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Research Article

A Retrospective Study Suggests that Chronic Insomnia Behaves as a Neurodegenerative Disorder

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ABSTRACT

Insomnia is a prevalent sleep disorder. We examined chronic insomnia in terms of subjective and objective measures, according to self-reported duration of disorder. 443 patients were included from a sleep clinic diagnosed with chronic insomnia (ICSD3 criteria). Patients were retrospectively evaluated in terms of medical interview, sleep questionnaires, a standard polysomnography study, and subdivided in subgroups according to disorder duration. We compared patient's results to a control group. Insomnia and control groups were significantly different in terms of TST, SE, SOL, N1 sleep, REM sleep, REM latency and number of REM episodes ($p<0.05$). For the group of ≤1 year of insomnia disorder all PSG parameters were statistically different from controls, except N2% and N3%, REM latency, and number of REM episodes. In the groups of 2 to 4 years, 10 to 19 years, and ≥ 20 years of insomnia we found the same differences except for REM sleep. On the contrary, in a subgroup analysis of 5 to 9 years of insomnia disorder duration, no differences to control group were found in TST, N1 or REM sleep to control group, adjusted for age. The polysomnographic sleep profile of chronic insomnia patients is different over time. It sketches an initial attempt of compensation in initial years of insomnia, which seems to disappear in long time chronic insomnia patients, as we usually see in others neurodegenerative disorders. Future studies are needed to clarify the natural history of chronic insomnia disorder and its behaviour as a neurodegenerative disorder.

Keywords: Insomnia disorder; Polysomnography; Degenerative process

INTRODUCTION

Insomnia is a common complaint defined by difficulties in falling asleep, maintaining sleep, and/or early morning awakening, coupled with daytime consequences such as fatigue, attention deficits, and mood instability [1]. As a transient phenomenon, insomnia is a commonplace and frequently remits spontaneously. For chronic insomnia, the symptoms must occur at least three times per week and persist over a period of at least three months [1]. As a disorder, it frequently accompanies other disorders, including other sleep disorders and many medical, neurological and psychiatric disorders [2]; it can precede the comorbid condition, persist despite an effective treatment of the comorbid condition, or aggravate the symptoms of the comorbid condition [2]. Results of longitudinal studies show that nearly 70% of individuals with insomnia at baseline continue to report insomnia one year later, and 50% still have insomnia up to three years later [3-5]. Chronic insomnia raises the risks for depression [6,7], hypertension [8], and, possibly, mortality [9,10] in older adults.

The natural history as well as the prognosis of untreated insomnia is not well documented.

Some studies have approached the neurobiological basis of insomnia by looking at structural differences between persons with insomnia and good sleeper controls with no sleep problems. Patients with primary insomnia demonstrated significantly reduced hippocampal volumes bilaterally compared to the good sleepers [11]. Riemann et al. tentatively concluded that insomnia may either result from, or contribute to, changes in brain structure [11]. Koo et al. showed again that sleep quality and fragmentation are closely related to atrophic changes in the

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hippocampus and putamen [12]. In addition, two studies have used diffusion tensor imaging (DTI) to evaluate differences in white matter tracts in persons with insomnia compared to matched controls [13,14]. By taking a whole-brain network perspective, Jespersen et al succeeded at integrating previous inconsistent findings, and revealed that reduced structural connectivity of the left insula and the connections between frontal and subcortical regions are central neurobiological features of insomnia disorder.

These results although not always reproducible, started to demonstrate that insomnia disorder patients have structural and functional brain differences compared to good sleepers and may raise the possibility that insomnia is more than a psychological or even psychiatric disorder, seeming to be a neurological disorder.

Clinically and in many research studies, insomnia is primarily diagnosed by the measurement of subjective symptoms and not by the determination of sleep parameters through polysomnography [15]. Polysomnographic research on insomnia revealed a remarkable discrepancy between the subjective experience of insomnia and a rather undisrupted sleep at polysomnography in many insomniacs [16]. However, currently polysomnography is the only objective and quantitative measure for insomnia. Although, no standardised quantitative definitions for insomnia exist, several criteria are suggested: average reported sleep latency of more than 30 minutes, wakefulness after sleep onset of more than 30 minutes, sleep efficiency of less than 85% or total sleep time lower than 6.5h in adults [17].

