Sodium Valproate is Associated with Cortical Thinning of Disease-Specific Areas in Juvenile Myoclonic Epilepsy

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Abstract

Background: Juvenile myoclonic epilepsy (JME) is associated with cortical thinning of the motor areas. The relative contribution of anti-seizure medication to cortical thickness is unknown. We aimed to investigate how valproate influences cortical morphology of JME.

Methods: In this cross-sectional study, individuals with JME with and without valproate, temporal lobe epilepsy (TLE) with valproate and controls were selected through propensity score matching. Participants underwent T1-weighted brain imaging and vertex-wise calculation of cortical thickness.

Results: We matched 36 individuals with JME on valproate with 36 individuals with JME without valproate, 36 controls and 19 individuals with TLE on valproate. JME on valproate showed thinning of the precentral gyri (left and right $p < .001$) compared to controls, and thinning of the left precentral gyrus when compared to JME not on valproate ($p < .01$) or to TLE on valproate ($p < .001$). Valproate dose correlated negatively with thickness of the precentral gyri, postcentral gyri and superior frontal gyrus in JME (left and right $p < .0001$), but not in TLE.

Conclusions: Valproate was associated with JME-specific and dose-dependent thinning of the cortical motor regions. This suggests that valproate may be a key modulator of cortical morphology in JME, an effect which may underlie its high efficacy in this syndrome.

Introduction

Sodium valproate (VPA) is a widely used anti-seizure medication (ASM), which is highly effective in juvenile myoclonic epilepsy (JME) and idiopathic generalized epilepsies (IGEs) in general.[1] The mechanisms behind this remain largely unknown. In JME, neuroimaging studies have revealed isolated reductions of gray matter in the precentral and medial prefrontal areas as a syndrome-specific feature.[2,3] Whether these changes reflect an underlying disease signature, consequence of ongoing seizure activity or drug-associated effects, is unknown. Here, we aimed to characterize the effects of VPA on cortical morphology in JME and test for syndrome-specificity. First, we estimated cortical thickness in a neuroimaging data set of people with JME and evaluated differences in cortical morphology between individuals with JME taking VPA, individuals with JME not on VPA as well as healthy controls. To assess syndrome specificity, we compared the JME group on VPA with a temporal lobe epilepsy (TLE) group also on VPA.

Methods

Participants

We analyzed imaging data obtained between 2009 and 2017 of people with JME, TLE and healthy controls recruited from epilepsy clinics at the University College London Hospitals (UCLH), London, United Kingdom and the Christian Doppler University Hospital in Salzburg, Austria (CDK). All participants had high-resolution T1-weighted MRI scans. We excluded individuals with insufficient image quality and brain lesions other than hippocampal sclerosis in the TLE subgroup. Individual ASM load was calculated by the ratio of the actual daily dose of a specific ASM by its defined daily dose (DDD), provided by the Collaborating Centre for Drug Statistics Methodology of the World Health Organization. The study was approved by the ethics committee of UCLH and Salzburg state. All participants provided written informed consent. We followed the recommendations of the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) reporting guidelines.

Image Preprocessing

The MRI acquisition protocols are described in eAppendix 1 in the Supplement. Cortical thickness was estimated vertex-wise through a surface-based framework using FreeSurfer and measurements were subsequently down-sampled to a common surface template (preprocessing pipeline described in eAppendix 2,

Supplement). Prior to statistical analysis, data were adjusted for scanner-related batch effects using the validated Combat Tool for Harmonization of Multi-Site Imaging Data in R.[4]

Statistical Analysis

To reduce selection bias, we propensity score matched JME individuals taking VPA at time of scan to i) JME individuals without VPA at time of scan, ii) healthy controls, and iii) TLE with valproate at time of scan. To this effect, we used a nearest-neighbor algorithm with replacement based on the following variables: age, sex, occurrence of generalized tonic-clonic seizures (GTCS) and drug resistance. Demographic and clinical data were analyzed with R studio (v2023.03.0+386). Kruskal-Wallis test was used to compare continuous clinical characteristics between subgroups. Pearson's Chi-Square was used for categorical data. Vertexwise cortical thickness measurements were analyzed with BrainStat for Matlab.[5] In group comparisons, a binary indicator of group, was the predictor of interest, whereas cortical thickness was the outcome of interest. As stated above, all surface metrics were corrected for age and sex, whereas group comparisons with JME and TLE were additionally corrected for total ASM load and prevalence of drug resistant disease. We report effect-sizes using Cohen's *d* considered significant after correction for multiple comparisons using random field theory[6] at family-wise error (FWE) <.05.

