

## Relating cognitive adverse events of antiepileptic drugs to functional network efficiency

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**Target audience:** Researchers interested in epilepsy, antiepileptic drugs and resting state fMRI

**Purpose:** Cognitive adverse events, such as mental slowing, often arise when antiepileptic drugs (AEDs) are used to treat epilepsy<sup>1</sup>. On the basis of previous research, in which cognitive performance is linked to the efficiency of brain networks<sup>2</sup>, we hypothesize that cognitive problems due to AEDs are associated with a less efficient brain network. To this end, the relation between graph theoretical measures derived from resting state fMRI, AED use and cognitive function was investigated.

**Methods:** Two groups of epilepsy patients were included: a 'low risk' group (31 epilepsy patients using lamotrigine or levetiracetam, AEDs associated with only mild cognitive adverse events) and a 'high risk' group (14 patients using topiramate or phenytoin, AEDs associated with more severe cognitive adverse events)<sup>1</sup>. To facilitate the inclusion, carbamazepine, clobazam, oxcarbazepine and valproate were allowed as additional AEDs.

Cognitive tests were used to measure cognitive functioning and resting state fMRI scans were used to assess brain connectivity. Cognitive tests included a Computerized Visual Searching Task (CVST), which measures mental slowing, and The Raven's Standard Progressive Matrices, which gives a measure for global cognitive performance. A Philips Achieva 3.0T MRI scanner was used to perform resting state fMRI (EPI sequence, 195 volumes, 32 slices, voxel size: 2x2x4 mm, TR/TE: 2000/35 ms, flip angle: 90°) and a T1-weighted scan (resolution: 1x1x1 mm, TR/TE: 8/4 ms, 180 slices, flip angle: 8°).

The preprocessing<sup>3</sup> included FreeSurfer for anatomical parcellation of the T1 scan into 82 cortical and subcortical brain areas. The functional images were corrected for differences in slice timing and motion, coregistered to the T1 image, spatially filtered (FWHM 6 mm), temporally filtered (band pass 0.01 – 0.1 Hz) and corrected for variations in the white matter and CSF signal by linear de-regression. Subsequently, an association matrix was created by calculating the Pearson's correlation coefficient between the average time signal of each combination of two regions. Negative correlations and correlations lower than 0.01 were set to zero.

The Brain Connectivity Toolbox<sup>4</sup> was used to calculate the normalized characteristic path length ( $\lambda$ ) and clustering coefficient ( $\gamma$ ) using 100 randomized versions of the correlation matrices. Analysis was performed on the 10 – 60% strongest connections, based on the mean connection strength. This analysis was performed twofold: whole brain and frontal lobe only, as adverse effects of frontal lobe functions are typically recognized<sup>1</sup>.

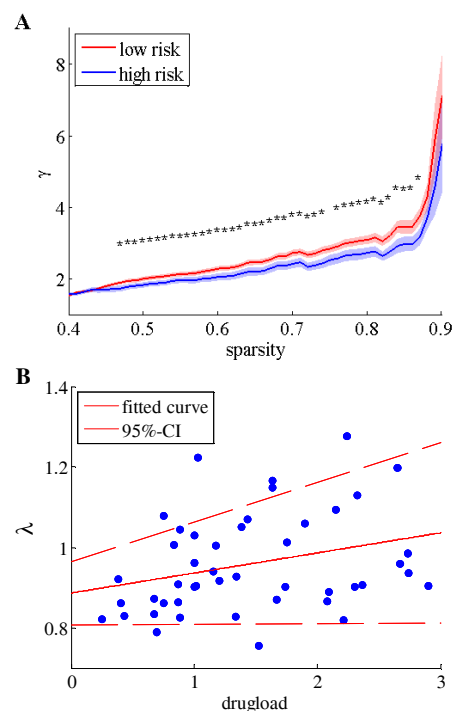
Linear regression analysis was used to test whether graph measures can be associated with AED use or cognitive functioning with the covariates: risk group, drugload, CVST score, Raven score (high vs low), age and gender at 51 sparsity levels equally distributed between 0.4 and 0.9 (0 is fully connected whereas 1 indicates no connections). p-values <0.05 were considered significant.

**Results:** For the frontal lobe, a consistent significant association was shown between risk group and  $\gamma$  in the analysis: high risk patients had a lower  $\gamma$  than low risk patients (Figure 1A).  $\lambda$  was significantly associated to drug load in the sparsity range 0.48-0.6 (Figure 1B, p<0.05) in the frontal areas, but no associations were found for other co-variables. For the whole brain, no consistent results were found for any of the co-variables.

**Discussion:** A significant association between risk group and clustering coefficient ( $\gamma$ ) was found in the frontal lobe, indicating that high risk patients had a lower and less robust local efficiency. This relation between AED use and  $\gamma$  was already suggested by Vlooswijk et al. (2011)<sup>5</sup>, who associated a higher drugload with a lower  $\gamma$  and cognitive decline. Our results further suggest a positive association between drugload and characteristic path length ( $\lambda$ ), indicative of the efficiency of the network and typically negatively associated with intelligence<sup>2</sup>. This is probably an effect of the epilepsy itself: patients with a higher drugload might have a more severe form of epilepsy, which can also affect the network efficiency<sup>5</sup>. In contrast to analysis of the frontal areas, whole brain analysis did not yield any significant results, suggesting that the frontal lobe is more sensitive for the effects of AEDs than the whole brain. At present, no associations between graph measures and impaired cognitive functioning have been found which needs further research.

**Conclusion:** The use of AEDs with a high risk of cognitive adverse events is associated with a lower local efficiency than the use of AEDs with a low risk of cognitive adverse events.

**References:** [1] P Kwan, MJ Brodie, The Lancet 357.9251 (2001): 216-222, [2] MP van den Heuvel et al., J. Neurosci. 29.23(2009): 7619-7624, [3] E Bullmore, O Sporns, Nat. Rev. Neurosci. 10 (2009): 186-198, [4] M Robinov, O Sporns, NeuroImage 52 (2010): 1059-1069 [5] MCG Vlooswijk et al, Neurology 77 (2011): 938-944



**Figure 1. A - Mean clustering coefficient ( $\gamma$ ) of the frontal lobe. The shaded areas show the standard error of the mean. Black asterisks indicate significant associations between the clustering coefficient and risk group. B - Drugload vs characteristic path length ( $\lambda$ ) at a sparsity level of 0.52 with the fitted curve and 95% confidence intervals (CI).**