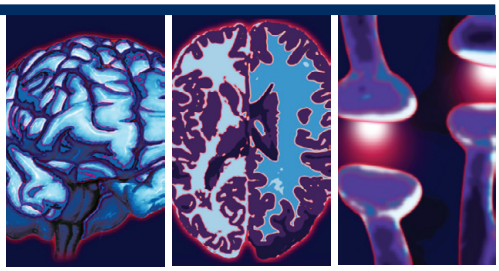

Bibliometric Analysis on Literature of Working Memory on the Patients with Epilepsy in China

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ABSTRACT

In order to provide scientific support and pave new avenues for future studies of superior cognitive function in patients with epilepsy, we systematically sorted the data of working memory research about Chinese epileptics by using bibliometric analysis. Our analysis found: (1) studies in the working memory of Chinese patients with epilepsy were rarely reported; (2) these studies are related to working memory impairment of epileptics, its factors and neurobiological underpinnings; (3) questionnaires and laboratory experiments were the main methodology used in these studies. Though some valuable results were gained from studies involved in working memory of Chinese patients with epilepsy, further research should be devoted to improve cognitive function of epileptics by using working memory training, strengthen interdisciplinary collaboration, and explore how to conduct psychological intervention for epileptics who received working memory training.

Keywords: Epilepsy; Working memory; Bibliometric analysis; Chinese

ntroduction

Epilepsy is a group of neurological disorders featured by epileptic seizures [1,2]. The characteristic of epilepsy is recurrent, unprovoked and transient dysfunction of central nervous system induced by neurons abnormal discharge (Guidelines to Chinese Epilepsy Diagnosis). The syndromes of epilepsy not only include commonly clinical epileptic seizures, but also contain different degrees of cognitive impairment characterized by impairments of memory, language, attention and executive function. Moreover, cognitive impairments could severely disrupt life of patients with epilepsy, and the severity of epilepsy is associated with the type of seizures, the age of onset and antiepileptic treatment [3].

Working memory, as the core of advanced cognitive functions, is defined as a system to temporarily store information during individuals executing cognitive tasks [4]. The formation of working memory requires complicated cohesive coordination of several brain areas [5]. As epilepsy tends to induce seizures in a long term, we can speculate that the damage of working memory in these patients might be physiological and functional. In the present bibliometric analysis study, we summarized articles and reports related to working memory of patients with epilepsy which published on Chinese professional journals, in order to systematically outline the research status of working memory studies in Chinese patients with epilepsy, provide scientific supports and pave new avenues for future studies of advanced cognition in epilepsy.

Methods

We conducted a retrieval of all documents involved in working memory and epilepsy by using China National Knowledge Infrastructure (CNKI) on 1st November 2019. Firstly, keywords (epilepsy, working memory) were used to search documents. Secondly, the index mode was precisely match. Thirdly, the index range was

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entire. These three index conditions yielded a list of 21 papers.

The selection of studies includes two steps. The first step was to read title and abstract of the research article. The second step was to read the full text. Both steps were conducted by a dedicated doctor of psychology. The search results were selected with following criteria: (1) empirical research reflecting research results by quantitative value; (2) research subjects including patients with epilepsy; (3) research method including working memory tasks; (4) published on Chinese professional journals. Finally, 13 documents were recruited for the quantitative analysis.

Table 1: Participant demographics involved in cognitive capability test.

