Research on Study Ability and Functional Connectivity of Hippocampus in Primary Insomnia

Hongju Zhang[1,2#], Enfeng Wang[2#], Shewei Dou [2], Liya Liu[2], Li Tong[3], Junfang Teng[1*], Yongli Li[2*]

[1]First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China.
[2]People's Hospital of Zhengzhou University, Zhengzhou, Henan, China.
[3]China National Digital Switching System Engineering and Technological Research Center, Zhengzhou, Henan, China
hongjuz@sina.com
[#] These authors contributed equally to this work and should be considered co-first authors.

Abstract: Object: This study intends to explore the changes of WHO-UCLA word study and the Digital Pin Test, as well as the functional connectivity on hippocampus with the whole brain, in order to find cognitive damage mechanism in primary insomnia (PI). Method: 40 primary insomniacs are chosen according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition, DSM-IV) and International Classification of Sleep Disorders (ICSD) criteria as well as 50 healthy subjects. The WHO-UCLA word learning and the Digital Pin Test are applied to evaluate the subjects' word study ability and vigilance. The above-mentioned subjects take a fMRI on the whole brain in a resting state, with left and right hippocampus as the seed points to establish functional connection with other encephalic regions, followed by a comparison of the test results of the two groups. Results: Pittsburgh Sleep Quality Index (PSQI) ($t=18.181, p<0.01$) and HAMA ($t=29.242, p<0.01$) of PI patients were significantly higher than those of the healthy control group, but the PI group's Digital Pin Test efficiency and WHO-UCLA word learning were significantly lower than those of the HC group. There exists a positive correlation between the PI group's subjective insomnia degree and their anxiety and the course of a disease. The PI group's WHO-UCLA word study ability has a negative correlation between the total PSQI score and the Digital Pin Test efficiency, and a positive correlation occurs in relation with an educational background. The right hippocampus of PI patients showed strengthened functional connection with the left limbic lobe, the right thalamus and the left brainstem. The left hippocampus of PI patients displayed enhanced functional connection with the bilateral thalamus. Conclusion: The ability of the PI patients on the WHO-UCLA word study and the Digital Pin Test efficiency decline, which keeps a negative correlation with depression, in relation with the course of the disease, sleep quality, and a positive correlation occurs with an educational background. The patients' hippocampus has a stronger functional connection with the bilateral thalamus, left limbic lobe, left brainstem, which is the mechanism leading to the cognitive damage of PI patients.

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1. Introduction

Primary insomnia is often accompanied by a decline in life quality and work efficiency [1]. Meanwhile, insomniacs often have anxious and depressive feelings and insomnia is seen as a predictive factor of depression [2]. Besides, insomnia causes frequent accidents and injuries that take up medical resources [3]. Experiments have shown that animals have weakened learning ability and impaired hippocampus after the deprivation of sleep[4]. Current researches on the impairment caused by primary insomnia to human's cognition (see for example + references) mainly focus on the studies of attention, memory, executive ability and alertness. As sleep plays an important part in learning and memory [5], insomnia may impair the normal sleep structure, thus disturbing the storage and consolidation of memory, which is mainly performed by hippocampus [6].

Previous studies (references) show that insomnia severity is related to a decreased volume of the CA3/Dentate GyrusHippocampal [7]. However, it is also believed that hippocampal volume and intracranial volume do not differ significantly between PIs and GSs [8]. According to functional neuroimaging, sleep deprivation involves distributed changes in encephalic regions including frontal and parietal control areas, secondary sensory processing areas, and thalamic areas [9]. McLaren DG, et al. [10] discovered that a patient with Alzheimer's showed abnormal functional connection between hippocampal and the whole brain. These findings indicate that dysfunction in the hippocampal can lead to a neurobiological mechanism for insomnia's cognitive disorder.

Regarding functional connection using a resting-state, the functional magnetic resonance

imaging (fMRI) has been used to study connecting networks of encephalic regions in psychiatric disorders, such as Alzheimer's disease and epilepsy. Abnormalities in a resting-state connection of the amygdala have been identified in a generalized anxiety disorder, posttraumatic stress disorder, bipolar disorder and schizophrenia. According to the recent studies (references) using resting-state fMRI, functional connection between the amygdala and insula, striatum, and thalamus declines, and the functional connection of the amygdala with the premotor and sensorimotor cortex strengthens in PI, the results suggests that dysfunction in the emotional circuit can lead to the neurobiological mechanisms, and a compensatory mechanism to overcome the negative effects of sleep disorders and maintain the psychomotor performances in PI patients[11].

