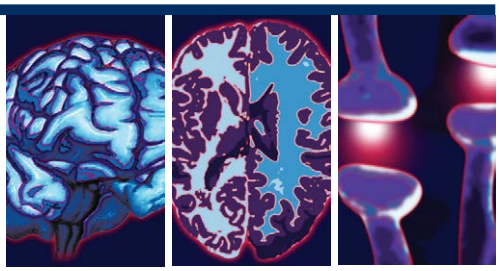

Discrepancies of Cognition Among Different Subtypes and Correlations with Sleep Parameters in the Patients with Chronic Insomnia Disorder

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Abstract

Backgrounds: Insomniacs have damaged memory. We intended to explore the differences of memory and polysomnogram sleep parameters in the patients with different subtypes of chronic insomnia disorder (CID) and the correlations between them.

Methods and Findings: 106 CID outpatients were divided into difficulty initiating sleep (DIS), early morning awakening (EMA), difficulty maintaining sleep (DMS) and mix sleep difficulty (MSD) groups. The polysomnography was completed during a night. Nine-Boxes Maze Test was used to assess the spatial/object working memories (SWM, OWM), spatial/object reference memories (SRM, ORM) and object recognition memory (ORcM). The results showed that compared to the DMS group, the EMA group had more SWM errors, and the MSD group additionally had more ORcM errors. Relative to the DMS group, the EMA and MSD groups had lower sleep efficiency, longer wake time after sleep onset, decreased REM% and increased N1%. Furthermore, the EMA group had longer REM latency and less REM density, the MSD group had shorter REM time, and the DIS group had enhanced N1%. For all the insomniacs, the linear regression analysis showed that a negative effect of sleep parameters on cognition measures existed in pairs as following: N2% vs. ORM errors; REM%/N3%/ REM density vs. SRM errors; REM%/N2% vs. SWM errors; N3% vs. ORcM. The canonical correlation analysis showed that SWM errors negatively correlated with REM, N2% and N3%.

Conclusions: The insomnia-related memory impairment was different among the subtypes in the CID patients, with the worst memory in the EMA and MSD subtypes. The decreased N2%, N3% and REM% might be associated with damaged spatial memory.

Keywords

Chronic insomnia disorder, Memory, Nine-Boxes Maze, Polysomnogram, Subtypes

Introduction

As known to all, there is a wide consensus that chronic insomnia disorder (CID) has a negative influence on memory. The neuroscientists and clinicians have increasingly pointed great importance to study on the relationships between the memory and sleep, especially under condition of CID [1-3]. Emerging evidence indicates that sleep plays a main role in the consolidation stage of memory storage, and this critical stage is vulnerable to sleep changes [4-6]. In CID patients, the studies find impairment in the sleep-consolidation of declarative memory [7,8]. The studies on the effects of sleep deprivation

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using animals show that the damage of memory consolidation under sleep loss, at least in part, is attributable to reduced synthesis of proteins related to synaptic plasticity [9,10]. However, the underlying mechanism of memory damage in the CID patients remains be cleared.

Although the evidence mentioned above proves that lack of sleep may damage the new memory formation, the debates have emerged due to less knowledge of what stage of sleep is relevant in the CID patients. Sleep consists of two periods, i.e., rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep [10]. In humans, NREM sleep can further be dissected into three stages, containing lighter sleep stages 1 (N1) and 2 (N2), as well as more restful, slow wave sleep (SWS) or N3 [10]. Given the diversity of sleep stages and memory categories, the influence and intervention of various sleep states on different aspects of memory are dynamic and considerably different [11]. More specifically, the important role of NREM sleep in the consolidation of declarative memory has been confirmed through an experiment that subjects performed an associative task consisting of card locations paired with a particular odor [12]. Spindles and slow waves are hallmarks of NREM sleep, and these oscillations are associated with neuronal plasticity, memory and cognition [13]. It has been found that spindle density and faster spindles have been related to cognitive potential and learning ability in different ages [14]. SWS is also proven to be beneficial to the consolidation of hippocampus-dependent memories [15,16]. Humans and rodents studies have shown an increase in NREM sleep, and NREM-associated processes such as slow wave activity and spindle density after a learning training [17,18]. Besides, researchers have also observed that procedural memory benefits from REM sleep, and suggest that REM sleep has a key role in language or emotional learning [19]. However, some other researchers have a different point of view that REM sleep may not be important for certain kinds of memory that are termed "explicit" or "declarative" memory [20]. It is probable that the different stages of sleep under insomniac condition are associated with distinct effects on sleep-related strengthen of different-form memories relative to normal-sleep condition.

