# Serum brain-derived neurotrophic factor (BDNF) in sleep-disordered patients: relation to sleep stage N3 and rapid eye movement (REM) sleep across diagnostic entities

MICHAEL DEUSCHLE[1], MICHAEL SCHREDL[1], CHRISTIAN WISCH[1], CLAUDIA SCHILLING[1], MARIA GILLES[1], OLGA GEISEL[2] and RAINER HELLWEG[2]

[1]Central Institute of Mental Health, Department of Psychiatry and Psychotherapy, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [2]Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany

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**Correspondence**
Michael Deuschle, MD, Central Institute of Mental Health, J5, 68159 Mannheim, Germany.
Tel.: 0049 621 1703 2331;
fax: 0049 621 1703 2325
e-mail: michael.deuschle@zi-mannheim.de

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**SUMMARY**

Experimental and clinical evidence suggests an association between neuroplasticity, brain-derived neurotrophic factor and sleep. We aimed at testing the hypotheses that brain-derived neurotrophic factor is associated with specific aspects of sleep architecture or sleep stages in patients with sleep disorders. We included 35 patients with primary insomnia, 31 patients with restless legs syndrome, 17 patients with idiopathic hypersomnia, 10 patients with narcolepsy and 37 healthy controls. Morning serum brain-derived neurotrophic factor concentrations were measured in patients and controls. In patients, blood sampling was followed by polysomnographic sleep investigation. Low brain-derived neurotrophic factor levels were associated with a low percentage of sleep stage N3 and rapid eye movement sleep across diagnostic entities. However, there was no difference in brain-derived neurotrophic factor levels between diagnostic groups. Our data indicate that serum levels of brain-derived neurotrophic factor, independent of a specific sleep disorder, are related to the proportion of sleep stage N3 and REM sleep. This preliminary observation is in accordance with the assumption that sleep stage N3 is involved in the regulation of neuroplasticity.

## INTRODUCTION

There is evidence from rodent research that neuroplasticity and sleep are intertwined phenomena. Especially, sleep stage N3, or slow-wave sleep, is assumed to be a sensitive marker of cortical synaptic strength and network synchronization (Esser *et al.*, 2007). Moreover, it has been shown that cortical brain-derived neurotrophic factor (BDNF), a modulator of neuroplasticity, induces sleep stage N3 in the subsequent sleep period (Faraguna *et al.*, 2008). From findings in adolescent mice it could be concluded that sleep is associated with neuronal spine loss (Maret *et al.*, 2012). Tononi's synaptic homeostasis hypothesis proposes that "sleep is the price the brain pays for plasticity": synaptic potentiation may occur primarily in the awake stage, when the individual interacts with the environment, while renormalization of synaptic strength and neuronal spine loss may happen mainly during sleep (Tononi and Cirelli, 2014). This hypothesis is based on rodent research, but may provide a framework for understanding the relationship between sleep, neuroplasticity and learning in healthy subjects and patients with neuropsychiatric disorders.

In humans, there are several sources of evidence associating neurotrophic factors with sleep. First, the BDNF Val66Met genotype is related to polysomnographic features, with Met carriers showing decreased spectral power in the alpha band in N1 stage and decreased theta power in N2 and sleep stage N3 (Guindalini *et al.*, 2014). In contrast, homozygous Val carriers had higher sleep stage N3 intensity compared with Val/Met carriers (Bachmann *et al.*, 2012). Second, in healthy controls and patients with a lifetime diagnosis of restless legs syndrome (RLS) or periodic limb movement (Giese *et al.*, 2013), as well as in female patients with disturbed sleep (Nishich *et al.*, 2013), sleep disturbances are related to low BDNF. In contrast, in patients with narcolepsy being characterized by daytime sleepiness and increased rapid eye movement (REM) sleep, serum BDNF was found to be increased (Klein *et al.*, 2013).