In brief, this study hypothesized that patients with insomnia would exhibit abnormalities in a resting-state functional connection in the hippocampal. In this study, the seed-based correlation analysis is applied to explore the resting-state functional connection of the hippocampal in PI patients.

2. Method

2.1Target group

Primary insomnia group: according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition, DSM-IV) [13] and the International classification of sleep disorders (ICSD) [12] criteria, forty patients, consisting of 12 men and 28 women, are chosen from the Neurology Sleep Disorder Outpatient Clinic of Henan People's Hospital. They are aged between 20-50 years old, with an average age of 38.78 ± 8.25 and a case history between 3 and 24 months. Concerning an education background, 17 of them have a college degree or above, 18 have finished secondary school or high school, and 5 have only finished primary school. All the subjects are Han Chinese and dextral.

For a Healthy control group, the criteria for HC group are: a normal sleeper, healthy, Han Chinese, dextral, similarly in age, gender distribution and an educational background with the insomniac group. Therefore, fifty hospital employees, their family members and their students were selected into this group, consisting of 21 men and 29 women, aged between 20 and 50, with an average age of 35.28±8.23. 23 of them have a college or above degree, 21 have finished secondary or high school and 6 have finished primary school.

All subjects retained for a screening visit were interviewed and examined by two sleep neurologists. The interview included the Pittsburgh Sleep Quality Index (PSQI), the Minimum Mental State Examination (MMSE), the Hamilton Depress scale (HAMD). Consequently, absence of mild and severe depression is evident from the HAMD. Subjects showing any polysomnographic (PSG) evidence of other sleep disorders, such as a sleep apnea syndrome (i.e., thermistors monitored apnea–hypopnea index >5) and periodic leg movements (i.e., periodic leg movement index>10) were excluded from the study. No history of psychopharmacological treatment for insomnia was found. As well as this, there are no neurological or other physical diseases such as respiratory, cardiac, renal, hepatic and endocrinal diseases as assessed by clinical history, physical examination or routine laboratory tests performed during the screening visit. Any medication that can affect sleep or regional cerebral function within 14 days should be excluded, such as antidepressant drug, benzodiazepine, anti-epileptic drug, alcohol dependence, and others. There is no irregular sleep schedules associated with shift work or frequent travel; no female in gestation period and lactation period; no dysaudia and dysopia. All subjects should have no metal in their bodies.

Healthy control group: HAMD<17, PSQI<5, MMSE≥28; Insomnia group: HAMD<17, PSQI>8, MMSE≥28.

The study was approved by Zhengzhou university medical Ethics Committee and a written informed consent was obtained from each subject and/or their legal guardians.

2.2 Evaluation of word study and Digital Pin Test

The Hamilton Anxiety scale (HAMA) is applied to evaluate the subjects' anxiety degree; WHO-UCLA learning study scaleto evaluate their study ability, including Transient recall, Short time delay recall, and longtime delay recall, Insert the test and Delay recognition; the Digital Pin Test to evaluate their attention and vigilance.

2.3 fMRI Examination

2.3.1 Routine MRI scanning:

All selected subjects arrive at the fMRI room half an hour before taking the test. They are given instructions by two graduate students in the research team on the test procedure before signing consents for the experiment. After that, they have a 10-minute break before the test and a silent break with eyes closed is suggested. Scanning was performed on a 3.0 T MRI system (Siemens Trio Tim; Siemens Medical System, Erlangen, Germany) and with a 12-channel phased array head coil in the Henan Provincial People's Hospital to have their brain structures and resting-state functions scanned. Those subjects with abnormal structures or unqualified data for the brain functions will be excluded. Foam padding and

headphones were used to limit head motion and reduce the scanning noise.