Spatial memory (SM) is a higher-degree cognitive function, which is responsible for identifying, coding, storage and retrieval of spatial information about the arrangement of objects or specific routes [21,22], and involved in declarative memory, procedural memory, working memory as well as various aspects of the reference memory and other memory systems [23]. Studies show that REM sleep plays an important role on SM dependently on the hippocampus [24,25], and deprived REM sleep is able to affect SM in mice [26]. In humans, the SM is the earliest impaired memory form during the normal aging and in some diseases characterized by loss of learning and memory, such as Alzheimer's disease [27,28]. However, to our best knowledge, there are few reports on the SM in insomniac patients, let alone the study in different subtypes of CID. Besides, it is necessary to choose a new task to exactly detect practical SM due to lack of paradigm. The Nine Box Maze Test is sensitive to the deficits of visuo-spatial memory [28]. It incorporates a within-participants design to provide measures of the complexities of SM and can assess the spatial, non-spatial (object), working (trial dependent), reference (trial independent) memories, and recognition memory simultaneously [28-30]. Our previous studies have shown that this task can detect mild damage of SM and recognition memory in the patients with CID [31] or chronic tension-type headache [32].

Therefore, it is a great of interest to hypothesize that different clinical-subtype patients with CID have diverse sleep structures that are associated with damages in different aspects of memory. To test this hypothesis, the aims of this study are to explore the differences of memory and PSG sleep parameters in the CID patients with different subtypes and the correlations between memory and sleep parameters.

Methods

■ Participants

106 insomniacs were enrolled according to the clinical manifestations and the classification of CID subtypes in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [33]. They were classified into four groups: difficulty initiating sleep (DIS, n = 11), early morning awakening (EMA, n = 22), difficulty maintaining sleep (DMS, n = 22) and mixed sleep difficulty (MSD, n = 51).

The subjects of inclusion were 18–64 years old and had completed ≥ 9 years of education. They were consecutively selected from the patients at the Clinic of Sleep Disorders in the Affiliated Chaohu Hospital of Anhui Medical University. They met the diagnosis criteria of CID in DSM-

5 [33] and the duration of symptoms was at least 6 months. All participants did not have a history of mania or hypomania and current bipolar disorders, obstructive sleep apnea syndrome, restless legs syndrome or other medical diseases that are associated with sleep disturbances [33,34]. They were not suffering from infections or inflammatory allergic reactions and did not take any medication that may affect sleep, mood and memory for at least 2 weeks before the study. The female subjects were not pregnant or lactating. The participants had no visual, hearing or movement disorders. All subjects gave written informed consent before the study began. The study was done with permission from the Clinical Trial Ethics Committee, the Affiliated Chaohu Hospital of Anhui Medical University.

■ Collection of general data

The demographic characteristics, including age, gender, and educational, medical and family histories, of all enrolled subjects were collected.

Evaluation of sleep quality

■ Subjective sleep quality

The subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI), a standard scale accessing sleep quality via recall of sleep behaviors in the past month [35] consisting of seven domains, including subjective sleep quality, sleep latency, sleeping duration, sleep efficiency, somnipathy, use of hypnotic drugs and diurnal dysfunction [35]. Each domain is scored from 0 to 3. The total score (0 to 21) is used to evaluate the sleep quality by summing across domains. In China, a PSQI score ≥ 7 has high diagnostic sensitivity and specificity in distinguishing patients with poor sleep from normal subjects [36].

■ Objective sleep quality

The overnight objective sleep quality was recorded by polysomnography (PSG) during one night with Compumedics Siesta 802 series of Australia. The environmental requirements, preparatory work, equipment, and technical specifications were provided according to the criterion of Recheschaffen. Subjects were asked to come to the sleep monitoring room at 8:00 p.m, wear sleep monitoring chambers, commissioning equipment, too familiar with the connection leads and sleep environment. They were told the monitoring process considerations. The data were obtained by the ProFusion sleep 3 software and in accordance with the American Academy of Sleep Medicine Association annual 2007 PSG criteria [37]. The parameters are shown in Table 1.

