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Insomnia Does Not Appear to be Associated With Substantial Structural Brain Changes

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Study Objectives: Sleep has been demonstrated to significantly modulate brain plasticity and the manifestation of mental disorders. However, previous studies on the effect of disrupted sleep on brain structure have reported inconsistent results. The goal of the current study was to investigate brain morphometry in a well-characterized large sample of patients with primary insomnia (PI) in comparison with good sleeper controls.
Design: Automated parcellation and pattern recognition approaches were supplemented by voxelwise analyses of gray and white matter volumes to analyze magnetic resonance images. All analyses included age, sex, and total intracranial volume as covariates.
Setting: Department of Psychiatry and Psychotherapy of the University of Freiburg Medical Center.
Participants: There were 28 patients with PI (10 males; 18 females; age 43.7 ± 14.2 y) and 38 healthy, good sleepers (17 males; 21 females; age 39.6 ± 8.9 y).
Interventions: N/A.
Results: No significant between-group differences were observed in any of the investigated brain morphometry variables.
Conclusions: Altered brain function in insomnia does not appear to have a substantial effect on brain morphometry on a macroscopic level.
Keywords: Hippocampus, MRI, primary insomnia, sleep, support vector machine, voxel-based morphometry
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INTRODUCTION

Chronic insomnia is one of the most prevalent health complaints worldwide and its prevalence is expected to further increase with the aging of society.[1] It affects approximately 10% of the population in western industrialized countries.[2] Primary insomnia (PI), defined as sleep complaints in the absence of any related medical or psychiatric condition, is estimated to affect 2% to 4% of the adult population.[2] In most affected individuals, insomnia is a chronic condition. More than 70% of the people currently experiencing insomnia will still suffer from it next year.[3] Chronic insomnia is associated with a marked reduction in quality of life, increased fatigue, cognitive impairments, mood disturbances, and physical complaints.[4,5] Importantly, insomnia confers an increased risk for psychiatric disorders, especially depression,[6] and there is evidence that chronic sleep loss is a risk factor for cardiovascular disease and increased mortality.[7] Accordingly, insomnia leads to a substantial increase in health care consumption and to a high rate of absenteeism, and consequently, to high costs for society. For the United States, the costs of insomnia due to low work performance and absenteeism have been estimated to exceed $60 billion per year.[8] Thus, insomnia significantly contributes to the major diseases of our aging society and to a significant part of the health expenses.

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Central nervous system hyperarousal is believed to represent a major pathophysiologic pathway in the development and maintenance of insomnia[9-11]; however, few neuroimaging studies have examined the neurologic abnormalities of the disorder. Three recent investigations have focused on the association between insomnia and morphometric changes of the brain.[12-14] In a pilot study, we investigated eight patients with PI and eight healthy good sleepers with a manual tracing method and found reduced bilateral hippocampal volumes,[12] which was supported by basic science research showing that chronic sleep deprivation has an effect on hippocampal morphology.[15,16] Furthermore, sleep duration was shown to be associated with hippocampal volumes in children[17] and insomnia severity was associated with hippocampal volumes in a study on patients with posttraumatic stress disorder.[18] However, a study by Winkelman et al.[13] failed to show reduced hippocampus gray matter volumes using manual tracing in 20 patients with PI in comparison with 15 healthy good sleepers. These inconsistent results might stem from methodologic differences (e.g., different segmentation protocols) and heterogeneity with regard to insomnia duration and severity. Additionally, age differences between study samples might account for differing results. Winkelman et al.[13] investigated a community sample with a mean age of approximately 40 y and used a segmentation protocol that was restricted to core areas of the hippocampus. We, instead, investigated clinically referred patients with a mean age of approximately 48 y and followed the Watson protocol to measure the volumes of the hippocampus.[19] In the third morphometric study in insomnia patients, Altena et al.[14] used voxel-based morphometry without *a priori* definition of regions of interest investigating an elderly sample (24 patients with PI, 13 healthy good sleepers) with a mean age of approximately 60 y. In this sample, the authors reported reduced orbitofrontal and precu-

neus gray matter volumes but no between-group differences in the hippocampal region.

