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Altered cerebral activity associated with topiramate and its withdrawal in patients with epilepsy with language impairment: An fMRI study using the verb generation task

Yingying Tang [a,1], Wei Xia [b,1], Xiaofeng Yu [a], Bo Zhou [c], Xintong Wu [a], Su Lui [d], Chunyan Luo [a], Xiaoqi Huang [d], Luo Ouyang [e], Qin Chen [a,*], Qiyong Gong [d,f,**], Dong Zhou [a,***]

[a] Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[b] Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China
[c] Department of Psychosomatic Medicine, Sichuan Province People's Hospital, Chengdu, Sichuan, China
[d] Huaxi MR Research Center, Department of Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[e] Southwestern Medical Center, University of Texas, Dallas, TX, USA
[f] Division of Medical Imaging, Faculty of Medicine, University of Liverpool, Liverpool L69 3BX, United Kingdom

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ABSTRACT

Objective: Topiramate (TPM) is well recognized for its negative effects on language in healthy volunteers and patients with epilepsy. The aim of this study was to investigate the brain activation and deactivation patterns in TPM-treated patients with epilepsy with language impairment and their dynamic alteration during TPM withdrawal using functional magnetic resonance imaging (fMRI) with the verb generation task (VGT).

Methods: Twelve patients with epilepsy experiencing subjective language disfluency after TPM add-on treatment (TPM-on) and thirty sex- and age-matched healthy controls (HCs) were recruited. All subjects received a battery of neuropsychological tests and an fMRI scan with the VGT. Withdrawal of TPM was attempted in all patients. Only six patients reached complete withdrawal without seizure relapses (TPM-off), and these patients underwent a reassessment of neuropsychological and neuroimaging tests.

Result: The neuropsychological tests demonstrated objective language impairments in TPM-on patients. Compared with the HCs, the bilateral medial prefrontal cortex and the posterior midline and lateral parts of the default mode network (DMN) (including the bilateral posterior cingulate cortex (PCC), the right medial prefrontal cortex, the right angular gyrus, the right inferior temporal gyrus, and the bilateral supramarginal gyrus) in TPM-on patients failed to deactivate during the VGT. Their task-induced activation patterns were largely similar to those of the HCs. After TPM withdrawal, partial improvement of both task-induced deactivation of the DMN (the left parahippocampal gyrus and the bilateral PCC) and task-related activation of the language network (the right middle frontal gyrus and the left superior occipital gyrus) was identified along with partial improvement of neuropsychological tests.

Conclusion: Task-induced deactivation is a more sensitive neuroimaging biomarker for the impaired language performance in patients administered TPM than task-induced activation. Disruption and reorganization of the balance between the DMN and the cortical language networks are found along with reversible TPM-related language impairment. These results may suggest an underlying brain mechanism by which TPM affects cognitive function.

1. Introduction

Topiramate (TPM) is an efficient antiepileptic drug (AED) for drug-resistant epilepsy and has been shown to be associated with central nervous system-related dysfunction [1–3]. The cognitive adverse effects of TPM are generally related to higher dosages, rapid titration, and polytherapy [4,5]. This is a clinically important issue in the management of patients suffering from drug-resistant epilepsy, not only for its early detection but also for the problems encountered when discontinuing the drug, given that TPM has a favorable effect on seizure control [5].

* Correspondence to: Q. Chen, Department of Neurology, West China Hospital, Sichuan University, No. 37 Guo Xue Lane, Chengdu 610041, China. Tel.: +86 18602898299; fax: +86 2885422550.
** Correspondence to: Q. Gong, Huaxi MR Research Center, Department of Radiology, Center for Medical Imaging, West China Hospital, Sichuan University, No. 37 Guo Xue Lane, Chengdu 610041, China. Tel.: +86 18980601593; fax: +86 2885423503.
*** Correspondence to: D. Zhou, Department of Neurology, West China Hospital, Sichuan University, No. 37 Guo Xue Lane, Chengdu 610041, China. Tel.: +86 13980008088; fax: +86 2885422550.
E-mail addresses: chenqin8124@gmail.com (Q. Chen), qiyonggong@hmrrc.org.cn (Q. Gong), zhoudong66@yahoo.de (D. Zhou).
[1] Yingying Tang and Wei Xia contributed equally to this manuscript.

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Table 1
Demographics and language performances of the patients with epilepsy with TPM add-on treatment and the healthy controls.

Characteristics	TPM-on patients	Healthy controls	p-Value
Number of patients	12	30	
Male/female	7/5	8/22	$p = 0.41^{*}$
Age (years)	27.50 ± 11.77	26.19 ± 10.01	$p = 0.71$
Disease duration (years)	8.58 ± 6.16	N/A	
Seizure frequency ($month^{-1}$)	0.93 ± 1.15	N/A	
Type of epilepsy (CPS:GTCS:CPS–GTCS)	3:5:4	N/A	
Seizure focus			
Temporal	4		
Extratemporal	2		
Unknown	6		
Duration of TPM treatment (months)	9.42 ± 5.33		
TPM dosage (mg/day)	95.83 ± 46.26		
Boston naming test	19.58 ± 3.73	26.1 ± 2.13	$p < 0.0001^{**}$
Verbal fluency test	23.67 ± 8.71	54 ± 9.8	$p < 0.0001^{**}$

Data are provided as the mean ± standard deviation unless otherwise indicated. TPM: topiramate, CPS: complex partial seizure, GTCS: generalized tonic–clonic seizure, N/A: not available.
** $p < 0.01$.
* $p < 0.05$.