■ Evaluation of depression

The depression was assessed using 17-term Hamilton's Depression Scale score (HAMD-17) that consists of 17 terms, including depressed mood, feelings of guilt, suicide, insomnia (difficulty of falling asleep, light sleep, and early awakening), work and activities, retardation, agitation, psychic anxiety, somatic anxiety, gastrointestinal symptoms, general somatic symptoms, general symptoms (loss libido, menstrual disturbances), hypochondriasis, loss of weight, and insight [38]. The total score ranges from 0 to 52 with the higher score, the more severity. The suggesting cutoffs are: 8–13 (mild depression), 14–18 (moderate depression), 19–22 (severe depression) and ≥ 23 (very severe depression) [39].

■ Evaluation of cognition

In the next morning after PSG was completed, the cognitive abilities were evaluated using the Chinese-Beijing Version of Montreal Cognitive Assessment (MoCA-C) [40] and a modified protocol of the Nine Box Maze Test [28].

■ Global cognition

The MoCA-C, a brief and useful screening tool for mild cognitive impairment under different clinical settings which had been employed in

Table 1: The list of indicators used to indicate objective sleep quality and memory.

Content	Indicators (Abbreviations)
Sleep quality	total sleep time
	sleep latency
	sleep efficiency
	wake time
	N1, N2 and N3 latencies; REM latency
	time in REM sleep (REM), time in 1, 2 and 3 stages of NREM sleep (N1, N2 and N3)
	percent of REM sleep (REM%), and percent of 1, 2 and 3 stages of NREM sleep (N1% , N2% and N3%)
	apnea hyponea index (AHI)
	wake time after sleep onset (WASO)
	time in bed (TIB)
	sleep period time (SPT)
	REM density
	the number of arousals
Memories	Spatial working memory (SWM)
	object working memory (OWM)
	spatial reference memory (SRM)
	object reference memory (SRM)
	object recognition memory (ORcM)

the nation-wide screening of cognitive function in China, was used to evaluate global cognition function [40]. It can assess visuo-spatial and executive functions, attention, short-term memory, language and orientation [40]. Its maximum of scores is 30 and overall scores ≥ 26 is considered as normal cognitive function in China [40].

■ Special memory

The procedure of Nine Box Maze Test [28] was mildly modified to evaluate multi-aspect abilities of memory [31,32], including spatial/object working memory (SWM, OWM), spatial/object reference memory (SRM, ORM), and object recognition memory (ORcM), see **Table 1**. In the center of a spacious and bright room with a picture in one inside-wall to provide a place cue, a 120-cm-diameter table was equidistantly located along its border with 9 identical opaque containers (height 9-cm and diameter 8-cm). During the object-familiarization phase, 10 common objects (a button, key, coin, battery, watch, pencil sharpener, nail clipper, shears, scotch tape and clothespin) were shown to the subject and the subject was instructed with each object's name. In the training period, 2 random objects from the object-familiarization phase were put into 2 random containers, and the subject was asked to remember the objects and containers housed them. The subject was required to move around the table twice clockwise and counterclockwise, respectively. Then, a photograph of the 10-common objects was displayed, and the subject was required to recognize the objects and the corresponding containers. If the subject responded correctly, the test would proceed to the next step. If an incorrect response was given, the subject should continue to point to the objects/containers until a correct response. The results in this period were not recorded. Subsequently, in the testing period, the subject was asked to remember 2 objects and their positions, which would not be moved until the entire test was over (to form object and spatial reference memories). Another 2 objects from the object-familiarization phase were put into another 2 containers. The subject was told to remember these objects and their locations, and the subsequent movements and sequential recognition of the context were identical to those in the training period. However, the objects and their locations were various from trial to trail in all five trails (to form object and spatial working memories). The numbers of errors were respectively recorded as performances of SWM (changed location), OWM (changed object), SRM (unchanged location) and ORM (unchanged object). The data entering statistical analysis were the sum of later four trails. Just end of the "testing period", the subject was required to make out the objects that had been displayed in the test from a photograph, which contained corresponding similar objects that had been used in the test. The numbers of errors were recorded as the performance of ORcM.