To our knowledge, there is no clinical data about changes in polysomnography related to duration of the insomnia disorder. Therefore, we extensively evaluated a clinical population of chronic insomnia patients from a Sleep Medicine Centre, including complaints, comorbidities, socio-demographic data and sleep questionnaires, together with Polysomnography (PSG) type 1. The objectives of this study were: 1) to evaluate our chronic insomnia patient data and to compare it with a control group; 2) to evaluate chronic insomnia PSG patterns according to self-reported duration of disorder.

METHODS

Participants

The population consisted of a retrospective analysis of 443 consecutive patients from a sleep clinic diagnosed with chronic insomnia, according to the ICSD3 criteria [1], determined by a board-certified sleep physician during a clinical interview between January 2014 and May 2018. Participant sleep difficulties had to be longer than 3 months, not related to any medical or another sleep disorder condition, or medication intake. In opposition, the control group did not meet ICSD3 criteria for insomnia, sleep satisfaction was preserved, had no reports on difficulty in initiating sleep, maintaining sleep, or early morning awakening and showed PSG night study without any change (Total Sleep Time (TST) >6.5h, Sleep Onset Latency (SOL) <30 minutes, Sleep Efficiency (SE) >85%, Index Apnea Hipopnea (IAH) <5/h, Periodic Limb Movements (PLMs) <15/h).

Exclusion criteria for all participants: (a) current presence of a medical or neurological disorder that could significantly disrupt sleep; (b) alcohol or drug abuse according to diagnostic criteria of substance-related disorders of DSM-V [18]; (c) evidence of another sleep disorder (e.g., sleep apnea, periodic limb movements during sleep, restless legs syndrome).

Procedures

All individuals had a clinical interview performed by a neurologist specialized in sleep medicine, followed by polysomnography type I measurements. In the clinical evaluation the detailed clinical history of the patient was obtained. Data like socio-demographic parameters (e.g. age, gender, marital status); toxic consumptions like tobacco, alcohol abuse, illicit drugs as well as licit drugs (prescribed and non-prescribed by a physician) like anti-depressive and hypnotic drugs, as well as self-prescribed melatonin use was recorded. All reported co-morbidities were assessed - depression, anxiety, psychiatric disorders, neurologic disorders and medical disorders (according to the diagnoses criteria of DSM V [18] and ICD-10 [19]. This is a retrospective study (clinical anonymized database analysis) as so, informed consent was not required. In the absence of an institutional review board, as an ethical committee, we followed the good clinical practices worldwide recommended including the principals' outlined by the Declaration of Helsinki.

Measures

Polysomnography: Overnight polysomnography was performed with one of the following PSG systems: Alice 5 Respironics; Nicolet System – Viasys Healthcare; Embla N7000; Domino Somnoscreen Plus - Somnomedics. The recorded parameters included in all of them: electroencephalography (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1); left and right electrooculogram; submental electromyogram; bilateral tibial electromyogram; electrocardiogram; oronasal airflow with 3-pronged thermistors; nasal pressure with a pressure transducer; rib cage and abdominal wall motion via respiratory impedance plethysmography. Arterial oxygen saturation with pulse waveform was also recorded, as well as digital video and audio. The sleep period was scored from "lights off" to "lights on," with lights off scheduled as close as possible with participant's normal sleep schedule. Objective sleep measures evaluated were: sleep onset latency (SOL), total sleep time (TST), sleep efficiency (SE in %) scores were derived by dividing total TST by TIB and multiplying by 100 to achieve a percentage, proportion (%) of sleep stages (1,2,3 and REM) in relation to TST, REM latency, number of REMs.

Questionnaires: Pittsburgh Sleep Quality Index - PSQI is a self-report 18 questions on subjective sleep quality over the last four weeks. The 18 items of the PSQI form seven component score ranging from 0 to 3 (sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication, daytime dysfunction) the sum generate a total score. Higher scores

represent worse sleep quality. The cut-off values established for "bad" sleep quality is a total score 5 [20].