In summary, previous findings regarding brain morphology alterations of insomnia patients have been based on relatively small samples and provided inconsistent results. Therefore, the current study aimed at investigating brain morphometry in a clinically referred and well-characterized large sample of patients with PI. We extended previous work by using a multimethod approach including an automated brain segmentation algorithm (FreeSurfer software, version 5.1.0 (http://surfer.nmr.mgh.harvard.edu/),[20] an automated classification algorithm (support vector machine)[21] based on FreeSurfer-derived cortical volume and thickness estimates, and voxel-based morphometry.[22] In comparison with the other methods, the machine-learning classification algorithm is multivariate and takes specific interregional dependencies into account. Its high sensitivity has been demonstrated for a number of neurologic and psychiatric conditions.[23] The specific hypotheses of the current study were: (1) patients with PI have reduced gray matter volumes in automatically segmented hippocampal volumes; (2) magnetic resonance imaging (MRI)-derived brain volume and cortical thickness estimates can reliably distinguish patients with PI from healthy good sleepers using an automated classification algorithm; (3) voxel-based morphometry reveals gray and/or white matter volume differences between patients with PI and healthy good sleepers.

MATERIAL AND METHODS

Participants

Twenty-eight patients meeting diagnostic criteria for PI according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision[24] and 40 good sleeper controls were included in the current study. Insomnia patients were referred to our sleep disorders clinic by their primary care provider or medical specialist. Healthy controls were recruited through local advertisements. Two control participants were excluded from the analysis because of pathologic MRI scans. Thus, the final sample consisted of 28 patients with PI and 38 good sleeper controls.

A semistandardized psychiatric and sleep-related interview was conducted by an experienced psychiatrist to rule out any history of psychiatric disorder, shift work, or sleep disorder (including hypersomnia, parasomnia, sleep related breathing disorder, sleep related movement disorder, and circadian rhythm sleep disorder). Furthermore, all participants underwent a standard physical examination, including electrocardiogram, electroencephalogram (EEG), and routine blood work (blood cell count; liver, renal and thyroid function) to exclude those with serious medical conditions. All participants were right-handed, as assessed with the Edinburgh Handedness Inventory[25] and free of any psychoactive medication at least 2 weeks prior to and during the study. Participants with periodic leg movements during sleep arousal index per total sleep time (TST) of more than 5.0 or a sleep apnea index per TST of more than 5.0 were not included in the current study.

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the University Medical Center Freiburg. All participants gave their informed written consent prior to inclusion in the study.

Polysomnography

All participants underwent 2 consecutive nights of polysomnography sleep monitoring. The first night served as an adaptation and screening night to rule out sleep apnea, periodic leg movements in sleep, and occult sleep disorder pathology. Sleep was recorded on 24-channel Sagura EEG-polysomnographs for 8 h from "lights out" (22:00 to 23:00) until "lights on" (06:00 to 07:00). All recordings included EEG (C3-A2; C4-A1), electrooculogram (horizontal and vertical) and electromyogram (submental), and were scored visually by experienced raters according to the American Academy of Sleep Medicine criteria.[26] All participants were screened for apneas and periodic leg movements by monitoring abdominal and thoracic effort, nasal airflow, oxymetry, and bilateral tibialis anterior EMG. Sleep recordings were evaluated for the following parameters of sleep continuity: TST; sleep efficiency (ratio of TST to time in bed × 100%); sleep onset latency defined as time from lights out until sleep onset (defined as first epoch of stage 2); wake after sleep onset (WASO) defined as difference between sleep period time (SPT; time from sleep onset until final awakening) and TST; number of awakenings; and arousal index. Sleep architecture parameters were amounts of stages 1 and 2 slow wave sleep (SWS) and rapid eye movement sleep (REM) as percentage of SPT. All participants had to refrain from alcohol, caffeine, and daytime naps during the recording days.