■ Statistical analysis

All statistical tests were performed using the standard SPSS package, Version 16.0 for Windows. The data distributions and the homogeneity of the variance of the data were analyzed to determine the most appropriate analysis methods. Kolmogorov–Smirnov and Levene tests were applied to evaluate the normality and homogeneity, respectively, of the results. The results were expressed as the mean ± standard deviation when the criteria for normal distributions were met, and one-way analysis of variance, followed by least significant difference test to perform the multi-comparison. When the data were not distributed normally, the data were expressed as the 25th, 50th, and 75th percentiles [P50 (P25, P75)] and analyzed using a Kruskal-Wallis H test with the Newman-Keuls test for the multi-comparison. The correlations between PSG parameters and memory measures were explored using partial correlation analysis and linear regression analysis, and in order to discover the further association between the two groups' parameters the canonical correspondence analysis was used. In all tests, $P<0.05$ was considered statistically significant.

Results

■ Basic data

The four-group patients had similar constitutions of age, sex and educated experience, and scores of PSQI, HAMD-17 and MoCA-C **(Table 2)**.

■ Memory performance

The Kruskal-Wallis test revealed that there were significant differences in the number of errors of SWM among the four groups (Ps<0.05, **Table 3**). In details, the DMS patients had the best and the EMA and MSD patients had the worst performances. Compared to the DMS group, the EMA and MSD groups had more errors of SWM and ORcM (Ps<0.05).

■ Changes in PSG sleep parameters

There were significant differences in the sleep efficiency and WASO among the four groups

Table 2: Demographic and clinical characteristics of participants.

Items	Difficulty initiating sleep	Early morning awakening	Difficulty maintaining sleep	Mixed sleep difficulty	Statistic	*P*-value
Numbers	11	22	22	51		
Sex (M/F)	4/7	6/16	6/16	19/32	$\chi^2 = 1.126$	0.771
Age (yr)	38.5±14.9	41.4±13.3	38.9±11.7	42.1±11.2	$F = 0.467$	0.706
Education (yr)	13.3±3.5	11.6±4.1	12.0(9.0,16.0)	12.0(9.0,15.0)	$z = 3.531$	0.317
PSQI (score)	13.8±3.5	14.4±3.6	15.6±3.6	14.8±2.7	$F = 0.801$	0.497
HAMD-17 (score)	8.8±3.8	11.2±3.6	9.9±3.6	11.2±4.1	$F = 1.183$	0.321
MoCA-C (score)	28.0(25.0,29.0)	26.0(23.0,29.0)	27.0(26.0, 28.5)	27.0(26.0, 28.5)	$z = 1.444$	0.695

Expressions: Mean ± SD (normally distributed variables) or P_{50} [P_{25}, P_{75}] (non-normally distributed variables)

Table 3: Comparison of patients with CID of different subtypes on memories (number of errors, P_{50} [P_{25}, P_{75}]).

Memories	Difficulty initiating sleep	Early morning awakening	Difficulty maintaining sleep	Mixed sleep difficulty	*Z*-value	*P*-value
ORM	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	2.533	0.469
SRM	0.0 (0.0, 3.0)	0.5 (0.0, 3.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	2.333	0.506
OWM	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	3.522	0.318
SWM	4.0 (2.0, 5.0)	**5.0 (3.5, 6.0) ***	2.0 (1.0, 3.3)	**5.0 (3.0, 7.0) ***	14.071	**0.003**
ORcM	0.0 (0.0, 1.0)	0.0 (0.0, 0.3)	0.0 (0.0, 0.0)	**0.0 (0.0, 1.0)***	4.257	0.235

Note: * Compared to the difficulty maintaining sleep group, $P < 0.05$

(*P*s<0.05). Further, compared to the DIS group, the EMA group had shorter sleep latency, and the DMS group had lower N1%. Compared to the EMA group, the DMS group had higher sleep efficiency and REM density, larger REM%, lower N1%, shorter REM latency and less WASO, and the MSD group had longer N2 latency and higher REM density. Compared to the DMS group, the MSD group had lower sleep efficiency, shorter REM, less REM%, more N1%, longer WASO (*P*s<0.05) (Table 4).