2.3.2 Sequence and parameter of routine MRI

The scanning sequence includes axial T1WI, T2WI, FLAIR and DWI. Structural images were obtained by using a three-dimensional magnetization prepared by rapid acquisition gradient echo (3D MPRAGE) sequence with the following parameters: TR/TE=1950ms/2.30ms, Ti=900ms, scan time=4.24min, matrix=248×256, slice thickness 1 mm, no distance, FOV=244×252.

2.3.3 Sequence and parameter of fMRI of the Brain in a resting state

When taking fMRI, the subjects are required to lie down and rest themselves with their eyes closed, and they should clear their mind and try to think about nothing. Functional data were acquired using a Siemens ep2_bold sequence (TR/TE=3000ms/2.50ms, matrix=64×64, slice thickness 5mm, slice interval 0.5mm, total layer 36, FOV=320×320). This acquisition sequence generated 140 volumes.

2.3.4 Functional MRI data analysis processing

The first 10 volumes of the functional images were discarded for the signal equilibrium and participants' adaptation to the scanning noise. The slice timing, head motion correction, and spatial normalization with re-sampling to 3mm×3mm×3mm were conducted using the Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). No participant should have head motion of more than maximum 1.5mm displacement in any of the x, y, or z directions, nor 1.5 of any angular motion throughout the course of scanning. The resting-state fMRI data analysis toolkit (http://www.restfmri.net/forum/REST) was then applied for removing the linear trend of time courses and for temporally band-pass filtering the data (0.01–0.08Hz). The result was spatially smoothed with a 4 mm full-width at half maximum (FWHM) Gaussian kernel. To further reduce the effects of confounding factors, we also applied a linear regression process to further remove the effects of head motion and other possible sources of artifacts: (1) six motion parameters, (2) the whole-brain signal averaged over the entire brain, (3) linear drift.

2.3.5 Functional connection analysis with the left and the right hippocampus as the seed points.

The WFU_PickAtlas tool is used to generate seed points and then samples are recollected. This experiment found that the data matches these samples. Next, the RESI is used for statistical analysis, drawing the average value of the right andthe left hippocampus time sequence, analyzing the time sequence with the left and the right hippocampus in the brain and charting the Z value of every subject after Fisher Z conversion. Single sample t-tests are conducted to the PI group and the control group respectively, with a significant threshold value set as $P<0.01$ and voxel cluster >20 voxels.

2.4. Statistical analysis

The following statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Statistical comparisons of the demographic data and clinical characteristics between the two groups were performed with an independent-samples t-test. In order to explore the relationship between the Digital Pin Test efficiency and insomnia severity, anxiety degree, the course of disease, and the Level of education, a linear regression analysis was performed to examine the correlation between the Digital Pin Test efficiency and the total PSQI score, the total HAMA score, the course of disease, and the educational background of PI patients. The level of statistical significance was set at $p<0.05$. The WHO-UCLA learning study scale showed the same consequence as Pearson's correlation.

The statistical threshold is set as $P < 0.05$, cluster size≥20 voxels to make it statistically significant. Two-sample t-test is used to conduct statistical comparison between the PI group and control group in term of the right and the left hippocampal functional connectivity.

3. Results

3.1. Demographic and clinical characteristic

There were no obvious difference of sex, age and education degree between the PI and the control groups. The PSQI ($t=18.181$, $p< 0.01$) and HAMA ($t=29.242$, $p< 0.01$) of the PI patients were significantly higher than those of healthy controls. Digital Pin Test efficiency ($t=2.142$,$p< 0.01$) and the rest of the content except delay recognition in WHO-UCLA word learning of the PI patients were significantly lower than those of healthy controls ($t=-2.16$, $t=-2.588$, $t=-3.49$, $t=-2.192$, $p<0.01$).There was no difference of delay recognition between PI and control groups ($t=-1.727$,$P>0.01$). The demographic and clinical characteristics of the subjects were shown in Table 1.

3.2 Correlation between the PI patients' PSQI score and the total HAMA score, their educational background and the course of disease (see table 2)

Table 1, Demographic and clinical characteristics of the subjects.