Questionnaires

Participants were asked to complete the Insomnia Severity Index (ISI),[27] the Pittsburgh Sleep Quality Index (PSQI),[28] the brief version of the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16),[29] the Glasgow Sleep Effort Scale (GSES),[30] the Pre-Sleep Arousal Scale (PSAS),[31] the Epworth Sleepiness Scale (ESS),[32] the Beck Depression Inventory (BDI),[33] and the State-Trait Anxiety Inventory (STAI).[34]

MRI Acquisition and Analysis

High-resolution T1-weighted MRI datasets were acquired on a 3-Tesla scanner (Magnetom TIM-Trio, Siemens, Erlangen, Germany) using an MPRAGE sequence (TR 2.2 sec; TE 2.6 msec; 160 sagittal slices of 256 × 256 voxels, 1.0 × 1.0 × 1.0 mm^3).[35] All scans were inspected for motion artefacts and for the absence of pathologic findings by a neurologist under the supervision of a board-certified neuroradiologist.

FreeSurfer-Based Univariate Analyses

Cortical surface reconstruction and volumetric segmentation was performed using the FreeSurfer software, version 5.1.0 (Athinoula A. Martinos Center for Biomedical Imaging; http://surfer.nmr.mgh.harvard.edu/). The technical details of this procedure have been described in previous publications[20,36,37] and good test-retest reliability has been demonstrated.[38] For quality control, segmentations were visually inspected for each participant by two independent raters (K.S. and W.R.) on a slice-by-slice basis. However, no manual corrections were necessary for the automatic segmentation results. Subcortical volumes ("aseg.stats" files) as well as cortical volume and thickness

values ("aparc.stats" files) based on the Killiany/Desikan cortical parcellation[39] were extracted from FreeSurfer, resulting in a total of 174 measures per participant. Statistical analyses were conducted in R (http://www.r-project.org/) with intracranial volume (ICV), age, and sex as covariates in all analyses. Analyses of covariance (ANCOVA) were carried out for investigating between-group differences in left and right hippocampal volumes. In these analyses, an uncorrected statistical threshold of $P < 0.05$ was used due to the *a priori* hypothesis concerning the hippocampus. Because several ANCOVAs were performed to assess between-group differences in hippocampus subsegments (subiculum, presubiculum, CA1, CA2/3, CA4/dentate gyrus, hippocampal fissure, and fimbria, as derived by the hippocampal subfield segmentation procedure of FreeSurfer), the thresholds for significance ($P < 0.05$) were adjusted to control for the false discovery rate (FDR).[40] Additionally, regression analyses were conducted to analyze the association between hippocampal volumes and the following parameters: ISI scores, TST in the second night, duration of insomnia, BDI scores, and trait STAI scores. The effect of lifetime history of hypnotic medication (none, benzodiazepine receptor agonists, other) on hippocampal volumes was determined by an ANCOVA analysis in the patients group. Between-group differences in the other FreeSurfer-derived measures were also tested with an FDR-adjusted threshold of $P < 0.05$ due to multiple testing. Analogous to the previously described analyses, between-group differences in hippocampal volumes and in the other FreeSurfer-derived variables were additionally investigated for the subsamples of sleep maintenance insomnia patients and mixed insomnia patients in comparison with the control group.