Next to these epidemiological and clinical observations, the association of sleep with BDNF has mainly been examined in pharmacological studies in depressed patients, as it is widely accepted that the expression of BDNF is reduced in the brain and blood of patients with affective disorders (Lee *et al*., 2007). First, it was shown that in depressed patients, sleep disturbance is related to low plasma levels of BDNF (Dell'Osso *et al*., 2010). In addition, ketamine has been identified to regulate sleep stage N3 and brain BDNF levels in depressed patients in a coordinated manner (Duncan *et al*., 2014). Lastly, it has repeatedly been shown that antidepressants acting on monoamines may increase BDNF concentrations in animals and depressed patients (Brunoni *et al*., 2008; Nibuya *et al*., 1995). Within this context, however, a considerable heterogeneity was observed with some antidepressants having strong effects, while others may hardly change BDNF concentrations (Molendijk *et al*., 2011). Our research showed the effect of various antidepressants on serum BDNF to differ (amitriptyline > paroxetine; mirtazapine > venlafaxine; Deuschle *et al*., 2013; Hellweg *et al*., 2008). Based on these data, it may be hypothesized that antidepressants with sleep-promoting properties (amitriptyline, mirtazapine) have stronger effects on serum BDNF than antidepressants without major effects on sleep (paroxetine, venlafaxine). These findings contributed to the neurotrophin hypothesis of depression (Duman and Monteggia, 2006), with stress and neuroplasticity being considered key elements in the pathophysiology of affective disorders (MacQueen and Frodl, 2011). In contrast to depression, BDNF levels in sleep disorders received less attention.

Taken together, substantial experimental and clinical evidence suggests an association between daytime neuroplasticity and BDNF on the one hand and nighttime sleep on the other. However, it is not clear whether BDNF, as a presumable marker of neuroplasticity, is related to sleep efficiency or duration per se or rather to a specific sleep stage. Our study tested the hypotheses that morning BDNF is related to: (1) specific sleep disorders; or (2) sleep efficiency or specific sleep stages in the following night. We investigated a heterogeneous group of patients with sleep disorders rather than a homogenous group of healthy controls in order to cover more variance of sleep variables.

## MATERIALS AND METHODS

### Subjects

This study was approved by the local ethics committee of the Medical Faculty Mannheim, University of Heidelberg, registered at German Clinical Trials Register (DRKS00008902), and all subjects gave fully informed written consent prior to the investigation. Thirty-five patients with primary insomnia, 31 patients with RLS, 17 patients with idiopathic hypersomnia, 10 patients with narcolepsy and 37 healthy controls were included (Table 1). In our patient sample, 19 subjects were smokers and 74 were non-smokers. Except in the RLS group, we included only subjects with periodic limb movement with arousal index (PLMI) $<5\ h^{-1}$ (all subjects: PLMI with arousals 0–4.8 $h^{-1}$). Also, we excluded all subjects with an apnea–hypopnea index (AHI) of 5 or more per hour (all subjects, except one narcolepsy patient: AHI: 0–4.5 $h^{-1}$). In line with their rather young age, there were only a few patients suffering from physical disorders, which were all considered not to be related to the sleep disorder: hypothyroidism (three RLS, seven insomnia, one hypersomnia); hypertension (six RLS, six insomnia); arthrosis; lumbago or pain (six RLS, two insomnia, one narcolepsy); type 2 diabetes (one RLS, one insomnia, one narcolepsy); airway disorders [one asthma bronchiale (insomnia); one chronic obstructive pulmonary disease (RLS)]; mostly with adequate treatments. Four patients had psychiatric diagnoses and suffered from current mild to moderate depression (one