■ Correlations among variables

After controlling sex, age, educated level and HAMD-17 score, the correlation analysis in all CID patients showed that MoCA-C score was negatively associated with N2 latency and TIB, ORM errors negatively correlated with N2 and N2%; the SRM errors negatively correlated with REM density; the errors of SWM negatively correlated with REM time and REM%, and positively correlated with N2 latency ($|r|$: 0.234~ 0.436, *P*s <0.05), as shown in Table 5.

In order to explore the association between the cognition measures and sleep parameters, the Linear Regression analysis was used, using the "stepwise" method with all requested variables (see Table 1) entered, and the results were shown in Table 6. The N2 latency and TIB exerted a negative effect on the MoCA-C score, and N3 exhibited a positive effect on it. For the special memory, N2% and sleep latency respectively had a negative or positive effect on the ORM error. REM%, N3% and REM density negatively affected the SRM errors, REM% and N2% negatively affected the SWM errors, and N3% negatively linked to the ORcM errors. Other variables of sleep parameters were excluded.

To discover the relationship between the sleep parameters and cognition measures, the canonical correspondence analysis was performed. The cognitive measures, including MoCA-C, and the error numbers of ORM, SRM, SWM and ORcM, consisted of canonical variance V, and the sleep parameters, including the latency of N1, N2, N3, the time of REM, N2, N3, REM%, N2%, N3%, AHI, TIB and REM density, consisted of canonical variance W. Table 7 shows the results of the canonical correspondence analysis results. Only the canonical correlations of canonical variance (V1, W1) was 0.675 ($P = 0.004$), which indicated that there were correlations between the measures of cognition mainly consisted of memories and the sleep parameters recorded by PSG. Table 8 shows the results of Standardized Canonical Coefficients for canonical variances V and W. The standardized linear transformations were shown as follows: V1 = – 0.111 MoCA-C – 0.065 ORM + 0.198 SRM – 0.163 OWM + 0.918 SWM + 0.057 ORcM; W1= – 0.492 REM – 0.340 REM% + 0.098 N1 latency + 0.306 N2 latency + 0.398 N2 – 0.676 N2% – 0.145 N3 latency – 0.243 N3 – 0.412 N3% – 0.108 AHI + 0.231 TIB – 0.076 REM density.

Table 4: The sleep parameters recorded by PSG in different subtypes.