Variable	PI patients Mean(SD)	Controls Mean(SD)	statistical parameter	p-value
case	40	50		
Male/female	12/28	21/29	χ^2=1.38	P>0.05#
Age	38.78(8.25)	35.28(8.23)	t =-1.883	P>0.05*
Level of education	17/18/5	23/21/6	χ^2=0.90	P>0.05#
MMSE	29.40(4.08)	30.54(3.68)	t =1.862	P>0.05*
PSQI score	11.35(2.76)*	2.08(1.23)	18.181	0.000*
HAMA score	13.43(2.55)*	1.05(1.40)	29.242	0.000*
Digital Pin Test efficiency (%)	60.03(13.95)*	66.32(13.73)	2.142	0.035*
Transient recall	48.07(9.81)*	52.58(7.54)	-2.168	0.036*
Short time delay recall	10.94(2.73)*	12.94(2.20)	-2.588	0.014*
Long time delay recall	10.11(2.29)*	11.95(2.42)	-3.493	0.001*
Insert the test	4.58(1.49)*	5.46(1.90)	-2.192	0.035*
Delay recognition	1.58(1.48)	1.04(1.44)	-1.727	0.088*

Notes: PSQI: Pittsburgh Sleep Quality Index; HAMA: Hamilton anxiety scale; MMSE:Minimum Mental State Examination.
*The p value was obtained by a two-sample two-tailed t-test.
#The p value was obtained using a Pearson χ^2 two-tailed test

Table 2. Correlation between the PI patients' PSQI score and the total HAMA score, their educational background and the course of disease

		HAMA score	education degree	course of disease
PSQI	r	0.692	-0.111	0.648
	P	0.000	0.496	0.000

There exists obvious positive relevance between the total PSQI score and the total HAMA score (r=0.692, P<0.01), and the course of disease (r=0.648, P<0.01). There exists no correlation between the total PSQI score and education degree (r=0.111, P>0.05).

3.3 Separate correlations of PI patients' word study ability and Digital Pin Test efficiency with PSQI, HAMA, educational background and the course of disease (see table 3)

Table 3. Separate correlations of PI patients' word study ability and Digital Pin Test efficiency with PSQI, HAMA, educational background and the course of disease

Variable	Transient recall		Short time delay recall		Long time delay recall		Insert the test		Digital Pin Test efficiency (%)	
	r	P	r	P	r	P	r	P	r	P
PSQI	-0.395	0.012	-0.391	0.014	-0.357	0.028	-0.405	0.011	-0.555	0
HAMA	-0.445	0.004	-0.443	0.005	-0.431	0.007	-0.444	0.005	-0.47	0.003
course of disease	-0.526	0	-0.453	0.004	-0.409	0.011	-0.459	0.003	-0.394	0.013
Education degree	0.608	0	0.506	0.001	0.435	0.006	0.417	0.008	0.407	0.01

The negative correlation obviously occurs between the WHO-UCLA word study ability and PSQI, anxiety, and the course of disease, including Transient recall (r=0.395、r=0.445、r=0.526，P<0.05), Short time delay recall(r=0.391、r=0.443、r=0.453，P<0.05), Long time delay recall (r=0.357、r=0.431、r=0.409，P<0.05), and Insert the test (r=0.405、r=0.444、r=0.459，P<0.05). There exists a positive correlation between the education background, Transient recall, Short time delay recall, Long time delay recall and Insert the test (r=0.608、r=0.506、r=0.435、r=0.417，P<0.01). The PI patients' Digital Pin Test efficiency is negatively correlated with the PSQI, HAMA and the course of disease (r=0.555、r=0.47、r=0.394，P<0.01) and positively correlated with their educational background (r=0.407,P<0.01).

3.4. Resting state fMRI results

Compared with the healthy controls, the right hippocampus of PI patients exhibited strengthened functional connection with the left limbic lobe, the right thalamus and the left brainstem (t=4.6167, t=3.2574, t=3.4679, P<0.05).

The left hippocampus of PI patients exhibited an increased functional connectivity with the bilateral thalamus (t=5.3436, 4.9798 P<0.05). (Tables 4 and 5; Figs. 1 and Figs. 2).

Table 4, PI patients' abnormal functional connection of the right hippocampus compared with healthy controls.