Results

A total of 192 participants met study criteria, of which 36 had JME and were on VPA, 43 had JME and were not on VPA, 35 had TLE and were on VPA and 78 were healthy controls. Propensity score matching resulted in 36 cases of JME on VPA, 36 of JME not on VPA, 19 of TLE on VPA and 36 healthy controls. All disease groups were comparable for age, sex, disease duration, presence of GTCS (or bilateral tonic clonic seizures in TLE) and drug resistant disease. The TLE on VPA group had a higher total ASM load than both JME groups (TLE on VPA 2.37 [1.43, 3.27] vs. JME on VPA 1.20 [0.67, 1.77] vs JME not on VPA 1.00 [0.46, 1.37], Kruskal-Wallis T = 10.11, p <.001). Centre affiliation was statistically different between all groups (p < 0.001). Table 1 provides detailed information on demographic and clinical data.

Table 1. Demographic and clinical characteristics

	Controls (n = 36)	**JME on VPA** (n = 36)	**JME not on VPA** (n = 36)	**TLE on VPA** (n = 19)	**Test statistic**	***P* value**	**Post-hoc *P* values**
Age at time of scan, years (IQR)	32 [25, 37]	28 [24, 32]	32 [25, 39]	34 [30, 44]	1.67	.103	
Female, No. (%)	18 (50)	22 (61)	14 (39)	11 (58)	1.13	.266	
Scanned at CDK, No. (%)	29 (81)	28 (78)	16 (44)	5 (26)	23.9	**<.001**	JME on VPA/JME non-VPA: **<.05** JME on VPA/TLE on VPA: **<.05** JME on VPA/ Controls: **<.01**
Drug resistant, No. (%)	NA	17 (47)	19 (53)	14 (74)	1.48	.163	
GTCS, No. (%)	NA	9 (25)	13 (36)	9 (47)	0.27	.246	
Disease duration, years (IQR)	NA	14 [10, 20]	16 [11, 28]	16 [8, 29]	0.25	.434	
Total ASM load at scanning, n (IQR)	NA	1.00 [0.46, 1.37]	1.20 [0.67, 1.77]	2.37 [1.43, 3.27]	10.11	**<.001**	JME on VPA/JME not on VPA: .211 JME on VPA/TLE on VPA: **<.05**

Abbreviations: CDK, Christian-Doppler Univerity Hospital; JME, juvenile myoclonic epilepsy; IQR, interquartile range; GTCS, generalized tonic-clonic seizures; TLE, temporal lobe epilepsy

Note: bold denotes statistical significance.

Effect of VPA use

There was no significant differences in cortical thickness between all individuals with JME and healthy controls (see eFigure 1 in Supplement). Compared to healthy controls, JME on VPA showed bilateral cortical thinning within the precentral gyri (left and right: d = -1.0, p_{FWE} <.001) and thickening of the right posterior cingulum and lingual gyrus (d = 0.71, p_{FWE} <.0001). Compared to individuals with JME not on VPA, the JME group on VPA showed cortical thinning in the left precentral gyrus (d = -0.89; p_{FWE} <.01) and thickening in the posterior cingulum bilaterally (left: d = 0.59, p_{FWE} <.0001; right: d = 0.61, p_{FWE} <.0001). Compared to TLE on VPA, JME on VPA showed grey matter atrophy in the left precentral gyrus and parts of the left middle frontal gyrus (d = *-0.18*, p_{FWE} <.001) as well as bilaterally in both parahippocampal gyri (left: d = -0.27, p_{FDR} <.001; right: d = -0.46, p_{FDR} <.0001). No significant differences were seen between JME not on VPA and healthy controls. Results are displayed in Figure 1A-D and provided in detail in eTable 1 in Supplement.

Effect of VPA dose

In those with JME on VPA, cortical thinning correlated with increasing doses of VPA and affected the pre- and postcentral gyri, the superior frontal gyrus and precuneus in on both hemispheres (left: t = -6,65, p_{FWE} <.0001;

right: t = -5,20, p_{FWE} <.0001). No significant effect was seen in the TLE group on VPA. Results are displayed in Figure 2 and provided in detail in eTable 2 in Supplement.