Support Vector Machine

A support vector machine[41] (SVM) was implemented in libsvm, an integrated software for support vector classification (http://www.csie.ntu.edu.tw/~cjlin/libsvm/). The SVM is a supervised pattern recognition approach. It is supervised in the sense that it learns to separate diagnostic groups (i.e., patients with PI versus good sleeper controls) from example images. The pattern detected from training data is then applied to new data not involved in the training. The SVM has two open parameters, the cost factor, C, and the filter fraction, F. The cost factor determines how much a misclassified example is penalized during training. The second parameter is the fraction of the features, ranked according to their t-score, that are used for classification. We tested the performance with either all, 1/2, 1/4, 1/8, or 1/16 of the features included in the analyses. The two parameters were optimized in a nested (two-level) leave-one-example-out cross-validation (LOO-CV) procedure to avoid optimistic results. Given N training examples, the LOO-CV procedure repeatedly leaves one example out, trains an "optimal model" with the parameter combination that yielded the highest performance using N-1 remaining examples, and then predicts the left-out example. As we included different numbers of patients with PI and good sleeper controls we report the balanced accuracy (BA) as the average of sensitivity and specificity.[42] One hundred seventy-four FreeSurfer-derived brain volume and cortical thickness values entered the classification pipeline as attributes describing macroscopic brain anatomy. Age, sex, and ICV entered the classification pipeline as additional attributes. The values were converted into z-scores (i.e., subtraction of mean and division by standard deviation) in order to homogenize the relative *a priori* relevance for classification. The performance of the classifier was reported as the mean BA, the 95% confidence interval limits, and the P value associated with the hypothesis that an equal or better result was obtained by chance.[42]

Voxel-Based Morphometry

Voxel-based morphometry (VBM) was performed using the Statistical Parametric Mapping (SPM8) software (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Structural images were segmented into gray matter, white matter, and cerebrospinal fluid using the standard segmentation procedure in SPM8, and the results were checked by visual inspection. A gray matter population template with a 1.5-mm cubic resolution was generated using DARTEL (diffeomorphic anatomical registration through exponentiated Lie algebra).[43] DARTEL-registered data were affine-transformed to Montreal Neurological Institute space (MNI; http://www.mni.mcgill.ca/). Then, all images were modulated to correct for volume changes during normalization, and smoothed with an 8-mm full-width at half-maximum gaussian smoothing kernel. Between-group differences in gray and white matter volumes were assessed using a threshold of $P < 0.05$, corrected for multiple comparisons by the family-wise error (FWE) method. As Altena et al.[14] reported reduced orbitofrontal and parietal gray matter volumes in patients with PI with a more liberal statistical approach, we additionally performed the previously mentioned analyses using an uncorrected voxel-wise threshold of $P < 0.001$ with a minimum cluster size of 25 voxels. Furthermore, regression analyses were performed to investigate associations between gray/white matter volumes and ISI scores (in the full sample) and insomnia duration (in the PI group) using an FWE-corrected threshold of $P < 0.05$. Age, sex, and total ICV were included as covariates of no interest in the statistical models applied.

RESULTS

Sample Characteristics

Demographic characteristics of the study sample are presented in Table 1. The groups did not differ significantly in sex distribution, age (patients with PI: 18-67 y, healthy good sleepers: 27-57 y) or body mass index. The patients with PI had significantly higher ISI, PSQI, DBAS-16, and GSES scores as well as higher scores on the cognitive subscale of the PSAS. BDI scores were increased in patients with PI even after excluding the two sleep related items (PI patients: 4.9 ± 3.8, healthy good sleepers: 3.0 ± 2.9, $t_{64} = 2.30$, $P = 0.025$). Furthermore, trait anxiety was increased as indicated by the trait subscale of the STAI. No significant group differences were found for the somatic subscale of the PSAS, the ESS, and the state subscale of the STAI.

Three insomnia patients suffered from sleep onset insomnia, eight from sleep-maintenance insomnia, and 16 from mixed insomnia. One patient had a complaint of nonrestorative sleep in the absence of difficulties initiating and maintaining sleep. The average duration of primary insomnia was 12.1 ± 11.0 y.