Insomnia Severity Index (ISI) is a valid and reliable self-report instrument measuring perceived insomnia severity. The severity of sleep disturbances, satisfaction relative to sleep, degree of impairment of daytime functioning caused by sleep, noticeability of impairment attributed to the sleep problem, and the degree of distress and concern related to the sleep problem are reported throughout the seven items on a 5-point (0 to 4) Likert scale. The total score ranges from 0 to 28 (higher scores reveal more severe insomnia symptoms) [21].

Epworth Sleepiness Scale (ESS) is a self-reported questionnaire composed by 8 items, which assesses the level of sleepiness in daily situations, rated on a 4 point Likert scale, ranging between "0 - no probability of falling asleep" and "3 - high probability of falling asleep". The total score is obtained by adding all items, ranging between 0 and 24. Results at or above 10 indicate abnormal or pathological daytime sleepiness and results at or above 17 indicate severe sleepiness [22].

Misperception: A total sleep time misperception (time in minutes) was calculated using objective (PSG recording) and subjective (oral information) data of night PSG study obtained after the morning awakening.

Statistical analysis

Absolute frequencies and proportions were used to summarize categorical variables. Continuous variables were described by mean values and standard deviations for normal distributions and by median whenever normality criteria were not met. Differences between groups on sociodemographic, psychological, and sleep characteristics were statistically assessed using the Student t-test or Mann-Witney test for continuous variables, according to data distribution, and the Chi-square test for categorical variables. Statistical assumptions of parametric tests were verified. In case of violation, nonparametric options were preferred. Anova followed by post-hoc Bonferoni was also performed related to sleep characteristics. Significance levels were set at $p<0.05$. SPSS was used for all analyses (IBM statistics, V24).

RESULTS

Sociodemographic variables

The sample comprised 443 insomnia patients (295 women, 16-83 years old, mean=44.8 years, SD=14.2), 51 controls (32 women, 19-74 years old, mean 43.3 years, SD=12). Statistical analysis showed that groups were similar according to age and gender ($p>0.05$). Additionally, none of the subjects had an apnea-hypopnea index ≥ 5, ruling out sleep apnea. Similarly, none of the subjects met AASM criteria [23] for an objective diagnosis of periodic limb movements disorder, restless legs syndrome or an underlying parasomnia.

Questionnaires

Subjective sleep parameters related to ISI were significantly different between groups (insomnia 18.2 ± 4.6 vs. controls 12.4 ± 2.8, $p=0.01$). PSQI also showed differences between both groups (insomnia patients 11.59 ± 3.72 vs. control group 6.6 ± 1.84, $p<0.001$). In the insomnia group, only 1.1% (5 patients) had a PSQI <5 meaning a good sleep quality. However, not significantly differences in Epworth Sleep Scale (insomnia 9.6 ± 5.1 vs. controls 10.2 ± 5, $p=0.614$) were found.

Objective sleep parameters

Insomnia and control groups were significantly different in TST (insomnia 348.4 ± 70.4 min vs. controls 409.0 ± 52.2 min, $p<0.001$), SE (insomnia 73.8 ± 13.3% vs. controls 89.2 ± 5.6%, $p<0.001$), SOL (insomnia 29.3 ± 29.9min vs. controls 11.2 ± 8.3 min, $p<0.001$), N1% (insomnia 9.3 ± 5.1% vs. controls 5.7 ± 2.7%, $p<0.001$), REM% (insomnia 16.9 ± 9.1% vs. controls 20.8 ± 6.0%, $p=0.001$), REM latency (insomnia 138.0 ± 76.4min vs. controls 102.8 ± 64.0 min, $p<0.001$) and number of REM episodes (insomnia 3.1 ± 1.2 vs. controls 3.9 ± 1.1, $p < 0.001$) (Table 1).