Authors	Patients number	Age	Gender	Years of education	Site of lesion	Duration (year)	Diagnosis	Control
Ma C. & Zhou N [9]	51	10-17 (13.04 ± 2.42)	M=31; F=20	6.80 ± 2.42	N/A	3.47 ± 2.92	No positive report of neurological and imaging exam; epilepsy	61
Ni B, Qian C, et al. [28]	6	N/A	M=4; F=2	N/A	N/A	5-25	Epilepsy	N/A
Wei F, Tao L, et al. [24]	15	17-48 (25.06 ± 7.88)	M=7; F=8	N/A	Medial temporal lobe; hippocampal sclerosis	1-25 (10.65 ± 7.83)	mTLE; hippocampal sclerosis	21
Wu C, Xiang Z [15]	48	18-46 (30.2 ± 9.3)	M=29; F=19	6-16	N/A	2-20 (12.1 ± 3.7)	GTCS(N=24); CPS(N=17); SPS(N=7)	45
Wang Y, Chen Zi, et al. [25]	15	19-46 (34 ± 4)	M=8; F=7	N/A	Medial temporal lobe	1.5-13 (4.2 ± 2.4)	mTLE	15
Yang E, Yu Q, et al. [10]	36	33.00 ± 10.72	M=6; F=14	11.70 ± 2.85	Medial temporal lobe	N/A	mTLE(N=20)	15
		28.06 ± 9.97	M=7; F=9	11.87 ± 2.55	Frontal lobe	N/A	FLE(N=16)	
Lv Z, Zheng J, et al. [27]	15	26.5 ± 7.3	M=6; F=9	10.7 ± 1.9	Right medial temporal lobe	N/A	rTLE	16
Huang W, Zheng J, et al. [26]	11	26.5 ± 6.7	M=4; F=7	9.9 ± 2.1	Left medial temporal lobe	5.9 ± 7.4	lTLE	16
Song Y, Wang K et al. [18]	62	18-69 (35.6 ± 17.5)	M=39; F=23	N/A	N/A	0.08-1 (0.29 ± 0.175)	PS-GTCS(N=31); CPS(N=23); SPS(N=8)	N/A
Song Y, Zhao, X [17]	83	16-68 (34.5 ± 16.5)	M=49; F=34	N/A	N/A	0.08-0.5 (0.125 ± 0.192)	PS-GTCS(N=41); CPS(N=32); SPS(N=10)	40
Li N, Song Y [18]	86	20-56 (26.6 ± 11.5)	M=54; F=32	N/A	N/A	0.08-1 (0.29 ± 0.175)	GTCS	30
Xiao GZ [16]	120	18-56 (25.02 ± 7.16)	M=58; F=62	12.53 ± 7.16	N/A	5.01 ± 4.06	Epilepsy	120
Zhu J, Li H, et al. [29]	19	16-53 (27.5 ± 2.4)	M=11; F=8	N/A	Frontal lobe	N/A	FLE	17

Notes: mTLE: medial temporal lobe epilepsy, rTLE: right temporal lobe epilepsy; lTLE: left temporal lobe epilepsy; FLE: frontal lobe epilepsy, GTCS: generalized tonic-clonic seizures, CPS: complex partial seizures, SPS: simple partial seizures, PS-GTCS: partial seizures (generalized tonic-clonic seizures), M= male, F= female

Results

Publication details

The publication time of 13 documents ranged from 2009 to 2019. Specific content is shown in **Table 1**. Thirteen documents were published on three different types of journal. Four documents were published on journals of university (30.7%), seven documents were published on journals of medical science (53.8%), and the rest on journals of biophysics (15.4%). The specific information is shown in **Figure 1**.

Research methods

Authors of these 13 documents came from two kinds of institutions which is school of medicine in university (2, 15.4%) and hospitals (11, 84.6%). Methodology used in these working memory studies was based on behavioral research (7, 53.8%) and brain functional research which included functional magnetic resonance imaging (fMRI) study (5, 38.5%) and electroencephalography (EEG) study (1, 7.7%), the details are shown in **Table 1**.

Research subjects and tools

Subjects involved in these studies contained adult (12, 92.3%) and children (1, 7.7%) with epilepsy. Thereinto, five documents were related to idiopathic epilepsy (38.5%). Seven documents (53.8%) and one (7.7%) document were related to symptomatic epilepsy and cryptogenic epilepsy, respectively. As for research tools, the digit span task and verbal fluency test were the most common tool to measure the capacity of working memory (6, 46.2%). Two studies used the n-back task (15.4%) and other two studies used delayed match task and its variants (15.4%). Self-revised working memory/executive function test was also used in two studies (2, 15.4%). Besides, one research (7.7%) used resting-state MRI scanning to assess visual and spatial working memory network (**Table 2**).