Table 1—Description of the study population (means ± standard deviations)

	Patients with PI	Healthy controls	t/χ^2	P
Sex (M/F)	10/18	17/21	0.54	0.461
Age (y)	43.7 ± 14.2	39.6 ± 8.9	1.42	0.160
BMI (kg/m²)	23.1 ± 2.2	23.2 ± 3.4	-0.15	0.882
ISI	15.5 ± 3.8	2.3 ± 2.3	17.30	< 0.001
PSQI	10.9 ± 3.0	3.9 ± 1.9	11.69	< 0.001
DBAS-16	4.5 ± 1.5	2.3 ± 1.1	6.89	< 0.001
GSES	6.6 ± 2.8	1.2 ± 1.5	10.09	< 0.001
PSAS - cognitive	17.8 ± 6.3	13.4 ± 4.2	3.42	0.001
PSAS - somatic	11.5 ± 3.8	10.2 ± 2.9	1.60	0.114
ESS	7.5 ± 4.7	6.7 ± 3.9	0.77	0.444
BDI	7.8 ± 4.3	3.5 ± 3.3	4.64	< 0.001
STAI - state	34.4 ± 7.7	34.0 ± 6.6	0.24	0.814
STAI - trait	39.4 ± 8.2	32.8 ± 7.3	3.43	0.001

BDI, Beck Depression Inventory; BMI, body mass index; DBAS, Dysfunctional Beliefs and Attitudes about Sleep Scale; ESS, Epworth Sleepiness Scale; GSES, Glasgow Sleep Effort Scale; ISI, Insomnia Severity Index; PSAS, Pre-Sleep Arousal Scale; PSQI, Pittsburgh Sleep Quality Index; STAI, State-Trait Anxiety Inventory.

Table 2—Polysomnographic data (means ± standard deviations)

First night	Patients with PI	Healthy controls	t	P
Total sleep time (min)	344.6 ± 62.6	380.5 ± 56.5	-2.43	0.018
Sleep efficiency (%)	72.0 ± 13.0	80.4 ± 10.0	-2.99	0.004
Sleep onset latency (min)	30.2 ± 18.0	20.6 ± 19.1	2.06	0.043
Wake after sleep onset (min)	93.4 ± 50.9	65.2 ± 39.9	2.53	0.014
Number of awakenings	33.3 ± 16.8	38.0 ± 15.8	-1.16	0.251
Arousal index / TST (h^{-1})	19.8 ± 7.6	20.1 ± 7.9	-0.15	0.884
Sleep apnea index / TST (h^{-1})	0.3 ± 0.7	0.4 ± 0.7	-0.83	0.409
PLMS arousal index / TST (h^{-1})	0.2 ± 0.5	0.4 ± 0.8	-0.77	0.442
Stage 1 (% SPT)	10.2 ± 4.9	11.2 ± 5.3	-0.77	0.445
Stage 2 (% SPT)	46.6 ± 10.0	50.1 ± 8.7	-1.51	0.137
SWS (% SPT)	7.7 ± 7.4	6.9 ± 6.6	0.45	0.651
REM (% SPT)	14.1 ± 4.2	17.2 ± 5.1	-2.63	0.011
Second night	**Patients with PI**	**Healthy controls**	**t**	**P**
Total sleep time (min)	379.1 ± 64.9	416.3 ± 24.0	-3.25	0.002
Sleep efficiency (%)	79.1 ± 13.6	86.7 ± 5.0	-3.22	0.002
Sleep onset latency (min)	18.6 ± 14.6	17.8 ± 16.5	0.22	0.829
Wake after sleep onset (min)	67.6 ± 56.1	41.6 ± 16.8	2.70	0.009
Number of awakenings	32.4 ± 16.4	35.4 ± 13.7	-0.82	0.418
Arousal index / TST (h-1)	16.9 ± 6.4	15.7 ± 6.4	0.72	0.476
Stage 1 (% SPT)	8.2 ± 3.8	8.7 ± 4.5	-0.53	0.599
Stage 2 (% SPT)	49.8 ± 11.2	53.8 ± 5.9	-1.87	0.065
SWS (% SPT)	10.5 ± 9.2	8.9 ± 7.2	0.79	0.431
REM (% SPT)	16.4 ± 6.1	19.5 ± 3.8	-2.53	0.014

PLMS, periodic leg movements in sleep; REM, rapid eye movement; SPT, sleep period time; SWS, slow wave sleep; TST, total sleep time.