The lack of insight into the underlying mechanism of TPM-induced language impairment is hindering its optimal clinical application.

With the advantage of being noninvasive, functional magnetic resonance imaging (fMRI) has been extensively applied to investigate the pathophysiology of patients with epilepsy, as well as patients with cognitive disorders [6–8]. However, few studies have used fMRI to detect cerebral activity related to TPM-induced language impairment in patients with epilepsy. Jansen et al. observed significantly less activation in language-mediating brain regions in patients with epilepsy administered TPM [9]. Another fMRI study revealed that TPM is associated with impaired verbal fluency and disruption of task-related deactivation of the default mode network (DMN) [10]. Thus, investigating task-related activation and deactivation patterns may provide more information regarding the language impairment resulting from TPM.

Previous studies have demonstrated approximately completely recovered language performance in TPM-treated patients after TPM withdrawal [11–13]. However, whether the effects of TPM on cerebral activities are reversible remains unknown, and no studies using fMRI to investigate the effect of TPM withdrawal have been published to date. Using fMRI to directly compare the brain activation/deactivation patterns of patients before and after TPM withdrawal may lead to a better understanding of the brain mechanisms by which TPM affects language function.

Consequently, we designed a longitudinal withdrawal study to examine the changes in cerebral activities in TPM-treated patients with epilepsy with speech disturbances by using fMRI with the verb generation task (VGT). In the present study, we sought to test the following hypotheses: 1) TPM-treated patients with epilepsy with speech disturbances exhibit a distinct cerebral activation/deactivation pattern compared with healthy controls (HCs) during the VGT and 2) the cerebral activation/deactivation patterns of patients with TPM-treated epilepsy are reorganized with improvements in language performance when TPM is withdrawn.

2. Materials and methods

2.1. Subjects

Twelve patients with epilepsy experiencing subjective language disfluency after TPM add-on treatment (TPM-on) were recruited at the Department of Neurology, West China Hospital of Sichuan University (see details in Tables 1 and S1). Seizure and syndrome classifications were based on the International League Against Epilepsy (ILAE) criteria [14]. All patients underwent a thorough history taking, physical and neurological examinations, and scalp electroencephalography. The exclusion criteria included 1) visible conventional MRI lesions, 2) other serious systemic diseases or psychological diseases, 3) being pregnant and nursing, and 4) experiencing seizures within 15 days prior to the fMRI scan. TPM was withdrawn for clinical purposes as determined by the patients' personal physicians. Based on the instructions and previous experience [15], TPM was reduced in 100-mg/day decrements at weekly intervals for safety. The absence of seizure relapses during the entire tapering and withdrawal period was termed a successful withdrawal (TPM-off). Topiramate also had to be completely withdrawn for at least three days before the reassessment for this period was assumed to be sufficient for complete plasma elimination. Thirty sex- and age-matched HCs were recruited from the local area using a poster advertisement. All subjects were native Chinese speakers and right-handed, as assessed by the Edinburgh Inventory handedness test.

This study was approved by the local ethics committee at West China Hospital of Sichuan University. All subjects provided written informed consent for their participation.

2.2. Neuropsychological assessment

According to a literature review and our own clinical experience, tests that were particularly sensitive to TPM-induced language impairment were chosen, including the verbal fluency test (VFT) and Boston naming test (BNT) [9–11,16]. The performance of these two tests was measured using the total number of correct responses. Verbal fluency test and BNT were conducted in HCs, and in the patients during both the TPM-on and TPM-off periods. Then, two-sample t-tests were performed to examine the differences for each language assessment between the TPM-on patients and the HCs, with $p < 0.05$ considered significant. A paired t-test was performed between the TPM-on and the TPM-off groups, with $p < 0.05$ considered significant.

2.3. Image acquisition

Functional images were obtained from HCs and patients during both the TPM-on and the TPM-off periods using a 3-T MRI scanner (Excite; General Electric, Milwaukee, Wisconsin). The task-related stimuli were backprojected onto a screen at the foot of the scanning table that patients could see via a mirror mounted on the head coil. Subjects

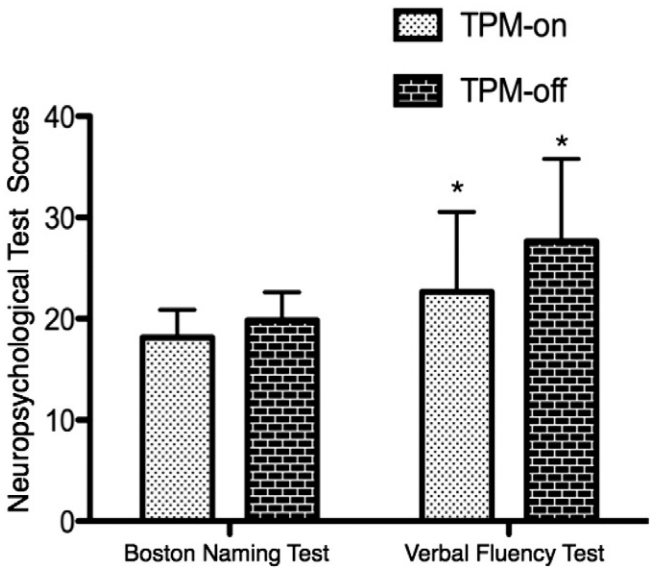

Fig. 1. Values of the neuropsychological tests before and after TPM withdrawal. *$p < 0.05$.