DOPAMINERGIC ROLE IN REGULATING NEUROPHYSIOLOGICAL MARKERS OF SLEEP HOMEOSTASIS IN HUMANS

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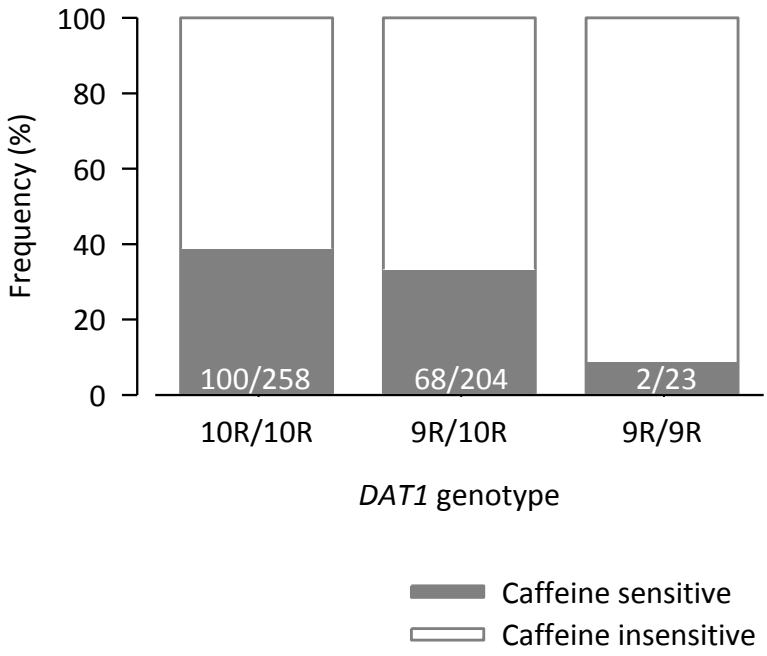
Online supporting supplemental information

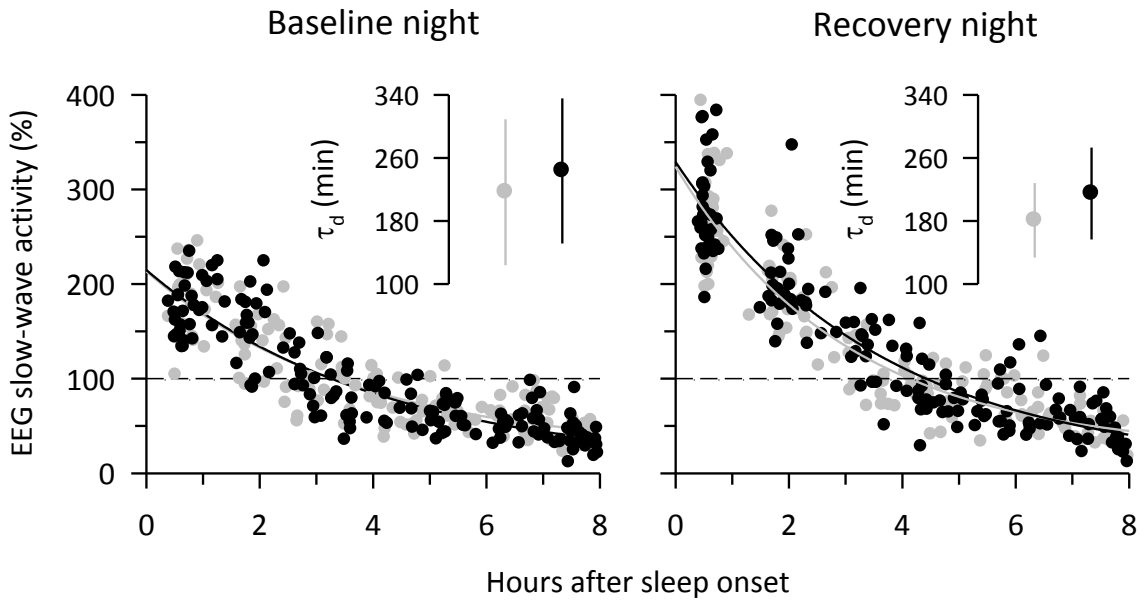
Dopamine transporter (DAT1) genotype affects self-rated caffeine sensitivity

Figure S1. *Five-hundred and four healthy adults rated themselves as either being caffeine sensitive or caffeine insensitive. Numerators and denominators at the bottom of the bar represent the numbers of caffeine sensitive individuals and the total numbers of subjects in each genotype. The proportion of sensitive individuals differed among the genotypes ($p < 0.008$, Fisher's exact test).*



Exponential decay of EEG slow wave activity in 10R/10R and 9R allele carriers of DAT1