Encephalic Regions	BA	MNI coordinates			clusters	T-values	*p*
		X	Y	Z			
left limbic lobe	36	-18	-1	-29	20	4.6167	<0.05
right thalamus		14	-25	-2	23	3.2574	<0.05
left brainstem		-10	-26	-9	27	3.4679	<0.05

Notes: The threshold was set at p< 0.05 with a minimum cluster size of 20 contiguous voxels. BA: Brodmann's area; MNI: Montreal Neurological Institute. Cluster size is in number of voxels.

Table 5, PI patients' abnormal functional connection of the left hippocampus in PI patients compared with healthy controls.

Encephalic Regions	MNI coordinates			clusters	T-values	*p*
	X	Y	Z			
left thalamus	-6	-22	1	56	5.3436	<0.05
right thalamus	9	-25	1	57	4.9798	<0.05

Notes: The threshold was set at p<0.05 with a minimum cluster size of 20 contiguous voxels. BA: Brodmann's area; MNI: Montreal Neurological Institute. Cluster size is in number of voxels.

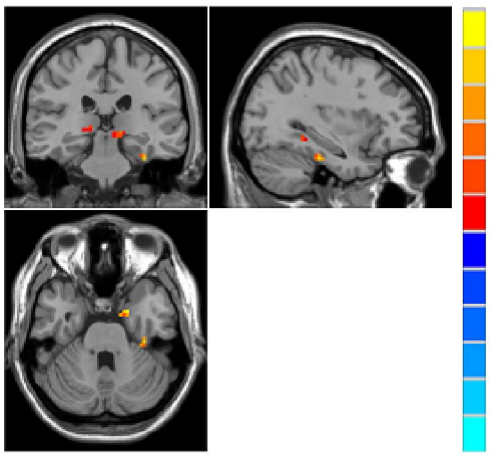

Figure 1. Compared with the healthy controls, the right hippocampus of the PI patients exhibited strengthened functional connection with the left limbic lobe, the right thalamus and the left brainstem. The threshold was set at p< 0.05 with a minimum cluster size of 20 contiguous voxels, (The red zone indicates a stronger functional connection.)

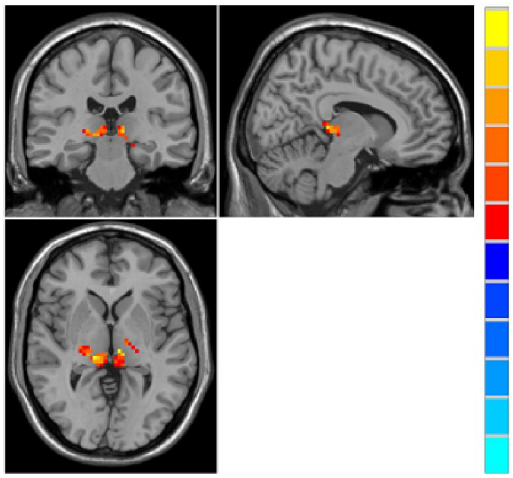

Figure 2. Compared with the healthy controls, the left hippocampus of the PI patients exhibited enhanced functional connection with the bilateral thalamus. The threshold was set at p < 0.05 with a minimum cluster size of 20 contiguous voxels, (The red zone indicates a stronger functional connection.)

4. Discussion

Primary insomniacs have unstable emotions, and sometimes even emotional disorders. Thus, insomnia is seen as a predictive factor of depression. By making comparison between PSQI and HAMA scales of primary insomniac group and healthy control group, this study discovers that the former have a higher PSQI and HAMA scale, indicating that primary insomniacs have worse sleep and apparent anxiety. According to the analysis of the relationship between subjective sleep quality and the length of case history, anxiety degree and an educational background, the decline in sleep quality is related to the length of insomnia and anxious emotions. The CRA cognitive reappraisal is the most frequently used and most effective coordinating strategy in the production of emotions, mainly for controlling negative emotions [14]. Relevant to, Mauss [15]'s research shows a decline in sleep quality can lead to a decline in CRA. If sleep is deprived, cognitive control area (e.g. dorsolateral prefrontal cortex) and emotion reaction area (e.g. amygdala) have a stronger connection when the subject is presented to a negative emotional picture [16]. Sleep deprivation may affect multiple cognitive functions and change the activation of related encephalic regions [17]. A long-term shortage of sleep and a decline in sleep quality can lead to an abnormality in emotion control and coordination, thus disturbing the coordination channel and reaction of negative emotions and causing anxiety and depression. This is one of the reasons why primary insomniacs have anxious feelings.

