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HOW A DRUG CAN MAKE YOUR BRAIN FORGET THE WORDS? A LANGUAGE FUNCTIONAL MRI STUDY WITH TOPIRAMATE IN EPILEPSY AND HEADACHE

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Abstract: Cognitive dysfunctions are common in epilepsy patients and can be aggravated by antiepileptic drugs such as topiramate (TPM). Word finding difficulties are the most common effect reported by TPM taking subjects, with and without epilepsy. Although widely used, the mechanism of such cognitive dysfunction is still unclear.

This project aims to investigate the effects of TPM through cognitive tests and functional magnetic resonance images of 51 subjects distributed in 3 groups: healthy controls, epilepsy patients taking TPM and headache patients taking TPM. The third group is essential to avoid the bias of poor cognitive performance being due to the epileptic seizures.

The language tests showed a reduced performance of TPM groups compared to controls. Brain activations and deactivations were reduced in subjects taking TPM, compared to controls.

Our results suggest that TPM causes disruptions in cerebral activations and deactivations, which may be related to word production difficulties.

Legal authorization: The present study is a branch of the main project “Avaliação dos efeitos cognitivos do topiramato através de estudo com ressonância magnética funcional.” approved by CEP-UNICAMP with the CAAE 01725412.5.0000.5404 under the supervision of Clarissa Lin Yasuda, professor at Faculty of Medical Sciences-UNICAMP.

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Introduction: Topiramate is an antiepileptic drug with broad spectrum, widely used as prophylatic treatment of headache (migraine subtype). Despite the excellent control of epilepsy seizures and headache, TOPIRAMATE (TPM) can cause *language* (especially word finding difficulties, as in figure 1) and *memory impairment*, mostly unnoticed by subjects [1, 2].

Figure 1: Simple representation of word finding difficulties after taking topiramate.

So far, it is unknown how TPM changes brain and causes these side effects. Here, we applied cognitive tests and language fMRI to healthy controls, subjects with migraine/headache (HEAD) and others with temporal lobe epilepsy (TLE) to investigate dysfunction on brain activations and deactivations.

We hypothesize that TPM disrupts the normal pattern of activations and deactivations, resulting in poor cognitive performance.

Materials and Methods:

Subjects

After Ethical approval, we performed a cross-sectional study, recruiting 24 healthy controls (18 women, mean age 42±13 years), 15 patients with migraine/headache taking TPM (HEAD-TPM, 12 women, 39±12 years) and 12 patients with unilateral temporal lobe epilepsy using TPM (TLE-TPM, 11 women, 39±13 years). Patients were recruited from both Epilepsy and Headache outpatient clinics at UNICAMP Hospital.

fMRI acquisition

All subjects were submitted to a magnetic resonance exam in UNICAMP Hospital's 3T PHILIPS scanner. In addition to the structural image, a high resolution T1 weighted MRI, they performed a blocked-design language paradigm under the instruction to covertly (silently, not loud) follow a screen that alternated between three different tasks (20 seconds each):

- *Phonemic task*: think about words beginning with the different letter given in the screen.
- *Categorical task*: think about the name of figures (animals and fruits) they were visually presented.
- *Resting State*: try not to focus on specific thought or task.

Cognitive tests

All subjects underwent cognitive testing with a psychologist. The participants received four tasks: generate words beginning with the specified letters F, A, S and random animal's names in determined amount of time (60 seconds for each task).

Imaging Processing and Statistics

First, all functional images were realigned, normalized, smoothed and co-registered with the structural image (T1 weighted) using a MATLAB toolbox UF²C[3].

We then performed a first-level analysis (individual study) on SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), to model phonemic task against categorical task and rest and obtain individual maps for each *stimuli*.

To expedite the whole process, we developed some scripts in MATLAB platform to automatically process the first-level for our initial 100 subjects. To accelerate the visual checking of each individual collection of activations and deactivations, a second MATLAB script was created to generate slice view figures for each subject containing a set of figures (Figure 2). Using another script in Perl, we created HTML pages which showed individual sets of SPM maps' figures in a web browser to optimize the checking step by a neurologist.