Polysomnography

Polysomnographic data are presented in Table 2. Patients with PI had a significantly lower TST, sleep efficiency, and REM% compared with good sleeper controls. Additionally, sleep onset latency in the first night and WASO in both nights were significantly increased in the PI patient group.

FreeSurfer-Based Univariate Analyses

ANCOVA analyses revealed no significant between-group differences in left ($F_{62} = 0.11$, $P = 0.74$) and right ($F_{62} < 0.01$, $P = 0.95$) hippocampal volumes (Figure 1). Furthermore, hippocampal subsegments were not statistically different between groups (FDR-corrected). Given the current sample size, the observed variance in hippocampal volumes and an α of 0.05, statistical power analysis revealed that 6.3% (left) and 6.0% (right) between-group differences could have been detected with a power of 80%.

ICV-, age-, and sex-adjusted regression analyses did not reveal any significant association between ISI values and left ($t_{62} = -1.30$, $P = 0.20$) and right ($t_{62} = -0.99$, $P = 0.33$) hippocampal volumes. Furthermore, the TST of the second night in the sleep laboratory was not significantly associated with left ($t_{62} = 0.47$, $P = 0.64$) and right ($t_{62} = -0.68$, $P = 0.50$) hippocampal volumes. With respect to the duration of PI, there were trends for the association with left ($t_{24} = -1.95$, $P = 0.063$, $\beta = -13.0$) and right ($t_{24} = -2.00$, $P = 0.057$, $\beta = -12.1$) hippocampal volumes within the PI patient group. However, these trends were not found for the subgroups of sleep-maintenance insomnia patients (left: $t_4 = -1.44$, $P = 0.25$; right: $t_4 = -0.58$, $P = 0.60$) or mixed insomnia patients (left: $t_{12} = -0.24$, $P = 0.82$; right: $t_{12} = 0.04$, $P = 0.97$). In the full sample, hippocampal volumes were neither significantly associated with BDI scores (left: $t_{62} = 0.58$, $P = 0.57$; right: $t_{62} = 0.11$, $P = 0.91$) nor with trait STAI scores (left: $t_{62} = 0.91$, $P = 0.37$; right: $t_{62} = 0.94$, $P = 0.35$). Furthermore, lifetime history of hypnotic medication (none, benzodiazepine receptor agonists, other) did not explain differences in the left ($F_{62} = 0.41$, $P = 0.70$) and right ($F_{62} = 1.52$, $P = 0.24$) hippocampal volumes within the PI group.

In the other FreeSurfer-derived brain volume and thickness values, no statistically significant between-group differences were found (FDR-corrected). Uncorrected P values of the ANCOVA analyses are presented in Figure 2, demonstrating that the distribution of P values approximates a random distribution.

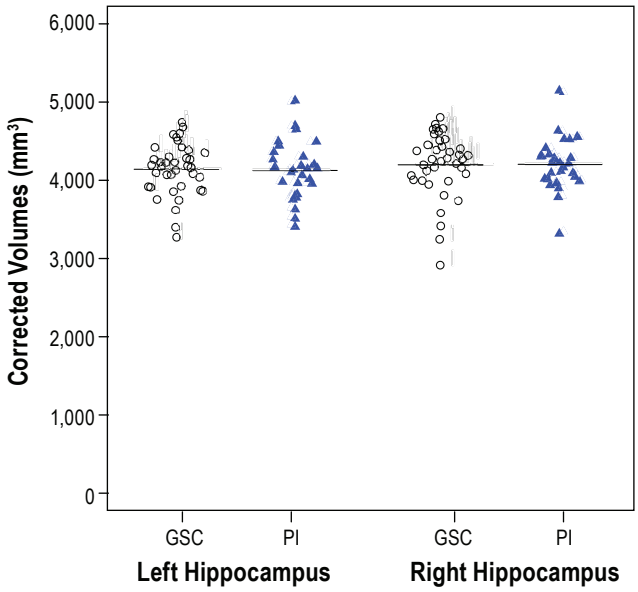

Figure 1—Left and right hippocampal volumes for patients with primary insomnia (PI) and healthy, good sleepers. Presented volumes are ICV-, age-, and sex-adjusted by using the residual method. Horizontal bars represent group means. GSC, good sleeper controls.