For those who reported the exact time of onset of insomnia, we looked for differences in PSG data by separating patients in five subgroups taking into account insomnia disorder duration: ≤ 1 year, 2 to 4 years, 5 to 9 years, 10 to 19 years and ≥ 20 years, in comparison with the control group. For the group of ≤ 1 year of insomnia disorder all PSG parameters were statistically different from controls, except N2% and N3% (both with $p=1.0$), REM latency ($p=0.862$), and number of REM episodes ($p=0.238$). In the groups of 2 to 4 years, 10 to 19 years, and ≥ 20 years of insomnia we found the same differences except for REM sleep (%, latency and number of REM episodes). However, in the group of 5 to 9 years of insomnia, no differences were found in TST ($p=0.23$), N1% ($p=0.587$), N2% ($p=1$), N3% ($p=1.0$) and REM sleep% ($p=1.0$), REM latency ($p=1.0$) and number of REM episodes ($p=0.295$) (Table 2 and Figure 1). Linear regression with the subgroups taking into account insomnia disorder duration did not find any interaction with age.

Sleep was underestimated in all chronic insomnia groups but also in the control group, however for all insomnia groups the misperception error was more than one hour (Table 2).

Table 1: Group differences based on sociodemographic variables, questionnaires and objective sleep parameters.

	Chronic Insomnia	Control group	p-value
N	443	51	
Sex, Female - % (N)	66.6 (295)	62.7 (32)	

Age (yrs)	44.8 ±14.2	43.3 ± 12	0.505
ESS	9.6 ± 5.1	10.2±5	0.614
ISS	18.2±4.6	12.4±2.8	0.01
PSQI	11.6 ± 3.7	6.6 ± 1.8	<0.001
PSG data			
TST*, min	348.4 ± 70.4	409.0 ± 52.2	<0.001
Sleep Onset Latency, min	29.3 ± 29.9	11.2 ± 8.3	<0.001
Sleep efficiency, %	73.8 ± 13.3	89.2 ± 5.6	<0.001
N1 % TST	9.3 ± 5.1	5.7 ± 2.7	<0.001
N2 % TST	53.3 ± 10.9	52.6 ± 8.4	0.53
N3% TST	21.9 ± 35.0	21.3 ± 7.7	0.51
REM % TST	16.9 ± 9.1	20.8 ± 6.0	0.001
REM Latency, min	138.0 ± 76.4	102.8 ± 64.0	<0.001
Number of REM episodes	3.1 ± 1.2	3.9 ± 1.1	<0.001
Average Heart Rate, bpm	63.7 ± 8.6	65.2 ± 8.1	0.356
Snore%	8.4 ± 15.7	11.8 ± 16.2	0.01
Apnea/hypopnea index (/h)	1.6 ± 1.9	1.8 ± 1.7	0.15
O2 mean saturation, %	95.6 ± 1.5	94.9 ± 2.2	0.06
Periodic Limb Movements i (/h)	2.4 ± 3.7	1.8 ± 3.3	0.23

Note: Mean values ± SD (range) are shown; ESS=Epworth Sleepiness Scale; ISS=Insomnia Severity Index; PSQI=Pittsburgh Sleep Quality Index; TTS=Total Sleep Time; SOL=Sleep Onset Latency; N1=N1 sleep; N2=N2 sleep; N3=N3 sleep; REM=REM sleep

Table 2: Group differences compared to control group based on polysomnographic parameters by separating patients in five subgroups taking into account insomnia disorder duration.

	Controls	≤1 yr	2-4 yrs	5-9 yrs	10-19 yrs	≥ 20 yrs
N	51	21	23	24	26	18
TTS, min	409.0 ± 52.2	320.1 ± 66***	352.3 ± 59.3**	368.0 ± 60.9	360.4 ± 62.1*	331.0 ± 98.3***
SOL, min	11.2 ± 8.3	29.8 ± 22.1**	25.1 ± 18.8*	26.2 ± 22.5*	28.2 ± 17.6*	33.8 ± 27.1**
SE, %	89.2 ± 5.6	68.6 ± 14.1***	76.0 ± 10.3***	77.4 ± 11.4**	75 ± 11.5***	70.0 ± 18.2***
N1, %TST	5.7 ± 2.7	9.1 ± 3.8**	9.1 ± 5.4**	7.7 ±2.9	9.4 ± 4.0**	9.7 ± 4.6**
N2, % TST	52.6 ± 8.4	50.6 ± 8.2	51.5 ± 11.6	54.6 ± 8.7	53.3 ± 7.7	56.3 ± 13.5
N3, % TST	21.3 ± 7.7	25.0 ± 9.1	22.6 ± 12.5	18.7 ± 10.5	19.4 ± 7.5	15.8 ± 10.4

