

# fMRI reveals declined activation of prefrontal cortex in epilepsy patients on topiramate therapy

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## Introduction

The antiepileptic drug topiramate (TPM) is beneficial for patients with epilepsy in terms of efficacy. However, TPM is also often associated with cognitive side effects, which are an important reason for TPM discontinuation, even when the drug has a favorable effect on seizure frequency [1]. We examined the effect of TPM treatment on patients with epilepsy using fMRI of covert word generation (including a sensitivity analysis of brain regions to TPM treatment) and neuropsychological testing to gain insight into the possible alterations of the functional neuroanatomy of language and underlying cortical activation patterns.

## Material and Methods

Five epilepsy patients using TPM as add-on treatment (TPM group), and 10 epilepsy patients without TPM (control group), but all on polytherapy, were included. The characteristics of the patient and control group matched (i.e. age, epilepsy type, seizure frequency, and full drug load). Language was assessed with a neuropsychological aphasia test battery, and a language performance score was attributed to each patient (1, severe cognitive language problems; to 5, no problems). MRI was performed with a 1.5-Tesla unit (Philips Intera, Philips Medical Systems). Functional MRI data were acquired using a whole-brain single-shot three-dimensional (3D) blood-oxygen-level-dependent echo-planar imaging sequence, with TR 2 s, TE 50 ms, flip angle 90°, voxel size 3.5×3.5×3.5 mm<sup>3</sup>, matrix 64×64, 34 contiguous slices per volume, 96 volumes per acquisition. For anatomical reference, we acquired a 3D T1-weighted fast field-echo image, TR 11 ms, TE 3.5 ms, flip angle 90°, matrix 256×256, 150 contiguous slices and 3.5×3.5×3.5 mm<sup>3</sup> sized voxels. During fMRI, subjects performed covert word generation in response to a visually presented begin-letter. Spatial data preprocessing was performed with SPM2 software. The number of activated voxels was determined in predefined brain regions, essential for language processing [2]. The quantitative analysis consisted of counting all voxels with an activation level, expressed as percent signal change, higher than a certain threshold with respect to baseline signal within the predefined language areas of all individual activation maps. To eliminate the rather strong variation of the noise between subjects, activation was thresholded according to the percent signal change rather than the Student's t-statistics. The threshold should be high enough to exclude a relatively large number of false-positively activated voxels but also low enough to reduce the number of false-negatively activated voxels (i.e. draining veins). Therefore, the threshold was obtained by calculating the global mean (averaged over all patients) plus twice the standard deviation of the activation level of the brain areas, other than the predefined language areas. To visualize which brain regions display the largest or, conversely, the smallest differences in activation level between the TPM and the control group, the average differences with corresponding standard deviation (SD) were calculated on a voxel-by-voxel basis for the whole brain. Then, from all voxels for which the absolute value of the activation difference level was larger than its SD, it was calculated how strong those voxels deviated from the global averaged activation difference level.

## Results

Neuropsychological assessment revealed that the language score was significantly ( $p = 0.002$ ) lower in the TPM group than in the control group (Fig. 1). Furthermore, fMRI demonstrated that the main region activated in both groups was an extensive area of the known expressive language network, including the left inferior prefrontal cortex (IPC), the medial prefrontal cortex (MPC), and the posterior parietal lobule, all predominantly at the left side. Figure 2 displays the number of voxels within the language areas as function of activation level. The threshold value for the quantitative analysis was 0.9 %. Quantitative analysis revealed that the TPM group showed significant ( $p = 0.01$ ) underactivation relative to the control group in the language areas (i.e. less voxels with an activation level higher than the threshold of 0.9 %) (Fig.1, Fig. 3a). The TPM group displayed a significant underactivation throughout the whole brain, however in order to elucidate which brain regions are more sensitive to TPM, we calculated which regions had a lower or a higher than average underactivation level. This analysis revealed that the language areas (IPC and MPC) of the TPM group uniformly displayed a larger than average activation decline, whereas the occipital cortex had sub-regions with lower as well as higher than average activation decline (Fig. 3b).

## Discussion

The covert word generation paradigm used reveals a significant underactivation in the language areas in epilepsy patients on TPM therapy, which is in accordance with the (neuropsychologically assessed) cognitive impairment. These observations indicate that TPM induces a local dysfunction of the IPC and MPC. The fact that the prefrontal language-related areas display a relatively stronger activation decline indicates that these regions have a higher sensitivity to TPM-induced activation-modifying effects. TPM has multiple mechanisms of action that have been hypothesized to contribute to its seizure control effects of which one also may be involved in the induction of cognitive impairment, namely gamma-amino butyric acid (GABA) potentiation. Preclinical studies link disruptions in the neurotransmission system of GABA with disturbances in the frontal lobe [3]. Since it has been shown that daily TPM therapy increases brain GABA concentration [4], an increase in the inhibiting effect of the total GABA pool, due to the GABAergic activity of TPM on neurotransmitter level, might be responsible for the cognitive problems, as these problems originate from the frontal lobe. In conclusion, by revealing brain function abnormalities within the language system and determining which regions are involved, the present findings help to visualize cognitive impairment induced by TPM.

## References

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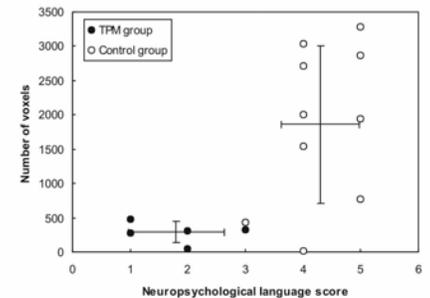


Fig.1: Number of suprathresholded voxels within the language areas as function of language score.

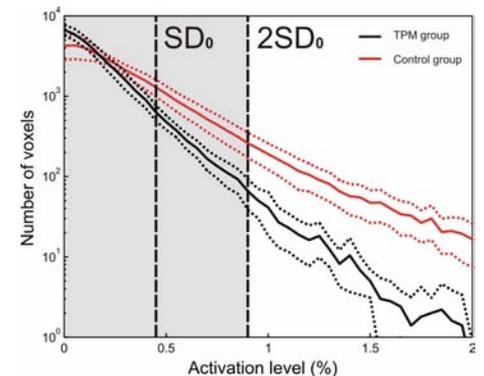


Fig.2: Distribution of the voxels within the language areas as function of the activation level.

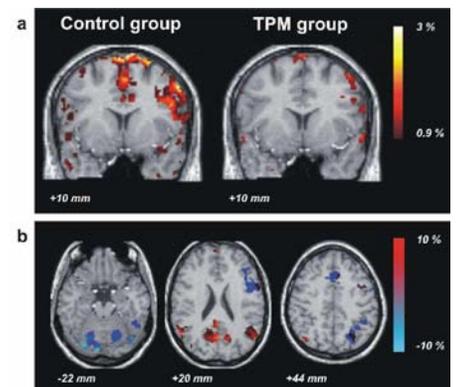


Fig.3: a) Coronal images of group mean functional MRI activation maps, obtained for the covert word generation paradigm overlaid on a normalized T1-weighted MR image, with left the control group, and right the topiramate group. b) Transverse images of average underactivation level for the whole brain of the TPM group as compared to the control group.