Discussion

We found an association between VPA treatment and cortical thinning of the motor areas in individuals with JME. Gray matter atrophy has been described in the context of VPA treatment, but results have not been consistent across studies[7-9]. In our study, whereas participants with JME on VPA showed cortical thinning in the precentral gyri and thickening of the posterior cingulum when compared to JME not on VPA, healthy controls, and, to a lesser extent, TLE on VPA, no significant changes were seen in cortical thickness between JME not on valproate and healthy controls. This precludes disease-related effects on cortical thickness and suggests that VPA modulates cortical morphology in disease-specific regions (i.e. the motor areas) and its effect is specific to JME. Our hypothesis is further corroborated by a dose-dependent effect of VPA on thinning of the cortical motor regions and other areas implicated in the pathophysiology of JME, e.g. the supplemental motor area and the medial aspect of the superior frontal gyrus, which is not seen in TLE. Our results are supported by a recent study showing reduced gray matter density of motor areas associated with VPA treatment in IGE patients[9]. Earlier investigations have reported parieto-occiptal gray matter changes linked to VPA, albeit in more heterogenous patient cohorts.[7,8] Furthermore, a recent study investigating cortical morphology in drug-naïve people with IGE suggests that cortical thinning is not present before ASM treatment.[10] Although the mechamisms by which VPA induces cortical thinning are unknown, new insights into VPA-mediated selective inhibition of the antineoplastic histone deacetylase indicate dysregulation of myelination processes as a a possible link.[11] In addition, our findings suggest that the thinning of the precentral gyri detected in IGE syndromes in the large-scale neuroimaging ENIGMA study may be attributable to some extent to VPA, which was not accounted for.[2]

The primary and supplemental motor areas are major hubs involved in the pathophysiology of IGE. This is mainly supported by functional MRI studies that identified abnormal hyperactivation patterns in these regions.[12-14] Such “failure to deactivate” of the motor areas upon cognitive demand likely facilitates seizure generation and has been shown to normalize with increasing VPA dose.[12-14] We propose that VPA-associated thinning of the motor cortices as identified in our study is related to the beformentioned network-stabilizing effects of VPA affecting the precentral gyri. We further speculate that this phenomenon may be seizure-protective.[13] However, to further corroborate this notion, our findings need to be correlated with disease activity.

The cross-sectional design of our study precludes making a causal inference between VPA exposure and cortical changes in JME. Longitudinal studies are needed to further investigate this relationship. Other limitations

include the relatively small group sizes, lack of information regarding duration of VPA treatment, neuropsychological testing and adequate markers of disease activity. The contributing factor of concomitant psychiatric comorbidity on cortical thickness was also not taken into account and should be addressed in subgroup analysis of larger follow-up studies. Furthermore, the JME group not on VPA also included individuals who had previously been on VPA, thereby restricting group homogeneity. Information regarding past VPA exposure was not available for all study participants, precluding an investigation of reversibility of VPA-associated effects on cortical morphology ("pseudoatrophy"). Indeed, this notion has been supported by previous reports.[15,8] Lastly, our findings highlight the need to account for VPA treatment in cortical morphology studies.

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Ethics approval

The study was approved by the ethics committee of University College London Insitute of Neurology and University College London Hospitals Joint Research Ethics Committee (Ref no. 11/LO/0439) as well as the Ethikkomission für das Bundesland Salzburg (Ref. 415-E/1638). All participants provided written informed consent.

Competing interests

BCP was supported by a scholarship from the Austrian Society of Epileptology, which was not directly related to this project. E.T. reports personal fees from EVER Pharma, Marinus, Argenx, Arvelle/Angelini, Medtronic, Bial–Portela & Cª, NewBridge, GL Pharma, GlaxoSmithKline, Hikma, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Genzyme Sanofi, GW Pharmaceuticals/Jazz, and Actavis outside the submitted work; his institution has received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Osterreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubilaumsfond der Österreichischen Nationalbank outside the submitted work. MK has received honoraria from Biocodex, Bial, GE, GSK, LivaNova, Eisai, UCB, Jazz Pharmaceuticals, and research funding from MRC, the Wellcome Trust, ER-UK, Henry Smith Foundation and Epilepsy Society. BW received salary support from the German Research Foundation (WA3135/1-1). The remaining authors have no conflicts of interest.

Contributions

BCP, MK, BW, ET and GK designed the study, drafted a significant proportion of the manuscript and contributed to the acquisition and analysis of data. FX, JH, LC, CV, MK, LC and JD contributed to data acquisition. All authors reviewed and approved the final manuscript.