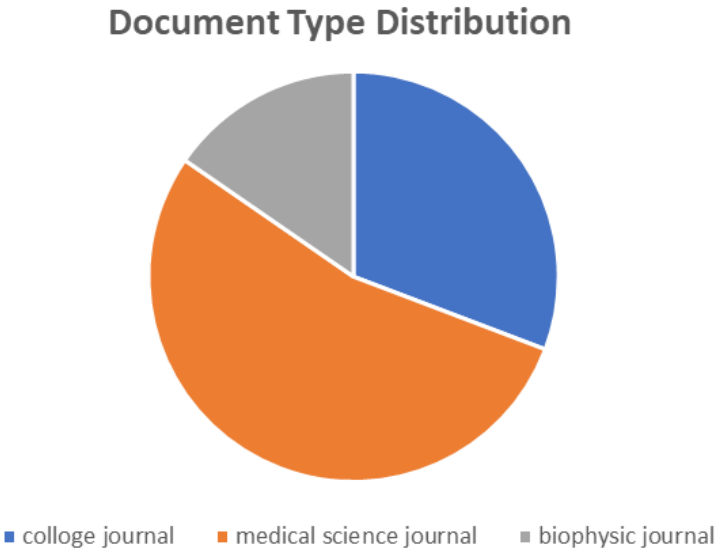

Figure 1: Document type of research focused on epileptic working memory in China.

Table 2: Cognitive capability test of patients with epilepsy.

Authors	Objectives	Test tools	Main findings
Ma C. & Zhou N [9]	To investigate basic cognitive capabilities in children with idiopathic or cryptogenic epilepsy	Raven's standard progressive matrices; Basic cognitive capability test (version 2.0)	IQ: no difference; Cognitive capability test: decreased total scores of basic cognitive capabilities were found in children with epilepsy.
Ni B, Qian C, et al. [28]	To study the time course of goal match enhancement in patients with epilepsy	Revised delayed match task by Dunch; EEG; MRI (SPRAGE sequence); CT	Left hippocampus played a vital role in mid-period of goal match enhancement; latent period of goal match enhancement was positively related to mean reflective time.

Wei F, Tao L, et al. [24]	To investigate the working memory impairment in patients with medial temporal lobe epilepsy	fMRI (GRE-EPI sequence); 2-back working memory task;	Decreased activation in some brain areas such as DLPFC, basal ganglia, hippocampus was found in mTLE patients performed working memory task; partial areas of DMN showed increased activation.
Wu C, Xiang Z [15]	To assess the association between depression and visual working memory impairment	HAMD; visual-object and visual-space working memory task	The scores of visual-space working memory in patients with epilepsy were decreased compared with control; depression could obviously impair the visual-object working memory in epileptics.
Wang Y, Chen Zi, et al. [25]	To explore the neural basis of working memory and its impairment in patients with TLE	Digit 2-back working memory; BOLD-fMRI;	The performance of TLE patients in 2-back working memory task was worse than normal control; working memory relevant brain areas and working memory network were impaired in TLE patients.
Yang E, Yu Q, et al. [10]	To investigate the characteristics of cognitive function in TLE and FLE patients	Working memory test; auditory verbal memory test; Rey-Osterrieth complex figure test; neuropsychological assessment of attention, executive functions and memory components	Attention, executive functions and memory impairment were found in both FLE and TLE patients; verbal memory in TLE was impaired worse than in TLE.
Lv Z, Zheng J, et al. [27]	To analyze resting-state brain network involved in VSWM of rTLE patients	RS-MRI; MICA	VSWM related RSN in rTLE patients was impaired and it indicated a functional plasticity to VSWM with increased FC within the ipsilateral cerebral network.
Huang W, Zheng J, et al. [26]	To investigate the FC of VWM in lTLE patients	Digit span test; task-based fMRI; RS-fMRI	The FC strength of main functional brain areas was decreased in lTLE patients; no positive correlation could be found between the FC strength and the performance of the digit span test.
Song Y, Wang K et al. [18]	To investigate the effect of levetiracetam on brain electrical activity and cognition in adult partial epilepsy	Electroencephalogram; trail making test; digit symbol test; verbal fluency test; digit span test	Levetiracetam could decrease even eliminate interictal epileptiform abnormalities without influencing brain electrical activity background, and improve the cognitive function.
Song Y, Zhao, X [17]	To assess the correlation between GFAP level in serum of patients with epilepsy and cognitive function	ELISA; trail making test; digit symbol test; digit span test; verbal fluency test	Serum level of GFAP was increased in patients with epilepsy; increased serum level of GFAP in patients with epilepsy was correlated with poor performance in cognitive capabilities test.
Li N, Song Y [18]	To investigate the cognitive function and serum levels of insulin-like growth factor-1 in patients with subclinical epileptiform discharges and clinical significance	EEG; ELISA; trail making test; digit symbol test; verbal fluency test; digit span test	Increased serum IGF-1 levels were correlated to subclinical epileptiform discharges; subclinical epileptiform discharges could induce brain damage and neuroprotection.
Xiao GZ [16]	To study the characteristics and factors of executive function in adult patients with idiopathic or symptomatic epilepsy	BRIEF-A; MMSE; HAMD-17	The executive function could be impaired in adult patients with idiopathic or symptomatic epilepsy; The severity of executive function impairment was closely related to seizures types, seizures frequency, the control of seizures and usage of antiepileptic drug.