Figure S2. *Exponential decay of homeostatically regulated EEG slow-wave activity (SWA, 0.5-4.5 Hz) in non-rapid-eye-movement (NREM) sleep in baseline (left) and recovery (right) nights. Individual SWA values in NREM sleep episodes 1-4, expressed as a percentage of the corresponding all-night value in baseline (horizontal dashed line at 100 %), were plotted at episode midpoint relative to sleep onset. The lines represent exponential decay fits of the homeostatic process S, in 10R/10R (black dots, black line) and 9R (grey dots, grey line) carriers. Insets: Time constants (τ_d ± 95% confidence interval) represent the best exponential decay fits. Overlapping confidence intervals suggest that τ_d did not differ between 10R/10R and 9R genotypes.*



Modeling of the homeostatic Process S was performed as described by (Rusterholz et al., Sleep 33:491–498, 2010). To summarize, individual SWA (0.5-4.5 Hz) in NREM sleep was normalized to whole-night baseline levels and plotted against individual NREM sleep episode midpoints. Decreasing exponential functions were fitted to mean episodic SWA values using the function:

$$S(t) = (S_0 - LA) \cdot \exp\left(-\frac{t}{\tau_d}\right) + LA$$

Where S(t) is the time dependent homeostatic process, S_0 is the level of S at sleep onset, *LA* is the lower asymptote required to be positive whereas the time constant, τ_d, reflects the dissipation of sleep pressure during sleep. To investigate effects of the DAT1 polymorphism, the fit was done separately in 10R/10R and 9R allele carriers in baseline and recovery nights.

Prolonged wakefulness increases number, amplitude, and slope of EEG slow waves in NREM sleep

Figure S3. *Effect of sleep deprivation on amplitude (**A** & **B**), slope (**C** & **D**) and number (**E** & **F**) of positive (left) and negative (right) slow (0.5-2.0 Hz) half-waves in NREM sleep in baseline (continuous lines) and recovery nights (dotted lines) in 10R/10R (gray, n = 30) and 9R (black, n = 27) genotypes of DAT1. Except for negative half-waves between 0.8-1.1 Hz, sleep deprivation increased amplitude,*

slope and number of half-waves (3-way mixed model ANOVA 'condition': $F_{1,55} > 93.7$, $p_{all} < 0.0001$). The sleep deprivation-induced increase in the number of negative and positive slow half was significantly larger in 10R/10R carriers than in 9R carriers of DAT1. Three-way mixed model ANOVA: 'condition': $F_{1,55} \geq 3977.0$, $p \leq 0.0001$; 'genotype': ns; 'frequency bin': $F_{15,825} \geq 55.3$, $p \leq 0.0001$; 'genotype' × 'deprivation': $F_{1,55} \geq 40.6$, $p \leq 0.0001$; 'condition' × 'frequency bins': $F_{15,840} \geq 35.9$, $p \leq 0.0001$; 'genotype' × 'frequency bins': ns. Triangles on top of the panels indicate frequency bins that were significantly affected by sleep deprivation ($p < 0.05$, 2-tailed paired t-tests).