REM, % TST	20.8 ± 6.0	15.1 ± 7.6**	16.8 ± 6.9	19.0 ± 5.5	17.8 ± 5.5	18.0 ± 6.5
REM Latency, min	102.8 ± 64.0	138.2 ± 79.2	126.5 ± 71.2	130.1 ± 57.2	119.4 ± 62.4	122.1 ± 85.4
Number of REMs	3.9 ± 1.1	3.1 ± 1.3	3.0 ± 1.1	3.2 ± 1.3	3.6 ± 1.1	3.3 ± 1.1
Sleep Misperception, min	27.4 ± 93.2	77.7 ± 104.1	72.5 ± 118.2	92.7 ± 109.6	77.7 ± 112.6	83.2 ± 113.3

Note: Mean values ± SD (range) are shown. TTS=Total Sleep Time; SOL=Sleep Onset Latency; N1=N1 sleep; N2=N2 sleep; N3=N3 sleep; REM=REM sleep. *Indicates a significant difference to control group at P < 0.05; ** Indicates a significant difference to control group at P<0.01; *** Indicates a significant difference to control group at P<0.001. Adjusted by age.

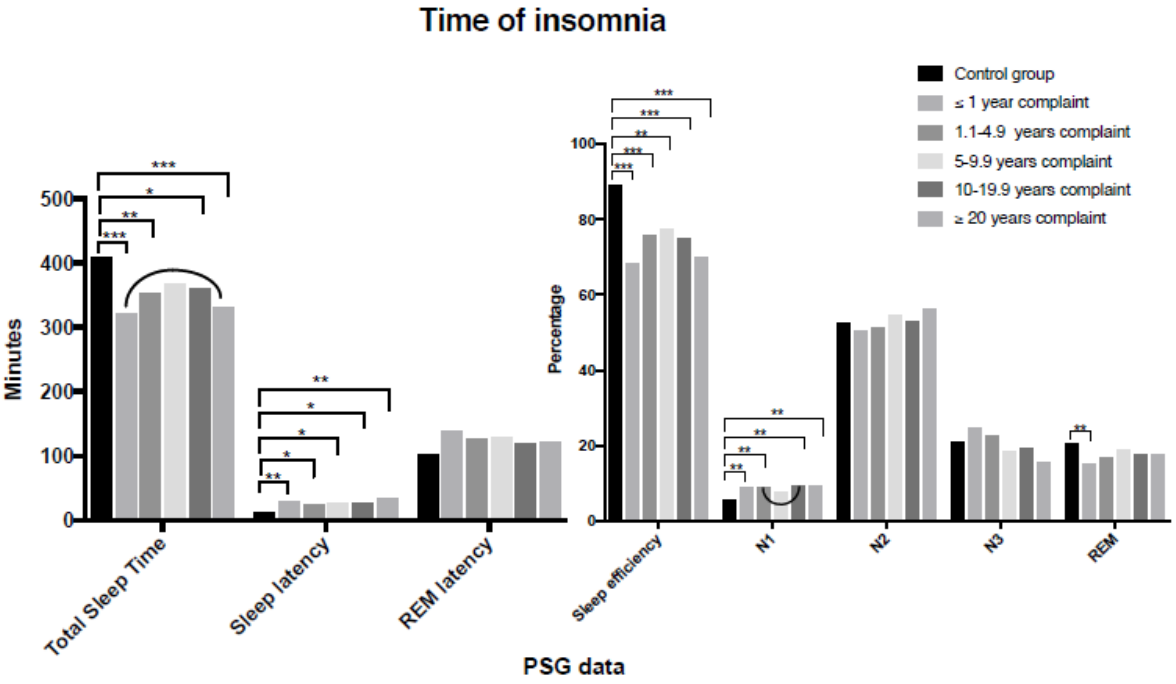

Figure 1: Group differences compare to control group based on polysomnographic parameters by separating patients in five subgroups taking into account insomnia disorder duration. Mean values ± SD (range) are shown. TTS=Total Sleep Time; SOL=Sleep Onset Latency; N=N1 sleep; N2=N2 sleep; N3=N3 sleep; REM=REM sleep. * Indicates a significant difference to control group at P<0.05; ** Indicates a significant difference to control group at P<0.01; *** Indicates a significant difference to control group at P<0.001. Adjusted by age.

DISCUSSION

The primary aim of this study was to determine whether differences existed in terms of sleep, both subjectively and objectively, between chronic insomnia patients and a control group. Subsequently we looked for differences in chronic insomnia groups considering the duration of the insomnia disorder.

The differences between chronic insomnia patients and controls were not surprising. TST, SE were lower and SOL was longer in insomnia patients as expected and in line with previous studies [17,24]. We also found differences in N1 and REM sleep (%, latency and number of episodes of REM) between insomnia patients and the control group. The increased N1 % is consistent with the hyperarousal model of insomnia [25,26]; the reduction of REM sleep in insomnia was also found in previous studies. It is thought to play a key role in alteration of the emotional system [27].

Furthermore, when we looked to the consequences of untreated chronic insomnia over time, in the first year of insomnia the differences found in the objective sleep measures in comparison to the control group were also in TST, SE, SOL, N1 and REM sleep (%). However, no differences related to REM latency or number of REMs were found. The same was found for the groups of 2 to 4 years, 10 to 19 years and ≥ 20 years of insomnia, with exception of REM sleep (%, latency and number of REM episodes). As mentioned before, previous studies already showed that primary insomnia patients spend 2% less time in REM sleep [24]. This is correlated with the alteration of emotional processes that usually follows insomnia [4].