Zhu J, Li H, et al. [29]	To investigate the characteristic of theta oscillation in FLE patients	EEG; short-time Fourier transform	Impaired working memory was found in FLE patients; the absence of theta oscillation during the working memory delayed period could be a neural mechanism for the working memory dysfunction in FLE.

Notes: fMRI: functional magnetic resonance imaging; EEG: electroencephalograph; CT: computed tomography; mTLE: medial temporal lobe epilepsy; DLPFC: dorsal lateral prefrontal cortex; DMN: default mode network; HAMD: Hamilton depression scale; TLE: temporal lobe epilepsy; BOLD-fMRI: blood oxygenation level dependent functional magnetic resonance imaging; VSWM: visuospatial working memory; RS-MRI: resting-state magnetic resonance imaging; MICA: multiple independent component analysis; FC: functional connectivity; VWM: verbal working memory; lTLE: left temporal lobe epilepsy; GFAP: glial fibrillary acidic protein; IGF-1: insulin-like growth factor-1; ELISA: enzyme-linked immunosorbent assay; BRIEF-A: behavior rating inventory of executive function, adult; MMSE: mini-mental state examination.

■ Research contents

Two research articles were related to the status of working memory in patients with epilepsy (15.4%). Research about pathophysiological basis of working memory impairment in patients with epilepsy accounted for the biggest part in these 13 documents (6, 46.2%). And five studies were involved in factors associated with working memory of epileptic patients (46.2%).

Discussion

■ Working memory impairment of epileptic patients

Epilepsy is a common neurological disorder which characterized as neurons abnormal discharge inducing transient central nervous system dysfunction. Long-term epileptic seizures could result in cognitive impairment, such as working memory impairment. As working memory is the core of advanced cognition, its impairment could lead to dysfunction of cognitive activities such as reading, problem solving and logical thinking [6].

Studies involved in working memory of patients with epilepsy were still rare in China. The study of Ma and Zhou (2009) used basic cognitive capability test to investigate cognitive capability of children with primary or cryptogenic epilepsy and normal children [7]. Their results showed that there was no significant difference in intelligence between children with epilepsy and normal children. However, children with epilepsy got lower scores in basic cognitive capability test compared with normal children. Except the scores of the double-word recognition test, the average scores of other tests (number recognition test, Chinese characters rapid comparison test, mental arithmetic practice test, digit symbol test, meaningless images recognition test and rotation variant recognition of handprinted Chinese characters) also decreased. Yang et al. [8] conducted neuropsychological assessment for patients with temporal lobe epilepsy and patients with frontal lobe epilepsy by using working memory test, auditory verbal learning test and Rey-Osterrieth complex figure test. Their results demonstrated that the scores of frontal lobe epilepsy group and temporal lobe epilepsy group in working memory, attention and executive capability was lower than that of control group. Moreover, the performance of frontal lobe epilepsy group in attention, working memory, control/inhibition ability, verbal memory and nonverbal memory was worse than temporal lobe memory group.