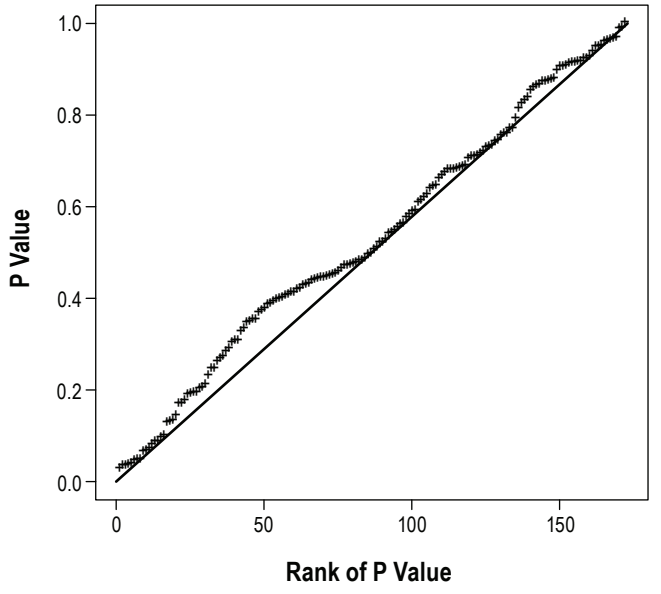

Figure 2—Distribution of uncorrected p-values of the between-group comparisons determined by analyses of covariance of 172 FreeSurfer-derived variables (excluding the left and right hippocampus). The slope represents the expected distribution of P values in the absence of significant between-group differences.

The subgroup analyses did not reveal any significant differences to healthy controls in left (sleep maintenance insomnia patients: $F_{42} = 0.08$, $P = 0.78$; mixed insomnia patients: $F_{50} = 0.01$, $P = 0.91$) and right (sleep maintenance insomnia patients: $F_{42} = 0.33$, $P = 0.57$; mixed insomnia patients: $F_{50} = 0.14$, $P = 0.71$) hippocampal volumes. Likewise, in the other FreeSurfer derived variables, no statistically significant between-group differences were found (FDR-corrected).

Support Vector Machine

The cross-validation BA (lower CI-upper CI, P value) using the Freesurfer data was 55.95% (44.32%-67.47%, P = 0.16). Therefore, the hypothesis that the observed performance was due to chance could not be rejected.

Voxel-Based Morphometry

Voxel-based morphometry did not reveal any significant between-group differences in gray or white matter volumes at $P < 0.05$ (FWE-corrected). Even when using a more liberal statistical approach (uncorrected voxel threshold of $P < 0.001$ with a cluster threshold of 25 voxels), we did not find any significant gray or white matter volume differences between patients with PI and good sleeper controls. Furthermore, ICV-, age-, and sex-controlled regression analyses did not reveal any significant associations between gray and white matter volumes and ISI scores in the full sample, or between gray and white matter volumes and insomnia duration in the PI group (FWE-corrected at $P < 0.05$).

DISCUSSION

The results of the current study suggest that PI, i.e. insomnia in the absence of a somatic or mental illness, is not associated with substantial macroscopic alterations of the brain structure. In the largest study so far, we used complementary approaches to investigate a clinically referred and well-characterized sample of patients with PI and good sleeper controls. Strengths of the current study include a detailed polysomnographic and psychometric characterization of the sample, the large sample size compared with that of prior studies, and the use of different methods of investigating brain morphometry.