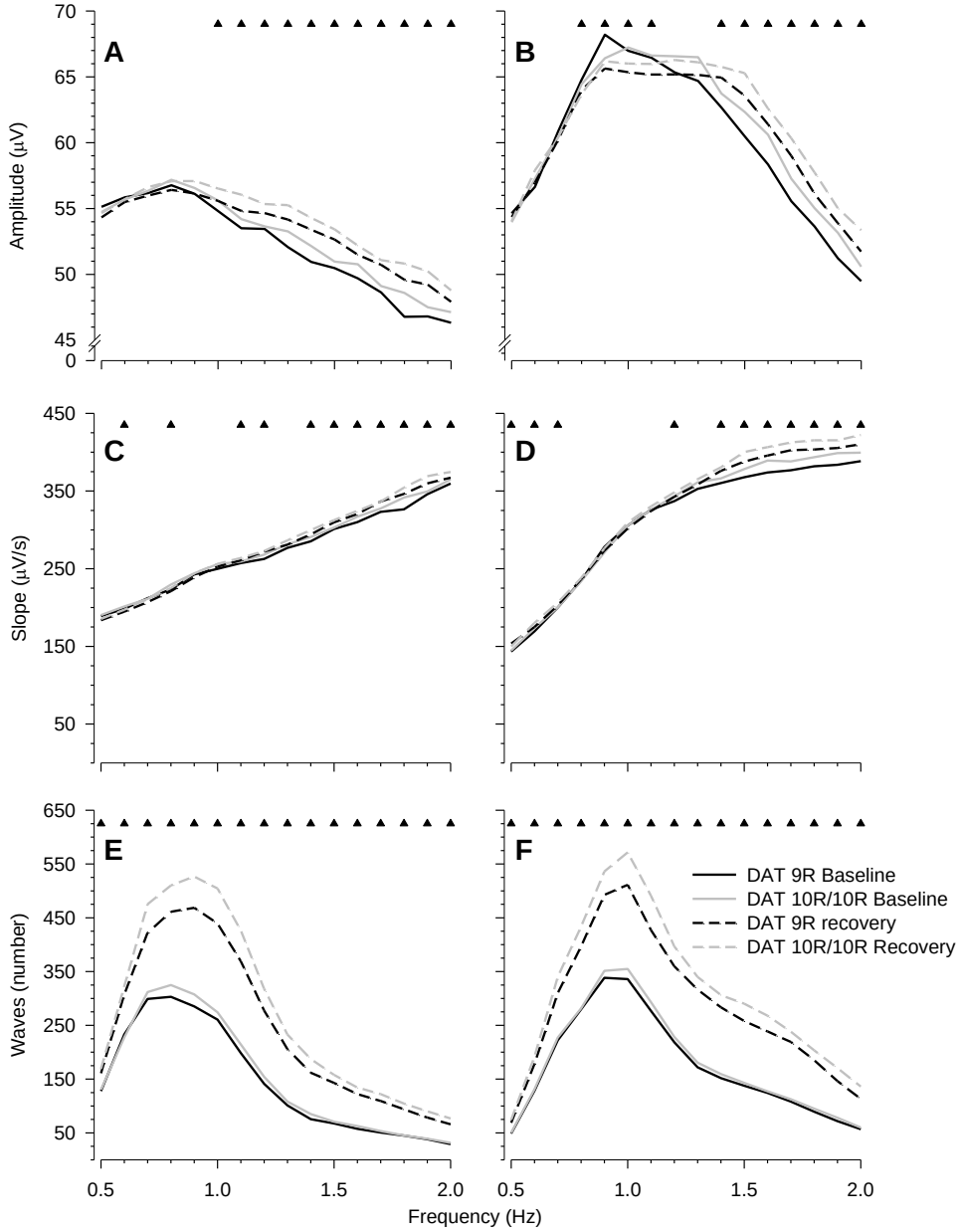


Table S1: Visually scored sleep variables in 10R/10R (n = 30) and 9R allele carriers (n = 27) of *DAT1*.

	10R/10R		9R allele carriers		*'genotype'*	*'condition'*	*'genotype'* x *'condition'*
	Baseline	Recovery	Baseline	Recovery	$F_{1,55}$, p	$F_{1,55}$, p	$F_{1,55}$, p
Sleep efficiency (%)	93.4 ± 0.7	97.2 ± 0.2	93.1 ± 0.7	97.1 ± 0.2	0.2, 0.67	61.8, <0.0001	0.1, 0.76
Stage 1 (min)	37.0 ± 2.5	18.9 ± 2.3	33.0 ± 2.4	16.6 ± 1.9	1.1, 0.30	163.0, <0.0001	0.4, 0.55
Stage 2 (min)	221.0 ± 6.4	200.0 ± 7.0	213.0 ± 5.3	203.0 ± 7.7	0.1, 0.77	21.3, <0.0001	3.0, 0.09
SWS (min)	93.6 ± 6.5	158.0 ± 7.1	100.0 ± 5.4	149.0 ± 6.8	0.0, 0.91	639.9, <0.0001	11.0, 0.002
NREM sleep (min)	315.0 ± 4.0	357.0 ± 4.6	313.0 ± 4.0	352.0 ± 5.7	0.4, 0.53	150.1, <0.0001	0.2, 0.64
REM sleep (min)	96.4 ± 3.3	90.2 ± 4.5	101.0 ± 3.3	97.3 ± 5.3	1.2, 0.27	2.5, 0.12	0.2, 0.63
MT (min)	9.4 ± 0.8	9.7 ± 0.8	10.7 ± 0.8	9.3 ± 0.6	0.2, 0.65	1.6, 0.21	3.2, 0.08
WASO (min)	9.0 ± 2.6	0.8 ± 0.4	5.3 ± 1.3	0.9 ± 0.3	1.4, 0.25	17.3, 0.0001	1.6, 0.22
Sleep latency (min)	13.1 ± 2.1	3.1 ± 0.4	17.2 ± 3.1	3.8 ± 0.5	1.6, 0.22	42.6, <0.0001	0.9, 0.34
REM latency (min)	70.1 ± 4.1	83.2 ± 7.8	64.6 ± 3.0	70.9 ± 3.5	0.2, 0.67	61.8, <0.0001	0.1, 0.76

Values represent means ± SEM in baseline and recovery nights. Analyses of the recovery nights were restricted to 480 minutes. Sleep efficiency: percentage of total sleep time per 480 minutes. Stages 1, stage 2 and SWS: non-rapid-eye-movement (NREM) sleep stages. REM sleep: rapid-eye-movement sleep. MT: movement time. WASO: wakefulness after sleep onset. Sleep latency: time from lights-out to the first occurrence of stage 2 sleep. REM latency: time from sleep onset to the first occurrence of REM sleep.

F- and p-values: Two-way mixed-model ANOVA with factors *'genotype'* (10R/10R, 9R) and *'condition'* (baseline, recovery).