**Table 1** BDNF serum concentrations as well as sleep parameters of patients with sleep disorders and healthy controls

| | *Primary insomnia (n = 35)* | *RLS (n = 31)* | *Idiopathic hypersomnia (n = 17)* | *Narcolepsy (n = 10)* | *Healthy controls (n = 37)* | *ANCOVA: effect of diagnosis (covariates: age, nicotine)* |
|---|---|---|---|---|---|---|
| Sex (f/m) | 22/13 | 15/16 | 6/11 | 5/5 | 24/13 | |
| Age (years) | 47.2 ± 11.4 | 45.8 ± 15.5 | 29.2 ± 10.1 | 37.3 ± 16.6 | 49.2 ± 11.3 | $F_{4,125} = 8.66$; $P = 0.001$ |
| BMI (kg $m^{-2}$) | 24.8 ± 3.5 | 25.1 ± 4.8 | 24.9 ± 4.0 | 26.2 ± 2.3 | 24.8 ± 3.5 | n.s. |
| Polysomnography | | | | | | |
| Total sleep time (min) | 365 ± 57 | 342 ± 66 | 385 ± 38 | 362 ± 52 | n.a. | $F_{3,89} = 2.21$; $P = 0.092$ |
| Sleep latency (min) | 15.5 ± 11.1 | 27.0 ± 38.9 | 13.3 ± 8.7 | 15.0 ± 9.9 | n.a. | n.s. |
| WASO (min) | 71 ± 47 | 59 ± 47 | 38 ± 28 | 65 ± 42 | | $F_{3,89} = 2.26$; $P = 0.087$ |
| Sleep efficiency (%) | 80.0 ± 11.7 | 78.0 ± 12.6 | 87.6 ± 6.8 | 76.9 ± 20.4 | n.a. | $F_{3,89} = 2.56$; $P = 0.060$ |
| N1 stage (%) | 10.1 ± 4.3 | 12.1 ± 7.6 | 9.0 ± 4.3 | 18.0 ± 11.0 | n.a. | $F_{3,89} = 4.84$; $P = 0.004$ |
| N2 stage (%) | 51.0 ± 9.7 | 47.0 ± 10.3 | 52.8 ± 4.7 | 40.4 ± 15.0 | n.a. | $F_{3,89} = 4.25$; $P = 0.007$ |
| N3 stage (%) | 7.6 ± 7.5 | 10.9 ± 11.8 | 12.3 ± 7.8 | 5.1 ± 8.5 | n.a. | n.s. |
| REM (%) | 14.8 ± 6.1 | 15.4 ± 5.9 | 16.9 ± 4.9 | 21.4 ± 9.2 | n.a. | $F_{3,89} = 3.22$; $P = 0.026$ |
| BDNF (pg $L^{-1}$) | 4352 ± 1403 | 4217 ± 1256 | 3804 ± 1329 | 3651 ± 1671 | 4139 ± 1359 | n.s. |

BDNF, brain-derived neurotrophic factor; BMI, body mass index; REM, rapid eye movement; RLS, restless legs syndrome; WASO, wake after sleep onset.

narcolepsy) or major depressive disorder in remission (two RLS) or obsessive compulsive disorder (one insomnia). Some patients had been using Z-drugs, benzodiazepines or sedating antidepressants that had been discontinued at least 6 days before polysomnography (18 insomnia, eight RLS). All other drug treatments were continued.

### Diagnostic and study procedures

Our sleep laboratory is a referral centre for patients with probable neuropsychiatric sleep disorders. Patients were recruited consecutively from our clinical outpatient department for inclusion in the study. All diagnostics were performed within routine diagnostic procedures according to ICSD-2 criteria. Organic, substance-related or psychiatric causes of sleep disorders were excluded by means of clinical interview, physical examination, electrocardiogram (ECG) and laboratory investigations. Blood was drawn after the adaptation night at 08:30 hours, and serum was immediately frozen and stored at −80°C. Similar to sleep laboratory patients, healthy controls underwent physical examination and clinical interview to exclude psychiatric disorders and physical disorders that may affect sleep or BDNF in serum. In healthy controls we found no clinical evidence for sleep disorders by examination or interview, and blood was drawn using the same procedures as in patients.

#### *Polysomnography*

In patients, but not in controls, polysomnography was performed using a standard polysomnography montage according to the criteria of the American Academy of Sleep Medicine (AASM). This included electroencephalography (EEG) in seven derivations (F4-A1, C4-A1, O2-A1, Cz-A1, F3-A2, C3-A2 and O1-A2), left and right electrooculography, chin electromyography, surface electromyography of both tibialis anterior muscles, and recording of ECG and respiratory variables. The EEG sampling rate was 256 $s^{-1}$. Sleep stage scoring and detection of arousals for each 30-s epoch was performed visually according to standard AASM procedures (Berry *et al.*, 2015). All patients were investigated by polysomnography for two consecutive nights, with the first night being considered an adaptation night. During the second night, we determined sleep latency and efficiency as well as percentage of sleep stages N1, N2 and N3 and REM sleep.