There was however a consistent approximation found between insomnia patients within 5 to 10 years duration and the control group related to objective sleep measures. In initial years of chronic insomnia, TST and N1 sleep PSG parameters assumes an inverted "U" shape and looks like a compensation response over time, which after 10 years tends to disappear; this approximation to the control group is achieved by increasing the

TST and decreasing N1. In chronic insomnia there is not only a sleep-wake regulation problem with an increase in awake state: brief periods of awakening, increased number of microarousals or with periods of wakefulness during night; but also a disturbance of the switch between sleep and wakefulness – as both NREM and REM microstructure seems to suggest [28]. In our results, chronic insomnia seems to have an initial evolution period (after the first year reaching its maximum between 5 and 9 years) with an attempt to alter the arousal system and the sleep continuity, increasing the total sleep time and decreasing N1 sleep. This mechanism behaves like a compensation response operating in the early phase of chronic insomnia to allow a restoration of the normal sleep-wake regulation.

Several molecules involved in sleep-wake regulation are produced by specific brain structures with widespread projection throughout the brain [29]. If sleep regulatory molecules (primarily wake-promoting/sleep-suppressing or sleep-promoting/wake-suppressing substances) affect neurons in the regions they are produce, it will affect the neural circuitry of sleep in which those neurons take part [30]. Yet, the sleep/wake system stops working properly and patients may have insomnia. In the field of speculation, we may hypothesize that even if a compensation mechanism may occur by recruiting other neurons and other circuits, overtime, the compensation could end rather due to the spread of the areas affected and the compensation stopped being effective. The long-term complications due to chronic insomnia could be related to the role of the impaired sleep-wake process and the consequently poor sleep.

Neurodegenerative diseases have two general characteristics: the pathology associated with the disease only affects particular neurons ('selective neuronal vulnerability') and the pathology worsens with time and impacts more regions in a stereotypical and predictable fashion [31]. Thus, we may say that chronic insomnia behaves as a neurodegenerative disorder as presenting selective neuronal vulnerability [30] and, as our results showed, worsening with time

An initial compensatory mechanism is found in other degenerative disorders, in which the natural response to the insult cannot resolve the problem, and may even give rise to further damage, but individuals, due to compensation mechanisms, may persist asymptomatic in initial phases of the disease (for example, Parkinson disease [32] or chronic kidney disease [33]) or exhibit minor manifestations for a long time (for example, Alzheimer disease (AD)) [34].

