

Damages in brain networks caused by a drug: Topiramate disrupts graph theory properties of brain connectivity.

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Abstract

Language and memory impairment is frequently observed in subjects taking topiramate, despite its efficacy. Graph theory approach was applied to evaluate network abnormalities, showing a lower performance in local efficiency of brain networks and relevant hubs losses, suggesting a negative impact of topiramate in functional brain connectivity.

Key words:

Antiepileptic drugs, graph theory, epilepsy.

Introduction

Despite the efficacy for epilepsy and migraine, cognitive dysfunction (mainly language) is a relatively common side effect of topiramate (TPM), for subjects with and without epilepsy. Here we applied Graph theory (GT) to evaluate the impact of TPM on functional connectivity (on both global and local properties), comparing parameters between controls and subjects taking TPM (patients with epilepsy and others with migraine).

Results and Discussion

Resting-state fMRI (RS) was acquired from 95 healthy controls [without topiramate, 15 TLE patients (TLE-TOP) and 16 migraine patients (MIG-TOP), both groups taking TPM]. All subjects underwent neuropsychological evaluation, with verbal fluency (FAS tests) and category fluency tests (naming animals). Each RS-fMRI was preprocessed with an in-house routine for SPM12/MATLAB and then parcellated into 90 regions of interest (based on AAL); by computing Pearson correlation values between all pairs, we finally constructed 90x90 matrices. Global and local parameters of GT (clustering coefficient, path length, local and global efficiency) were calculated for a range of sparsity values. We also found hubs distribution in the whole networks for each group. Finally, the significance between-group comparison procedure were examined at each sparsity on SPSS22, with Tukey's HSD test. Cognitive tests were examined with MANOVA.

Both groups of patients presented lower performance for verbal fluency and category, compared to controls ($p < 0.05$). MIG-TPM performed similarly to TLE-TPM. Considering GT parameters (for a sparsity range between 0.15 – 0.3), statistical analysis revealed that MIG-TPM presented significant reduction of local efficiency related to controls ($p < 0.05$); in addition there were no differences between MIG-TPM and TLE-TPM groups ($p > 0.05$). Considering the relevance of each hub distribution for networks, we found six significant AAL regions for controls, four significant regions for TLE-TPM and three regions of interest for MIG-TPM. This parameter showed decreased number of

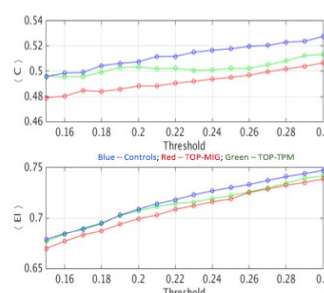


Fig. 1 Graph theory network parameters for different sparsities. (C – clustering coefficient; L – path length; EI – Local efficiency; Eg – Global efficiency)

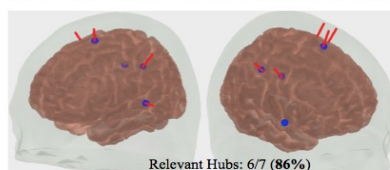


Fig. 2 Hubs identified for Control subjects



Fig. 3 Hubs identified for TLE-TPM subjects

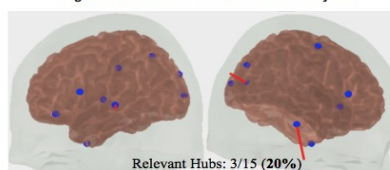


Fig. 4 Hubs identified for MIG-TPM subjects

Conclusions

These results suggest that MIG-TPM behave similarly to TLE-TPM regarding cognition and brain connectivity. The lowest performance of GT parameters for MIG-TPM suggest a negative impact of TPM on brain connectivity which may be associated with cognitive dysfunction commonly observed in subjects taking this drug.

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