

# Do antiepileptic drugs affect brain structure? A cross-sectional investigation of morphometric differences associated with sodium valproate.

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## Introduction

The primary method for managing epilepsy is medication. In studies of the morphometric properties of epilepsy brains using MRI, patients will often be taking one or more antiepileptic drugs. The drug combination is tailored to the individual patient and is rarely homogenous across the group. The situation is further complicated by the wide variety of antiepileptic drugs available. Morphometric analyses of structural brain differences associated with epilepsy generally do not attempt to incorporate the potential effects of different antiepileptic drugs on brain structure. In this study we investigate whether epilepsy patients taking sodium valproate have any morphometric differences in comparison to epilepsy patients not taking sodium valproate, and neurologically normal unmedicated controls. Sodium valproate was investigated because of reported transient morphometric neurological changes associated with valproate use [1], and adverse effects of acute valproate ingestion [2].

## Methods

Epilepsy patients were included from the Comprehensive Epilepsy Program, Austin Hospital Melbourne. 76 patients were referred for 3T imaging. 10 subjects ( $33.8 \pm 7.7$  years, all male) were taking sodium valproate at the time of imaging and 66 subjects ( $34.9 \pm 11.4$  years, 28 male) were not currently taking sodium valproate. 81.6% of patients were currently taking two or more antiepileptic drugs. 94 neurologically normal participants ( $29.4 \pm 9.7$  years, 45 male) were included as a control group. Whole brain 0.9 mm isotropic T1-weighted MRI was acquired using an MPRAGE acquisition on a Siemens TIM Trio MRI scanner. Images were processed using FreeSurfer version 5.1. Morphometric properties investigated were brain volume (not including ventricles) as a fraction of intracranial volume, and cortical thickness of the frontal, parietal, temporal and occipital cortical lobes. Potential differences between groups were modelled using the general linear model, with brain volume or lobar thickness as the dependent variable, and patient status (valproate, not taking valproate, and control), age and sex as independent variables.

## Results

There was no significant difference between the number of antiepileptic drugs currently taken by patients on sodium valproate and patients not taking sodium valproate ( $p = 0.38$ ). Lobar-based cortical thickness analysis revealed reduced parietal lobe cortical thickness in the valproate group in comparison to epilepsy patients not taking valproate and neurologically normal controls (Figure 2,  $p < 0.05$ ). The average thickness difference was 0.09 mm compared to epilepsy patients not taking valproate and 0.1 mm compared to controls. A similar effect was observed in the occipital lobe, although the  $p$ -value was not below 0.05 ( $p = 0.054$ ). No significant cortical thickness differences were observed in the frontal or temporal lobes. No systematic brain volume differences were observed between epilepsy patients currently taking valproate, compared with epilepsy patients not taking valproate and neurologically normal controls ( $p = 0.18$ ).

## Conclusions

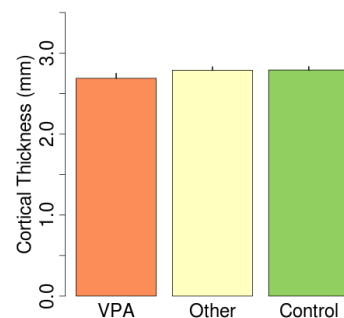
The results of this preliminary study suggest that there are subtle parietal and possible occipital cortical changes associated with using sodium valproate as an antiepileptic medication. The effect was observed when comparing against both epilepsy patients not taking valproate and neurologically normal controls, suggesting that the difference is not due to other epilepsy related neurological factors such as lesions. It is interesting to note that a previous magnetic resonance spectroscopy study identified metabolic differences in the parietal lobe in epilepsy patients treated with valproate compared to neurologically normal controls [3]. Conducting a meaningful cross-sectional investigation of neuroanatomical differences associated with antiepileptic drugs is complicated by the variety of antiepileptic drugs available and the increasing use of polytherapy. A further complication is the combination of different epilepsy syndromes and the impact of lesions on morphometric analyses. A longitudinal investigation of morphometric changes associated with commencement of treatment with valproate would be an appropriate approach to confirming the neuroanatomical changes identified in this study.

## References

[1] Guerrini et al, *Epilepsia* 1998 39(1):27-32 [2] Eyer et al, *Journal of Clinical Psychopharmacology* 2005 25(4):376-80 [3] Garcia et al, *Epilepsia* 2009 50(3):486-92



**Figure 1** Cortical thickness reduction in epilepsy patients taking valproate relative to patients not taking valproate. The map indicates diffuse thickness reductions, mainly located in posterior cortical regions.



**Figure 2** Parietal thickness changes in epilepsy patients taking valproate (VPA) compared with epilepsy patients taking other medication and controls ( $p < 0.05$ ). The thickness values are adjusted for age and sex. Error bars indicate standard error.