A neurodegenerative process in chronic insomnia, growing over several years, also may explain some differences found in MRI studies mentioned in the introduction. Winkelman et al. did not replicate the results of Riemann et al., that showed changes in MRI in chronic insomnia patients and the reason may be related to sample composition [11,35]. Winkelman had a sample with 20 patients which reported a continuous history of insomnia for at least six months, 19 for at least one year and 12 for at least five years [35]. In Riemann study, eight patients were included and had suffered from insomnia for a mean duration 11.6 ± 8.9 years. The changes in MRI studies may only happen with a longer disease duration. Koo et al. [12], which showed again that insomnia disorder is closely related to atrophic changes in hippocampus and putamen, had a sample of 27 insomnia patients with an average time since onset of insomnia of 8.4 ± 9.1 years. The last two samples, with a duration of insomnia enough to lose initial compensatory mechanism that we now showed. Also, in terms of MRI changes, chronic insomnia disorder may behave like AD, where the accumulation of amyloid plaques and neurofibrillary tangles is contemplated to induce neural and synaptic loss that finally leads to cortical atrophy [36]. As in AD, which has atrophic changes that occur first in the hippocampus, are not specific enough and can only been seen years after the first memory symptoms, insomnia disorder may have MRI images changes only several years after initial insomnia complaints.

Furthermore, cognitive behaviour therapy for insomnia (CBT-I) seems to be the most efficacious treatment for chronic insomnia. CBT-I is effective across a variety of populations, including those with medical and psychologic comorbidities. Unexpectedly, McCrae et al, presented novel evidence suggesting that CBT-I may slow or reverse cortical gray matter atrophy in patients with fibromyalgia and insomnia [37], showing that psychologic strategies may change circuits and even structural damage.

Sleep misperception was present in chronic insomniacs. We found that sleep misperception error increased in the first 10 years of insomnia symptom. At the same time % of REM sleep also increases. The previous and current results support the suggestion that REM sleep might be related with the mechanisms of sleep misperception [16].

LIMITATIONS OF THE STUDY

This is a retrospective study, which may be associated with potential methodological shortcomings (e.g., recall bias). However, with such a window of time (more than 20 years) a prospective study has complex design and with a follow up period that will lead to an important number of drop offs. Still, these new results highlight the need of such a study in the future. It will also be interesting to look to sleep microstructure, namely microarousals, and spectral EEG components, namely, spindles and *alpha* activity intrusion. As strengths we highlight the insomnia sample size, which is an unfrequented number of chronic insomnia patients with PSG data.

CONCLUSION

The focus of the study was to examine the consequences of the presence of untreated chronic insomnia over time in PSG. So, if insomnia is in fact a primarily remitting condition what should happen to the smaller group of patients with a persistent disorder? As the Spielman's model proposed insomnia can start with an initial precipitant event and may resolve over time. In our point of view, for those that did not remit, an initial attempt to compensate will include an increase on TST, decrease of N1% and increase of REM%. However, this compensation works only for a few years and when lost, the persistent disorder may worse over time, increasing the risk for future onset of psychopathology or even cognitive impairment. A similar

mechanism has been described in the development of dementia, in which an initial compensation occurs due to a cognitive reserve hiding the brain damage already existing. In that sense, chronic insomnia behaves as a neurodegenerative disease in terms of progressive degeneration of the function of the central nervous system, namely the sleep/wake system, with an initial compensation response and ulterior deterioration, including structural MRI changes. Further studies are however needed to prove this hypothesis.

CONFLICTS OF INTEREST

All the authors declare that they have no Conflicts of Interest.

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AUTHOR CONTRIBUTIONS

DN, TA and TP developed the study concept and design. DN, TA and CR performed the research and the data analysis. All authors contributed to the data interpretation and drafted the manuscript.

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