Figures

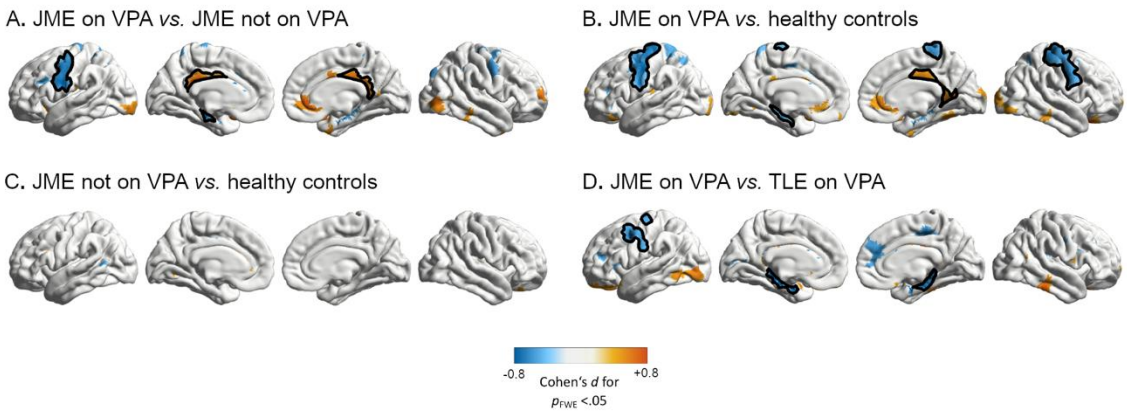

Figure 1. Effect of VPA on cortical thickness across groups

Mass univariate analysis showing group comparisons of cortical thickness between individuals with JME on VPA, JME not on VPA, TLE on VPA and healthy controls. The JME group on VPA shows significant cortical thickness deficits in the left precentral gyrus and a thickened posterior cingulum when compared to the JME group not taking VPA (A) as well as to healthy controls (B). Similar, yet less extensive cortical thinning within the left precentral gyrus is seen on the JME on VPA group when compared to the TLE on VPA group (D), suggesting effect-specificity to JME. No significant structural abnormalities were detected when comparing the JME group not on VPA with healthy controls (C), thereby ruling out syndrome-related effects. Clusters are color-coded according to the corresponding effect size estimates as reported by Cohen's d (see color bar). Clusters that survived multiple comparisons correction using random field theory at pFWE <.05 were manually outlined in black.

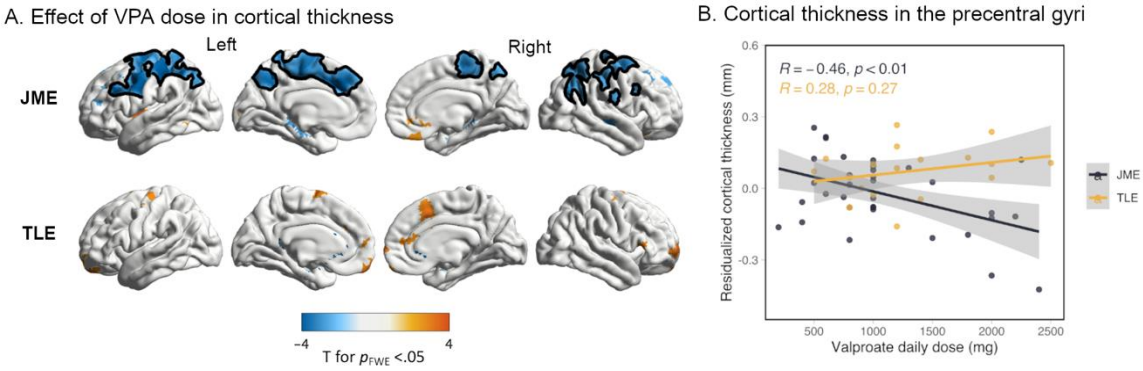

Figure 2. VPA dose and cortical thickness across JME and TLE

In (A), vertexwise linear regression T-map shows changes in cortical thickness as predicted by sodium valproate (VPA) dose in juvenile myoclonic epilepsy (JME) and temporal lobe epilepsy (TLE) after adjusting for total anti-seizure medication (ASM) load, age and sex. Clusters are color-coded according to the corresponding T statistic (see color bar). Clusters that survived multiple comparisons correction using random field theory at p_{FWE} <.05 were manually outlined in black. (B) shows linear regression scatterplots illustrating the association between VPA dose and cortical thickness specifically in the bilateral precentral gyri. Individualized cortical thickness values were extracted from parcellations of the Destrieux brain atlas incorporated in Freesurfer corresponding to the left and right precentral gyrus. Cortical thickness values were averaged across both parcels and adjusted for age, sex and total ASM load via multiple regression. Displayed are the residualized cortical thickness values plotted against the VPA dose in JME and TLE patients.