There is overwhelming evidence from psychologic,[10,44-47] electrophysiologic,[48] and pioneering neuroimaging studies[49,50] that brain function is altered in patients with insomnia. However, the current findings suggest that these changes do not relate to substantial alterations of brain morphometry on a macroscopic level. What are the clinical implications for patients with insomnia? They can be reassured that insomnia, according to the current level of knowledge, does not appear to be associated with substantial structural brain changes. This is potentially important because excessive worry about the consequences of poor sleep plays a central role for the development and maintenance of insomnia by triggering emotional and physiologic arousal.[10,47]

Our power analysis suggests that the absence of statistically significant differences between patients with PI and healthy good sleepers is not due to a lack of statistical power. With respect to hippocampal volumes, between-group differences of approximately 6% could have been detected with a power of 80%. This is in the range of hippocampal volume reductions in other psychiatric disorders. Meta-analyses have revealed bilateral reductions of 5% to 8% in depression,[51] posttraumatic stress disorder,[52] and schizophrenia.[53] However, it has to be noted that we did not have the power to detect smaller brain morphometry changes, which thus can not be ruled out with certainty. The SVM constructs a discriminative model without making any assumptions about the distributions underlying the multivariate data. Thus, it is difficult to convert the sensitivity

of an SVM into a power analysis but its high sensitivity has been shown empirically.[54-56]

For the association between hippocampal volumes and insomnia duration, we observed a statistical trend within the PI patient group. This finding suggests that 10 y of insomnia may be associated with a unilateral volume reduction of 120-130 mm^3. However, as the corresponding statistical analyses failed to reach significance, conclusions about this issue have to be drawn carefully. We would like to suggest that future studies on brain morphometry in insomnia may focus specifically on a group of long-term (maybe idiopathic) insomnia patients.

Several limitations of the current investigation have to be acknowledged. First, the patients with PI in the current study were selected without reference to polysomnographically determined sleep parameters. Although this finding is in line with diagnostic criteria and improves the ecologic validity of our results, some studies suggest that polysomnographically determined short sleep duration may be a marker of biologic severity of insomnia.[57,58] Accordingly, one may speculate that brain morphometry is specifically altered in the population of insomnia patients with short sleep duration. However, we did not find any significant relationship between insomnia severity as determined by ISI scores or polysomnographically determined TST, and hippocampal volumes in the current study.

Second, patients with PI had higher depression and trait anxiety scores than good sleeper controls. Although none of our participants had a clinically significant affective or anxiety disorder, a subtle effect of subclinical depression or anxiety on brain morphometry cannot be excluded. However, we did not find any significant association between BDI scores or trait STAI scores and hippocampal volumes in the current investigation.

Third, despite a careful screening for relevant sleep problems, we cannot rule out that some of our healthy participants had a period in their life characterized by erratic or chronically restricted sleep due to other reasons than shift work possibly biasing our results. Furthermore, the current sample of healthy controls tended to show comparably poor sleep in contrast to some previous investigations, particularly with respect to the number of awakenings. However, these data are in line with previously published data from a large dataset from our sleep laboratory showing no significant effect of PI on the number of nocturnal awakenings.[59] Additionally, a mean sleep efficiency below 90% is not an uncommon finding in polysomnographic investigations of middle-aged healthy samples.[60]

Fourth, because this was a cross-sectional study with negative findings, conclusions about the significance of the results for insomnia research have to be drawn cautiously. Despite being expensive and very labor intensive, a longitudinal design would allow for more confidence in the conclusions.

In summary, we did not observe any statistically significant brain morphometry changes in a large and well-characterized sample of patients with PI in comparison with good sleeper controls. This might be reassuring for insomnia patients. Yet, the substantial effect of insomnia on quality of life and health care costs is, of course, not affected by a lack of macroscopic brain changes. Given the high prevalence and consequences of insomnia, it remains a public health priority to understand the neurobiology of the disorder to facilitate the development of widely applicable and effective treatment strategies for 10% of the population. Future studies may focus on functional neuroimaging research in insomnia patients, or, in order to complement the current structural approach, on white matter integrity using diffusion tensor imaging.

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DISCLOSURE STATEMENT

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