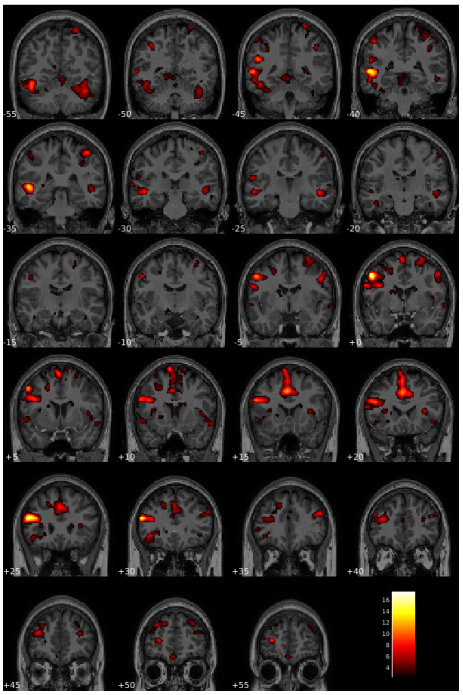

Figure 2: Example of individual activation map generated in MATLAB.

Lastly, these maps were carried to a second-level analysis (group analysis) in SPM with full-factorial model. Here, we also used scripts in MATLAB to automatically perform series of group comparisons. Statistical analyses of cognitive tests were performed with IBM SPSS22.

Results and discussion: Groups were balanced for age (p=0.8) and gender (p=0.5). A multivariate analysis of language tests ([$F_{(4,92)}$=6, p<0.0001, Pillai's Trace=0.4, partial η2=0.2]) showed significant reduction of word production with letters (FAS test) for both HEAD-TPM and TLE-TPM (p<0.001)** compared to controls; no significant differences were observed for categorical (animals) word production (p>0.05) for these 2 groups, compared to controls (Chart 1).

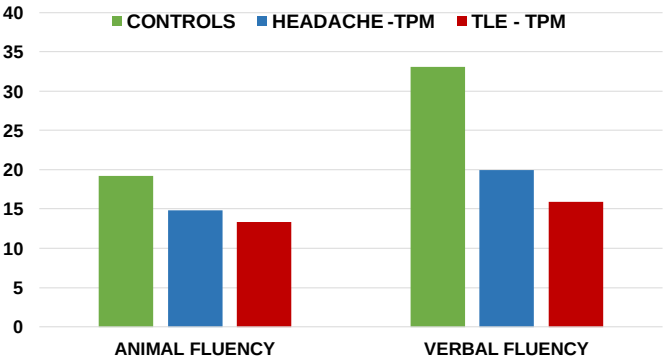

Chart 1: Negative effect of topiramate on language

On fMRI results we observed less activations in language area (HOT MAPS) and deactivations (COLD MAPS) in resting state area for both HEAD-TPM and TLE-TPM compared to controls (Figure 3).

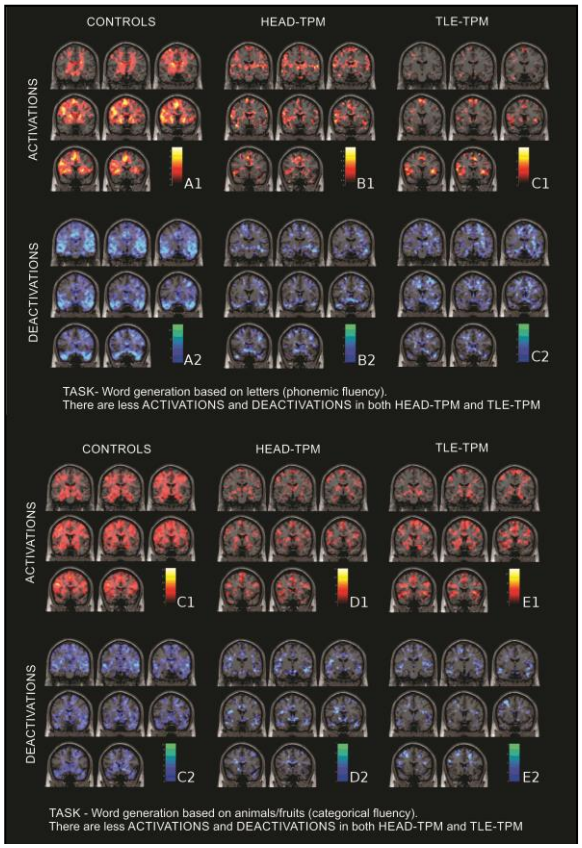

Figure 3: Second level maps of all groups in both fluency tasks.

Our data suggest that TPM prevents normal brain activations and deactivations during language production, which may be associated with poor performance on words generation.

Conclusions:

Taking the advantage of a series of scripts for MATLAB/SPM12 and Perl, we processed data from 100 subjects in very short time. In addition to avoid human error due to repetitive manual processes, the automation of such analysis allowed us to reach very relevant clinical results.

Despite its efficacy in seizure control and headache, TPM significantly impairs language performance and normal brain function during verbal tasks. Careful attention is necessary to prescribe such drug to avoid excessive cognitive dysfunction.

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