Items	Difficulty initiating sleep	Early morning awakening	Difficulty maintaining sleep	Mixed sleep difficulty	Statistic	*P*-value
Total sleep time (min)	363.1 ± 86.9	366.9 ± 83.1	384.5 ± 91.5	349.2 ± 102.1	$F = 0.740$	0.531
Sleep latency (min)	**31.0 (11.0, 32.0) ***	**18.5 (13.4, 23.0) ǂ**	16.0 (11.1, 22.6)	17.0 (11.5, 48.0)	$z = 3.620$	0.306
Sleep efficiency (%)	72.3 (61.7, 85.1)	**71.1 (58.6, 81.3) #**	**82.1 (62.9, 88.2) ***	**72.0 (52.8, 80.1) #**	$z = 8.464$	**0.037**
REM latency (min)	159.9 ± 90.9	**162.1 ± 92.6 #**	**117.3 ± 64.0***	129.4 ± 66.4	$F = 1.858$	0.142
REM (min)	68.2 ± 29.9	67.5 ± 27.2	81.9 ± 32.3	**64.6 ± 30.9 #**	$F = 1.692$	0.173
REM%	19.7 (12.8, 21.3)	**16.6 (13.3, 22.2) #**	**22.3 (18.4, 25.4) ***	**17.6 (14.3, 22.1) #**	$z = 7.477$	0.058
N1 latency (min)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	$z = 2.160$	0.540
N1 (min)	58.9 ± 19.8	54.5 ± 23.8	46.6 ± 20.9	52.7 ± 27.5	$F = 0.702$	0.553
N1%	**14.9 (13.6, 19.5) #**	**12.7 (10.2, 21.8) #**	**10.4 (7.1, 13.2) ǂ ***	**15.3 (9.6, 21.2) #**	$z = 7.404$	0.060
N2 latency (min)	3.0 (1.0, 3.5)	1.5 (0.5, 3.6)	1.5 (0.5, 2.8)	**2.5 (1.0, 5.5) ***	$z = 6.503$	0.090
N2 (min)	183.3 ± 51.7	192.5 ± 58.0	197.0 ± 45.6	179.5 ± 64.9	$F = 0.562$	0.641
N2%	50.1 ± 4.9	52.1 ± 8.4	52.1 ± 8.6	51.2 ± 10.8	$F = 0.153$	0.927
N3 latency (min)	23.0 (8.5, 161.5)	28.3 (15.8, 100.8)	22.5 (14.6, 28.9)	21.0 (14.0, 42.0)	$z = 2.303$	0.512
N3 (min)	57.3 ± 22.1	50.6 ± 36.7	59.6 ± 31.3	52.7 ± 29.0	$F = 0.404$	0.751
N3%	14.8 ± 4.9	14.3 ± 9.2	15.1 ± 6.4	15.4 ± 7.8	$F = 0.103$	0.958
AHI	0.2 (0.0, 0.5)	0.3 (0.0, 2.3)	0.1 (0.0, 0.7)	0.2 (0.0, 0.9)	$z = 0.844$	0.839
WASO (min)	142.5 (63.5,195.0)	**121.3 (71.3, 200.5) #**	**69.0 (38.4, 132.8) ***	**121.0 (90.0, 198.0) #**	$z = 8.784$	**0.032**
TIB (min)	500.4 ± 54.9	509.1 ± 50.3	505.4 ± 74.6	527.8 ± 54.5	$F = 1.297$	0.280
SPT (min)	461.5 ± 45.8	453.3 ± 62.8	472.3 ± 82.2	462.9 ± 88.7	$F = 0.211$	0.888
REM density	5.7 ± 1.4	**5.4 ± 2.2 #**	**6.7 ± 1.8***	**6.6 ± 2.2***	$F = 2.383$	0.074
The number of arousals	132.1 ± 73.8	130.5 ± 65.3	121.7 ± 66.5	133.4 ± 64.5	$F = 0.164$	0.921

Expressions: Mean ± SD (normally distributed variables) or P_{50} [P_{25}, P_{75}] (non-normally distributed variables)

Note: ǂ Compared to the difficulty initiating sleep group, $P < 0.05$

* Compared to the early morning awakening group, $P < 0.05$

\# Compared to the difficulty maintaining sleep group, $P < 0.05$

Table 5: Partial correlation coefficients between the measures of cognitive functions and sleep parameters recorded by PSG in the CID patients .

Items	MoCA-C	ORM	SRM	OWM	SWM	ORcM
Total sleep time (min)	-0.119	-0.175	0.052	0.050	0.047	-0.105
Sleep latency (min)	-0.040	0.190	-0.105	-0.102	-0.030	0.013
Sleep efficiency (%)	0.021	-0.134	0.067	0.057	-0.044	-0.072
REM latency (min)	-0.056	0.184	0.072	0.035	0.033	0.011
REM (min)	0.064	-0.117	-0.049	-0.067	**-0.436****	-0.127
REM%	0.048	-0.099	-0.173	-0.137	**-0.406****	0.015
N1 latency (min)	-0.048	-0.143	0.207	-0.105	0.043	-0.008
N1 (min)	-0.104	-0.053	-0.125	0.021	0.074	-0.100
N1%	-0.006	0.083	-0.108	0.011	0.086	-0.063
N2 latency (min)	**-0.281***	0.182	0.052	-0.042	**0.344***	0.026
N2 (min)	-0.105	**-0.275***	0.051	0.092	-0.084	0.014
N2%	-0.051	**-0.234***	0.003	0.122	-0.183	0.132
N3 latency (min)	-0.031	-0.057	-0.061	-0.057	-0.094	-0.003
N3 (min)	0.169	0.025	-0.038	-0.035	-0.062	-0.164
N3%	0.127	0.054	-0.122	0.033	-0.084	-0.220
AHI	0.050	0.028	0.053	0.216	0.013	-0.178
WASO (min)	-0.061	0.058	-0.103	-0.026	0.115	0.055
TIB (min)	**-0.256***	-0.077	-0.143	-0.007	0.146	-0.091
SPT (min)	-0.154	-0.074	-0.082	0.072	0.083	-0.084
REM density	0.034	0.081	**-0.315***	-0.139	-0.035	-0.073
Arousals number	-0.024	-0.128	-0.193	-0.099	0.004	-0.121
Rollover frequency	0.023	-0.126	-0.206	0.037	0.066	-0.064

