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SHORT COMMUNICATION

The effect of topiramate on cognitive fMRI

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Summary
Purpose: Topiramate (TPM) is known to cause language impairment in healthy volunteers and patients with epilepsy. We assessed the effects of TPM on functional language networks in both patients with focal epilepsies and healthy controls using functional magnetic resonance imaging (fMRI).
Methods: We obtained fMRI data in 24 controls and 35 patients with frontal lobe epilepsy using a simple verbal fluency (VF) paradigm. Eight of the 35 patients were treated with TPM in polytherapy. We compared cognitive task related activations and de-activations in patients taking TPM with patients taking other AEDs and healthy controls. In a longitudinal pilot study with VF-fMRI paradigm, we studied two patients with focal epilepsies twice, prior to starting and on stable doses of TPM, two patients twice, before and after tapering TPM completely and two healthy controls twice, before and after single doses of 200 mg TPM.
Key findings: Cross sectional analyses of VF-fMRI showed a reduction in the task-related deactivation of the default mode network (DMN) in patients taking TPM. The longitudinal study corroborated these findings as both chronic administration and a single dose of TPM were associated with impaired categorical verbal fluency and disruption of task-related deactivations.
Significance: Similar neuropsychological and fMRI findings in patients and healthy controls indicate a specific effect of TPM in default mode network areas that may be essential components of the language network. Our preliminary data suggest a mechanism by which TPM impairs cognitive processing during language function and highlights the sensitivity of fMRI to detect the effects of AEDs on cognitive brain networks.

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Introduction

A major concern when selecting appropriate anti-epileptic drug (AED) treatment is adverse effects on cognition and behavior (Thompson et al., 2000; Loring et al., 2011). Expressive language difficulties, particularly word-finding and dysnomia as well as working memory impairment (Lee et al., 2003; Szaflarski and Allendorfer, 2012), are rather specific for topiramate (TPM), and rarely seen with other AED. These effects have been described not only in patients with epilepsy, but also in people with migraine (De et al., 2008). However, the mechanisms involved are poorly understood and there is no clinical test available that reliably predicts who is at risk of developing side-effects (Brandes et al., 2004; Loring et al., 2011). FMRI revealed decreased activation of prefrontal cortex in response to a verbal task in TPM-treated epilepsy patients (Jansen et al., 2006; Szaflarski and Allendorfer, 2012) while withdrawal of TPM was associated with improved cognitive measures sensitive to frontal lobe functioning (Kockelmann et al., 2003). A recent study demonstrated a dose-related effect of TPM on language fMRI, affecting areas of resting state network (Szaflarski and Allendorfer, 2012) in patients with TLE.

In this study we aimed to investigate regional effects of TPM on cognitive fMRI activation patterns and used two approaches. First, we analyzed fMRI studies in a cohort of frontal lobe epilepsy (FLE) patients with regards to AEDs taken; second, in a prospective, open-label pilot study, we compared cognitive task related activations and deactivations in two healthy controls who received single doses of 200 mg TPM, and four patients who either started or stopped TPM for clinical reasons.

Methods

For the cross-sectional study we obtained verbal fluency (VF) fMRI and neuropsychological data of 35 patients (15 females, age: median 33 — interquartile range [IQR]: 18 years) with either cryptogenic frontal lobe epilepsy (FLE) or FLE due to focal cortical dysplasia (17 right-sided frontal focus, 13 left-sided and 5 uncertain frontal lobe lateralization). Patients with large lesions were excluded from this study. Patients were recruited from the epilepsy clinics at our center (London, UK) (Vollmar et al., 2011). Twenty-four healthy controls (13 females, age: median 30 — IQR: 7 years) without a history of epilepsy or other neurological condition were included for comparison. Eight of the 35 patients were treated with TPM (dose range: 50—500 mg; median 187.5 mg) given in polytherapy, the remaining 27 patients formed the other-AED group. Clinical data are displayed in Table 1A.

For the longitudinal pilot study, four patients with focal epilepsies (1 temporal lobe epilepsy (TLE) and 3 extra-TLE) were studied as part of their pre-surgical assessment with the same VF-fMRI paradigm (Bonelli et al., 2011). FMRI was acquired in two patients prior to starting TPM (TPM-off), and repeated once patients were taking a working dose (TPM-on), and in two patients before withdrawal (TPM-on) and again after complete cessation (TPM-off). These changes were made for clinical reasons. In addition, two healthy male controls were studied before (TPM-off) and 3 h after a single oral dose of 200 mg TPM (TPM-on).

The study was approved by the Research Ethics Committee of the UCL Institute of Neurology and UCL Hospitals. (Informed consent was obtained from each participant.)

All subjects underwent a brief neuropsychological evaluation of verbal fluency (letter S and category) and backwards Digit Span in close proximity to their fMRI scans (clinical data are displayed in Table 1B). Neuropsychological test performance was compared using Wilcoxon tests.

All fMRI studies were performed on a 3T GE Excite HDx scanner as described previously (Vollmar et al., 2011), with acquisition of gradient-echo planar T2*-weighted images (TE = 25 ms, TR = 2500 ms), providing blood oxygenation level-dependent (BOLD) contrast. The VF-fMRI paradigm consisted of a 5.5 min blocked design with alternating periods of 30 s of a task (subjects requested to covertly generate different words beginning with a visually presented letter, A, S, W, D and E) and baseline (cross-hair fixation) (Bonelli et al., 2011). We analyzed the fMRI data within the framework of the general linear model using SPM5 (http://www.fil.ion.ucl.ac.uk/spm5), including two level random effects analysis. Prior to analysis, the data was realigned and spatially normalized (using a T1-weighted structural image co-registered to the time-series to determine the parameters). The first level model included the task blocks with the baseline coded implicitly and the six movement regressors. The second level was used to test:

1) VF activations and deactivations in each group (TPM, other-AEDs, controls);
2) Changes in BOLD signal associated to different TPM doses.

Activations are reported at a threshold of $p < 0.05$ (corrected for multiple comparisons with false discovery rate method). Deactivations are reported with threshold ($p < 0.001$) uncorrected for multiple comparisons due to the preliminary nature of this work.

1) FMRI data was analyzed with a fixed-effect statistical model to:
2) Identify activation and deactivations for VF for each acquisition (TPM-on/-off);
3) Compare the differences in deactivations between the two acquisitions (TPM-on versus TPM-off) for each subject;
4) To investigate commonalities amongst subjects using a conjunction analysis (Friston et al., 2005).

Resulting maps were thresholded at $p < 0.001$, uncorrected for multiple comparisons.

Patients performed a letter fluency test outside the scanner, in which they were instructed to say as many words as possible starting with the letter ''S'' in 1 min (Bonelli et al., 2011). For correlation analysis the individual fMRI maps were regressed against the TPM doses. To compare clinical and neuropsychological scores we used Mann—Whitney *U*-test.

Results

Letter fluency ''S'' was reduced for patients taking TPM compared to other FLE patients ($p = 0.053$). A single dose of