#### *BDNF*

Blood was drawn, centrifuged (800 ***g*** for 15 min) and serum samples stored at −80°C until concentrations of BDNF were determined. BDNF serum concentrations were quantified by a modified enzyme immunoassay (Promega, Madison, WI, USA), as described previously (Deuschle *et al.*, 2013; Hellweg *et al.*, 2008). This assay has a detection limit of 0.7 pg $mL^{-1}$ serum BDNF, the coefficients of inter- and intra-assay variation are 34.1% and 6.7%, respectively (Hellweg *et al.*, 2006, 2008; Ziegenhorn *et al.*, 2007).

#### *Statistics*

First, we tested the association of age, body mass index (BMI), sex and smoking status (Giese *et al.*, 2014) with BDNF using ANCOVA in order to identify confounders. Age ($F_{1,87} = 2.3$; $P = 0.12$; $r = 0.19$; $P = 0.07$) and nicotine use ($F_{1,87} = 3.7$; $P = 0.059$) were related, by trend, with BDNF and were considered covariates in the next steps of analysis, while BMI and sex were not related to BDNF. In the second step, we used ANCOVA with age and nicotine use as covariates to test the association of sleep disorder diagnoses with BDNF. In the third step, we used univariate ANOVA and multiple linear regression with sleep parameters (sleep efficiency; percentage of REM, N3 and combined stage N1 and N2 sleep) as independent parameters, age and nicotine use as covariates, and BDNF as dependent parameter. In a fourth and explorative step, we added the latency of the first REM period or arousal index in total sleep time or wakefulness after sleep onset to the model. Because the Kolmogorov–Smirnov test rejected the hypothesis of normal distribution for all relevant sleep variables (sleep-onset latency, sleep efficiency, combined stage N1 and N2 sleep, sleep stage N3 sleep, REM sleep), we used ln-transformed variables. Statistical significance was assumed at the alpha level of 0.05.

## RESULTS

### Sleep disorders and polysomnography

Controlling for age and nicotine use, we found significant differences with regard to stage N1 and stage N2 and REM sleep between the groups of patients with sleep disorders. All polysomnography sleep parameters showed a pattern that was in accordance with the clinical diagnoses (Table 1).

### BDNF and sleep disorders

Age differed significantly between groups of patients with sleep disorders and healthy controls (*t*-test: $P = 0.013$), as well as within diagnostic subgroups (ANOVA: $F_{3,89} = 8.33$; $P = 0.001$). Especially, patients with primary hypersomnia were significantly younger than healthy controls. Also, age was related to BDNF and, therefore, controlled for as a potential confounder. Using ANCOVA, controlled for age and nicotine use, we did not find significant group differences in BDNF levels between sleep disorder patients and healthy controls (Table 1).

### BDNF and sleep parameters

Controlling for age and nicotine use, our model (independent variables: sleep efficiency; percentage of REM, N3 and

combined stage N1 and N2 sleep) was of significance with regard to BDNF ($F_{6,79} = 2.57$; $P = 0.025$): the covariate age ($F_{1,79} = 4.03$, $\beta = 0.28$; $P = 0.061$), but not nicotine use, was related by trend with BDNF. Regarding the sleep variables, we found significant associations of sleep stage N3 ($F_{1,78} = 5.37$; $P = 0.023$) and REM sleep ($F_{1,79} = 5.31$; $P = 0.024$) with BDNF. There was no association of stage 1 and 2 sleep or sleep efficiency (all $F < 2.1$) with BDNF. Accordingly, a multiple linear regression model with BDNF as dependent variable and sleep stage N3 ($\beta = 0.40$; $P = 0.007$), REM ($\beta = 0.31$; $P = 0.020$), sleep efficiency (n.s.), stage N1 and N2 sleep (n.s.) and age ($\beta = 0.29$; $P = 0.021$) as independent variables was of significance ($F_{5,80} = 2.88$; $P = 0.019$).

