing in humans. The lack of such interactions may reflect the different regional distributions of DAT and COMT proteins in the brain. DAT is solely found in striatum (Ciliax et al., 1995), whereas COMT is mostly expressed in prefrontal cortex and to a lower extent in striatum (Meyer-Lindenberg et al., 2005; Tunbridge et al., 2006). Although the basal ganglia, including striatum, may be actively involved in regulating sleep–wake behavior (Lazarus et al., 2013), the main role of the dopaminergic neurons in the striatum is the regulation of motor activity. Indeed, $Dat^{-/-}$ mice display clear hyperactivity (Giros et al., 1996), and a *DAT* loss of function mutation in humans causes infantile Parkinsonism-Dystonia with slow movements, rigidity and rest tremor (Kurian et al., 2009). Although our data were obtained in a rather small number of healthy individuals and await independent replication, they may be in line with the clinical manifestation of this fatal mutation.

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DECLARATION OF INTEREST

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