Basic conclusions can be drawn from the above, cognitive impairment is an inevitable result for patients with temporal lobe epilepsy as well as clinical epileptic seizures. However, results showed that patients with epilepsy in remission may have the same opportunity to receive education and work as normal people, and the neuropsychological function of them is also at normal stage [9]. This indicated that the processes of cognitive impairment in epileptic patients may be reversible. Therefore, physicians should pay attention to basically cognitive capability of patients with epilepsy during therapeutic procedures so that side effects of treatment could be reduced.

■ Influence factors in working memory research of epileptics

Epilepsy could damage brain neurons and morphological changes of synapses, which leads to impairment of memory [10,11]. For patients with epilepsy, the severity of working memory impairment is different from each patient due to type of seizure, causes of disease, usage of medication and individual variations [12]. In China, studies involved in the influence factors

of working memory impairment of epileptic patients mainly included several aspects as follows:

Firstly, individual variations of epileptic patients influenced their working memory performance. Wu and Xiang used Hamilton depression scale, visual-object and visual-space working memory task to explore depression and visual working memory of patients with epilepsy. It found that patients with epilepsy had higher level of depression and worse performance of working memory in contrast to healthy people [13]. They also found that depression could influence performance of epileptics in visual working memory test. Besides, in the study of Zhou and Xiao, they recruited adult patients with idiopathic epilepsy or symptomatic epilepsy and healthy adults whose gender, age, marriage and education were matched with each patient as subjects [14]. After that, they used Behavior Rating Inventory of Executive Function-Adult version (BRIEF-A) to study characteristics of executive function and its effects in adult patients with idiopathic epilepsy or symptomatic epilepsy [15]. The results demonstrated that the executive function index of epileptics was worse than that of control group. Besides, the type of seizures, epileptic frequency and usage of antiepileptics were strongly related to the performance of executive function.

Secondly, antiepileptics could influence performance of working memory in patients with epilepsy. Specifically, the study of Song and colleagues (2014) [16] used adult patients with partial epilepsy as subjects to investigate the effects of levetiracetam on cognition and electrical activities of brain. Their results demonstrated that the EEG of these patients was the same before and after levetiracetam treatment. Epileptic discharge of patients diminished or decreased at least 50% after 12 weeks of levetiracetam treatment. Moreover, the performance of patients in cognition test was better than that of before treatment. In another study of Song, they used enzyme-linked immune sorbent assay (ELISA) to measure the serum level of glial fibrillary acidic protein (GFAP) combined with trail making test, digit symbol test, digit span test and verbal fluency test to investigate the relation between serum level of GFAP and cognition in patients with epilepsy [17]. The results showed that serum level of GFAP in patients with epilepsy was negatively correlated with patients' performance in digit symbol test and verbal fluency test, while positively correlated with patients' performance in trail making test.

Thirdly, subclinical epileptiform discharges have effects on cognition such as working memory. Song and Li recruited idiopathic epilepsy patients with generalized tonic-clonic seizure as subjects to investigate the relation between serum level of insulin-like growth factor 1 (IGF-1) and cognition [18]. The results demonstrated that serum level of IGF-1 in subclinical epileptiform discharges group was higher than normal EEG group. And serum level of IGF-1 in subclinical epileptiform discharge group was negatively correlated with performance of cognition in patients with epilepsy.

According to conclusions above, these studies not only investigated the effects of seizures type, etiology and psychological variations on working memory from perspective of individual differences, but also disclosed the effects of antiepileptics on working memory from the perspective of pathology.

■ Pathophysiology of working memory impairments in epilepsy

In recent years, more and more studies showed that structural abnormality and abnormal intrinsic functional connectivity of brain are speculated as the causes of neuropathy and mental disorders [19-22]. As an advanced cognition, normal function of working memory requires working memory networks consisted of cerebral cortex (frontal lobe, parietal lobe and temporal lobe), cerebral subcortex and cerebella properly works [23]. Investigating the pathophysiology of epileptic's working memory could be helpful to understand the mechanism of epileptic's cognitive impairment and enrich the research of working memory networks. Studies related to mechanism of epileptic's working memory in China mainly involved in several aspects as follows:

Firstly, from the perspective of structure and function, some studies used fMRI to reflect working memory impairment of patients with epilepsy. The study of Wei used fMRI to study working memory of epileptic patients when they were conducting the working memory task [24]. Compared with control group, the activities of dorsolateral prefrontal cortex, bilateral parietal lobe, thalamus, basal ganglia and hippocampus in TLE patients were down-regulated while the activities of some brain areas (precuneus and bilateral cingulate gyrus) were up-regulated. In

Wang's study, the results of fMRI showed that when conducting 2-back working memory task, TLE patients had a worse performance and lower activation level of forehead and parietal brain area than that of control group [25].