### BDNF and latency of first REM episode, arousal index, wakefulness after sleep onset

In an explorative approach we added other sleep variables to the above-mentioned model. Adding the latency of the first REM episode showed a significant association with BDNF ($F_{1,75} = 6.02$; $P = 0.016$) without changing the effects of N3 ($F_{1,75} = 4.78$; $P = 0.032$) or REM sleep ($F_{1,75} = 10.56$; $P = 0.002$). Adding wake after sleep onset (WASO) to the model revealed a trend association ($F_{1,78} = 3.65$; $P = 0.060$) and diminished the effects of sleep stage N3 ($F_{1,78} = 2.25$; n.s.) and REM sleep ($F_{1,78} = 3.95$; $P = 0.050$). Adding arousal index in total sleep time ($F_{1,78} = 0.005$; n.s.) or total sleep time ($F_{1,78} = 0.041$; n.s.) to the model did not reveal additional effects.

## DISCUSSION

We tested the hypotheses that morning BDNF is related to: (1) specific sleep disorders; or (2) specific sleep stages in the following night and, to the best of our knowledge, this is the first study using polysomnography to investigate a potential association between BDNF in serum and specific sleep stages in patients with sleep disorders. First, our data indicate that BDNF in serum is not significantly related to a specific sleep disorder. Second, independent of the nature of a specific sleep disorder, low percentage of sleep stage N3 sleep as well as low percentage of REM sleep are related to low serum BDNF.

With regard to our first observation, there is evidence that narcolepsy is related to increased BDNF (Klein *et al*., 2013) and insomnia to low BDNF (Giese *et al*., 2014). However, this is the first systematic study including and comparing various sleep disorders. Our data do not confirm the assumption that a specific sleep disorder or diagnosis is related to BDNF and, thus, BDNF may not be considered a 'diagnostic marker' for a specific sleep disorder.

Regarding our second observation of BDNF being positively associated to stage N3 sleep and REM sleep latency and duration, we are not aware of other studies relating BDNF to specific sleep stages. The association of stage N3 with BDNF lost significance after adding WASO to the model, which might be due to the strong interaction of these variables. Several psychiatric and sleep disorders are showing both specific changes of sleep stages and BDNF. Depression, for example, is related to low BDNF (Brunoni *et al*., 2008) as well as impaired sleep stage N3 (Riemann *et al*., 2001). Also, narcolepsy is related to both increased REM sleep and BDNF (Klein *et al*., 2013). Moreover, there is limited evidence that REM sleep deprivation inhibits BDNF expression in the rat brain (Sei *et al*., 2000; Shaffery and Lopez, 2013). Thus, our findings are in accordance with independent clinical and experimental observations.

Of course, due to the non-interventional nature of our data, we may only speculate about the direction of this association. However, there is some evidence for BDNF to be involved in the regulation of sleep stage N3 sleep. For example, slow-wave activity in recovery sleep after sleep deprivation was found to be higher in BDNF Val/Val compared with Val/Met genotype (Bachmann *et al*., 2012). Moreover, BDNF was shown to have direct effects on rodents' sleep stage N3 regulation: intracerebroventricular BDNF application during waking state was found to increase slow-wave activity in subsequent sleep in rats (Faraguna *et al*., 2008), but also REM sleep in rabbits (Sei *et al*., 2000). Our findings are in accordance with these reports and show BDNF to be positively related to sleep stage N3 sleep and REM. With regard to the clinical example of major depressive disorder, some antidepressants may induce BDNF thereby potentially leading to improved sleep (Deuschle *et al*., 2013).

Finally, we consider it a limitation that our healthy controls could not be investigated with polysomnography. However, the inclusion of healthy controls did allow us to show that patients with sleep disorders do not have a general deviation of BDNF in serum. Also, the heterogeneity, especially with regard to age, may be considered a limitation for our analyses. Ideally, future studies should provide information on power in the delta range.

Taken together, our data indicate that low sleep stage N3 and REM sleep, independent of a specific sleep disorder, are related to low BDNF. These findings extend the increasingly acknowledged impact of an interplay between stress and sleep on BDNF levels (Schmitt *et al*., 2016).

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## AUTHOR CONTRIBUTORSHIP

MD and MS designed the study; MS and CS were responsible for polysomnography and sleep analysis; CW organized the data bank and was (together with MD and MG) responsible for the statistical analysis; OG and RH did the laboratory work; MD wrote the first draft of the paper; and all authors contributed to the discussion.

## CONFLICT OF INTEREST

None of the authors reports any conflict of interest.

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