Note: Controlling for the factors: sex, age, educated level and HAMD-17 ; * $P < 0.05$; ** $P < 0.01$

Table 6: Linear regression analysis for sleep parameters and cognition measures (Beta).

	MoCA-C	ORM	SRM	OWM	SWM	ORcM
Sleep latency (min)		0.295**				
REM%			-0.201*		-0.367**	
N2 latency (min)	-0.214*					
N2%		-0.189*			-0.262**	
N3 (min)	0.261*					
N3%			-0.227*			-0.197*
TIB (min)	-0.351**					
REM density			-0.195*			

Method: Stepwise

Independent variables: all requested variables (total sleep time, sleep latency, sleep efficiency, wake time, REM latency, REM%, N1 latency, N1, N1%, N2 latency, N2, N2%, N3 latency, N3, N3%, AHI, WASO, TIB, SPT, REM density, the number of arousals, rollover frequency) analyzed simultaneously

Dependent variables: MoCA-C, ORM, SRM, OWM, SWM and ORcM analyzed respectively

*$P < 0.05$; ** $P < 0.01$

Table 7: Canonical correspondence analysis between sleep parameters and cognition measures.

Can. Var.	*Can. Cor.*	*Wilks' Lambda*	*% of Variance*	*Cumulative %*	χ^2	*P*
(V1, W1)	0.675	0.202	0.256	0.256	108.041	**0.004**
(V2, W2)	0.534	0.371	0.097	0.353	67.016	0.128
(V3, W3)	0.508	0.518	0.112	0.465	44.360	0.293
(V4, W4)	0.433	0.699	0.208	0.773	24.181	0.620
(V5, W5)	0.300	0.860	0.151	0.924	10.162	0.858
(V6, W6)	0.234	0.945	0.176	1.000	3.804	0.802

Abbreviations: Canonical variance (Can. Var.); Canonical correlations (Can. Cor.)

Table 8: Standardized Canonical Coefficients for V and W.

Can. Var.		*1*	*2*	*3*	*4*	*5*	*6*
V	MoCA-C	-0.111	-0.552	-0.431	-0.599	-0.271	-0.597
	ORM	-0.065	-0.123	-0.758	-0.177	-0.465	0.708
	SRM	0.198	-0.893	0.661	-0.117	0.199	0.301
	OWM	-0.163	0.857	0.349	-0.674	-0.148	-0.098
	SWM	**0.918**	-0.008	-0.352	-0.191	0.130	-0.652
	ORcM	0.057	0.049	0.395	0.255	-0.894	-0.103
W	REM	**-0.492**	0.054	-0.121	-0.086	0.443	0.907
	REM%	-0.340	0.054	0.193	0.511	-0.256	-0.141
	N1 latency	0.098	-0.616	0.157	0.165	0.584	0.047
	N2 latency	0.306	0.147	-0.117	0.113	0.187	0.341
	N2	0.398	0.108	0.387	0.253	0.050	-0.977
	N2%	**-0.676**	0.456	0.301	-0.210	0.004	0.309
	N3 latency	-0.145	-0.089	0.097	0.261	0.044	-0.026
	N3	-0.243	-0.370	-0.076	-0.182	0.290	-0.245
	N3%	**-0.412**	0.251	-0.153	-0.011	0.365	-0.429
	AHI	-0.108	0.401	0.077	-0.710	0.219	0.211
	TIB	0.231	0.563	-0.012	0.193	0.359	0.386
	REM density	-0.076	0.248	-0.581	0.014	-0.054	-0.026

According to the absolute value of standardized coefficients, the variable V1 reflecting cognitive function was almost indicated by the SWM, and variable W1 reflecting sleep quality was mainly indicated by the REM, REM%, N2 latency, N2, N2% and N3%. From the sign of standardized coefficients, SWM errors negatively correlated with the REM, N2% and N3%.