Some other studies used the resting-state fMRI to extract working memory networks and compare the differences between patients with epilepsy and normal group. Huang et al. used the resting-state fMRI combined with digit span test to study verbal working memory (VWM)'s functional connectivity and its relation with cognition in patients with left temporal lobe epilepsy (LTLE) [26]. They found that the scores of LTLE group in digit span test were lower than that of control group. And the strength of functional connectivity among left prefrontal cortex, bilateral parietal lobe and the right cerebellar cortex was significantly decreased in LTLE group, while the scores of LTLE group in digit span test was independent with the strength of functional connectivity. In study of Lv et al, they used resting-state fMRI to compare spatial distribution and functional connectivity of visuospatial working memory (VSWM) between groups based on group independent component analysis method. Patients with right temporal lobe epilepsy and normal group were recruited as subjects [27]. Results showed that there was no difference in distribution of VSWM related brain networks between RTLE group and healthy control. However, when RTLE group was under resting-state, the functional connectivity of brain networks of VSWM in right dorsolateral prefrontal, right parietal lobe (BA8) and left inferior parietal lobe was weaker than that of control group. As for the functional connectivity in BA10, left cerebellar lobe and right superior parietal lobule, RTLE group was stronger than healthy people.

Secondly, some studies recorded brain electrical activities to investigate the processes of working memory impairment in patients with epilepsy and damage severity of different components of working memory. Ni and colleagues [28] investigated the role of hippocampus in goal match enhancement and time processes of goal match enhancement by implanting deep brain stimulation in bilateral hippocampus of patients with epilepsy.The findings demonstrated that the left hippocampus played an important role in the goal match enhancement. Moreover, the enhancement effect was detected after 600-650ms of stimulation. Zhu and colleagues [29]they used EEG to study properties of theta oscillations of working memory in patients with frontal lobe epilepsy (FLE). They collected signals of theta oscillations under resting-state state and delayed match task. The results showed that FLE group had a delayed response in working memory task in contrast to control group. In addition, in FLE group, the energy density of Fz electrode and frontal theta oscillations in resting-state were significantly increased compared with control group while decreased in delayed match task.

The studies above indicated that studies related to the pathophysiology of working memory on Chinese epileptic patients gave us a holistic map of working memory impairment in these patients to some extent. Specifically, the neural basis of working memory is a network which includes frontal lobe as dominant component combined with several brain areas of parietal lobe and temporal lobe. Patients with epilepsy have different damage severity of impairment on working memory brain areas and networks when performing working memory tasks or staying at resting state. The absence of theta oscillations in latency of working memory might be one of the mechanisms. Besides, hippocampus plays a vital role in working memory tasks related to spatial locations. Goal match enhancement effect happened after perceptual processes, which indicated that different components of working memory were separated in hippocampus. However, it is also required more studies involving in properties and mechanisms of working memory impairment so that working memory impairment in epilepsy could be prevented or decreased.

According to studies above, controlling seizures, avoiding multi-drug therapy, selecting new antiepileptics with little side effects and monitoring therapeutic effect by recording brain electrical activity regularly might be the effective methods to prevent or decrease working memory impairment in epileptic patients. At the same time, The role of diet and food quality has been shown to be important with relevance to working memory performance and the control of epilepsy. Dietary activators are important to the activation of genes that are important to memory performance and the prevention of epilepsy. Controlling seizures by avoiding multidrug therapy, use of new antiepileptics and monitoring therapeutic effects may be linked to diet and food quality to decrease working memory impairment in epileptic patients in China [30-33].

Declaration of Interest

The authors have declared that no competing interests exist.

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