It is shown in this study that in terms of immediate memory, insertion tests, short and long delayed memory, the primary insomniac group have much lower marks than normal sleep control group and a lower efficiency in write-off experiments, indicating that the primary insomniac group becomes inattentive with a worsened memory. According to a linear regression analysis on the relationship of word-learning ability and write-off efficiency with sleep quality, the length of case history, anxiety degree and educational background, word-learning ability and write-off efficiency are negatively correlated with a degree of anxiety, length of case history and are subjected to a degree of insomnia while positively correlated with a background education. Sleep is a necessary condition for producing and consolidating sleep, and especially the synapse is reorganized during the slow sleep and rapid eye movement sleep [18]. The fMRI results show that the activation of dorsolateral prefrontal cortex, parietal lobe and occipital lobe, which are related to learning ability, this declines after sleep deprivation,[19] while a task-state fMRI shows that the activation of primary insomniacs' prefrontal lobe, parietal lobe and occipital lobe declines,[20] causing worse attention and memory.

This study indicates that primary insomniacs' right hippocampus has a stronger functional connection with the left limbic lobe, right thalamus and left brainstem. The left hippocampus and bilateral thalamus also have a stronger functional connection. As an important structure for producing memory and a participant in memory storage and consolidation, the hippocampus is the coding and storage area for synapse's fragmentary and short-term memory [22]. Limbic lobe participates in regulating emotions [4]; a Thalamus and a brainstem are anatomic areas that have multiple neurotransmitter projection, regulating waking-up and sleep. The brainstem has projection fibers for cholinergic and monoamine neurotransmitters with a "REM sleep switch" [23]; the Thalamus is where the biological clock lies, and it also has projection fibers for histamine neurotransmitters, Orexin and γ-aminobutyric acid neurotransmitters. The interactions of all the above-mentioned brain structures determine whether a man is in a sober or sleeping state. Previous fMRI studies (references) have discovered that insomniacs have smaller hippocampus [24] and the severity of insomnia is related to the reduction of the size of CA3/dentate gyrus of hippocampus[7]. When the memory of a word reappears, the activated area of hippocampus becomes smaller while the activated area of dorsolateral prefrontal cortex expands, indicating the memory fragments are transferred to the prefrontal lobe and transformed into long-term memory through sleep[5]. However, for a primary insomniac with an impaired hippocampus, more sleep is required to facilitate the transformation to store the memory. Meanwhile, the thalamus and the brainstem could regulate sleep, therefore the connection between the hippocampus and the thalamus and the brainstem is strengthened to ensure the continuous consolidation of memory. In addition, the strengthened functional connection of primary insomniacs' limbic lobe is related to their anxious emotions.

All in all, primary insomniacs have impaired cognition and emotional regulation, the degree of which is related to the severity of the insomnia. The changed functional connection of primary insomniacs can be related to the impaired hippocampus and strengthened feedback functional connection. It also indicates the biological demand that the memory production requires more sleep. The change of the functional connection shown in the resting-state fMRI provides objective imageological evidence for

understanding the impairment of cognitive function and evaluating the clinical treatment of insomniacs.

5. Conclusion

The PI patients show a decline in word-learning ability and write-off efficiency, which is negatively correlated with anxious feelings, the length of case history, the sleep quality, and are positively correlated with an educational background. The functional connection between the patients' hippocampus and their bilateral thalamus, the left limbic lobe and the left brainstem is strengthened probably because insomniacs have impaired hippocampus hence the feedback and functional connection of the sleep regulation regions are strengthened to satisfy the learning requirements.

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[*]**Corresponding author;**
Dr. Junfang Teng
Department of Neurology
First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China.
Email: 13838210077@163.com

M.D. Yongli Li
Department of radiology
People's Hospital of Zhengzhou University, Zhengzhou, Henan, China
Email: shyliyongli@126.com

[#] These authors contributed equally to this work and should be considered co-first authors.

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