Discussion

In the current study, we aimed to explore the differences of memory and PSG sleep parameters in the CID patients with different subtypes and the correlations between memory and sleep parameters of PSG. We found that: 1) a significant difference existed in SWM and ORcM among the different-subtype CID patients, with

worse SWM in the EMA group and worse SWM and ORcM in the MSD group compared to the DMS group. 2) There were significantly different sleep parameters of PSG, with lower sleep efficiency, longer WASO, decreased REM% and increased N1%. 3). The correlations between sleep parameters and memories were complicated, and reduced REM time, N2% and N3% were associated with damaged SWM for CID patients without distinguishing subtypes.

The study of relationships between sleep and memory has become popular. In recent years, the findings indicated that CID patients had not only defect of subjective memory [41], but also damage of objective memory [42]. It seemed that the more complex the task is, the higher the detection rate of sleepless-related memory impairment is [43]. In our previous and this studies, the results showed that the patients with CID did have memory defects assessed by the Nine-Boxes Maze Test [31], and significant differences of memories (mainly SWM) existed among 4 different subtype groups, as indicated by the error numbers of SWM **(Table 3)**.

So far, it has not been explored deeply about whether there are differences in objective impairment of memory among CID subtypes. We have reported that the individuals in the EMA group performed worse than those in the DIS and DMS groups in the procedural memory (finger motion sequence test) and declarative memory (free word delayed recall and delayed recognition memory) [44]. But in that study, we just divided insomniacs into 3 subtypes. In order to reflect the clinical situation, we divided CID patients into 4 groups, adding the MSD group. We found that patients in DMS group had the best performance among them, and the patients in EMA and MSD had the worst performance. Although the results were not at the exactly the same, the overall trend is the same with our previous results [44].

Reduced sleep efficiency can lead to poor mood and cognition [45,46]. Insomniac patients with specific SWS (0.5~2.0 Hz) defects had impairment of cognitive function [47]. In addition, the disorders of natural cycle of SWS and REM sleep also can damage the memory [48,49]. Previous studies have suggested that the impairment of learning and memory in patients with insomnia may be related to the characteristics of insomnia [50,51]. In our study, the patients with DMS, who had better memories (mainly the SWM) than the patients with EMA and MSD **(Table 3)**, had higher sleep efficiency and REM density, larger REM%, less N1%, shorter REM latency and WASO **(Table 4)**. These suggested that overnight high-quality sleep (high sleep efficiency, deep and continuous NREM sleep, sufficient REM sleep) is important for SWM [52,53].

Human memory is an adaptive system. We do not only consolidate experiences as literal records of the past, but also transform those experiences into new representations that might substantially differ from what is originally encoded [54]. Spatial memory contains the whole progress of memory [21,22] and involves many memory systems e.g. declarative memory, non-declarative memory, et al [23]. Both REM and SWS contribute to memory encoding, consolidation, and neural plasticity [55], and they were crucial in the reprocessing of memory [56]. The N2 sleep promoted both the declarative and non-declarative memories [8,57]. Although the results of our partial correlation and regression analysis were not the exactly same, they showed the complex relationship between different cognitive indexes and sleep parameters in the CID patients **(Tables 5 and 6)**. The results supported this view. To detect the exact correlation between the two groups of parameters, we performed the canonical correspondence analysis **(Tables 7 and 8)**. The results showed that compared to other sleep parameters, N2%, N3% and REM time might play positive roles on the SWM in the clinical CID patients. The decreased N2%, N3% and REM% might be associated with damaged SM. It suggested that sleep plays an obvious role on the consolidation of SM [51,58].

In short, patients with different subtypes of CID have different memory impairments and different sleep parameters. The patients with the EMA and MSD had worse memories (mainly the SWM) than the MSD patients, with higher sleep efficiency and REM density, larger REM%, less N1%, shorter REM latency and WASO. For all insomniacs with different subtypes, the decreased N2%, N3% and RME% might provide more contributions to SM impairment than other sleep parameters.

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