Levetiracetam reduces abnormal network activations in temporal lobe epilepsy

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ABSTRACT

Objective: We used functional MRI (fMRI) and a left-lateralizing verbal and a right-lateralizing visual-spatial working memory (WM) paradigm to investigate the effects of levetiracetam (LEV) on cognitive network activations in patients with drug-resistant temporal lobe epilepsy (TLE).

Methods: In a retrospective study, we compared task-related fMRI activations and deactivations in 53 patients with left and 54 patients with right TLE treated with (59) or without (48) LEV. In patients on LEV, activation patterns were correlated with the daily LEV dose.

Results: We isolated task- and syndrome-specific effects. Patients on LEV showed normalization of functional network deactivations in the right temporal lobe in right TLE during the right-lateralizing visual-spatial task and in the left temporal lobe in left TLE during the verbal task. In a post hoc analysis, a significant dose-dependent effect was demonstrated in right TLE during the visual-spatial WM task: the lower the LEV dose, the greater the abnormal right hippocampal activation. At a less stringent threshold ($p < 0.05$, uncorrected for multiple comparisons), a similar dose effect was observed in left TLE during the verbal task: both hippocampi were more abnormally activated in patients with lower doses, but more prominently on the left.

Conclusions: Our findings suggest that LEV is associated with restoration of normal activation patterns. Longitudinal studies are necessary to establish whether the neural patterns translate to drug response.

Classification of evidence: This study provides Class III evidence that in patients with drug-resistant TLE, levetiracetam has a dose-dependent facilitation of deactivation of mesial temporal structures. *Neurology*® 2014;83:1508–1512

GLOSSARY

BOLD = blood oxygenation level–dependent; **CBZ** = carbamazepine; **fMRI** = functional MRI; **GLM** = general linear model; **HS** = hippocampal sclerosis; **JME** = juvenile myoclonic epilepsy; **LEV** = levetiracetam; **LTG** = lamotrigine; **NHNN** = National Hospital for Neurology and Neurosurgery; **TLE** = temporal lobe epilepsy; **TPM** = topiramate; **VPA** = valproate; **WM** = working memory; **ZNS** = zonisamide.

In a previous working memory (WM) functional MRI (fMRI) study, we observed a valproate (VPA) dose-dependent normalization of impaired deactivation within the motor system in patients with juvenile myoclonic epilepsy (JME).[1] During the same task, patients with temporal lobe epilepsy (TLE) due to hippocampal sclerosis (HS) failed to deactivate the diseased hippocampus with increasing cognitive demands,[2] which was associated with poor performance.[2,3]

Levetiracetam (LEV) is efficacious in focal epilepsies with a positive cognitive side effect profile.[4,5] The aim of this retrospective study was to assess the effect of LEV on fMRI activation and deactivation patterns during WM tasks in patients with TLE. We hypothesized that patients on

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LEV show greater deactivation within temporal lobe epileptogenic networks compared to those without LEV.

METHODS **Standard protocol approvals, registrations, and patient consents.** The Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery (NHNN) approved this study. All subjects gave written and informed consent.

Primary research question and classification of level of evidence. To assess the effect of LEV on fMRI activation and deactivation patterns during WM tasks in patients with TLE (level of evidence: Class III).

Subjects. We included 107 consecutive patients with pharmacoresistant TLE (53 left TLE) undergoing presurgical evaluation at the NHNN. For demographic and clinical characteristics, see table 1.

Fifty-nine patients (30 left TLE) were treated with LEV in addition to other AEDs, the most frequent being carbamazepine (CBZ) and lamotrigine (LTG) (table e-1 and figure e-1 on the *Neurology*® Web site at Neurology.org). Across groups, there was an equal distribution of topiramate (TPM) and zonisamide (ZNS) comedication, which are known to have potential cognitive side effects (TPM: $\chi^2 = 2.845$, $p = 0.416$; ZNS: $\chi^2 = 3.009$, $p = 0.390$). All patients had a structural 3T MRI and video-EEG to confirm side of seizure onset.

HS was the most frequent pathology, in particular in patients with left TLE on LEV ($\chi^2 = 5.618$, $p = 0.019$, see table e-2).

MRI data acquisition and fMRI paradigms. MRI scans were obtained with a GE (Little Chalfont, UK) Excite HDx 3T scanner.[1] We employed modified versions of the n-back WM task. In the visual-spatial task, subjects monitor the sequence of dots randomly appearing in 4 different locations on a screen. Participants are instructed to move a joystick to the current position of the dot (0-back) or to the positions 1 or 2 presentations earlier (1- or 2-back).[6] In the verbal task, a sequence of words was presented. Participants had to respond using a joystick whenever they read the word bird (control condition) or whenever a word had been displayed 2 presentations earlier (2-back condition).

MRI data analysis. A priori models were chosen with regard to our experimental design. Models were estimated using a general linear model (GLM) implemented in SPM8 (Statistical Parametric Mapping; www.fil.ion.ucl.ac.uk/spm). The GLM then estimated which voxels with greater change in blood oxygenation level–dependent (BOLD) signal fit which condition specified in the model, i.e., the BOLD signal was the outcome variable.

Both tasks were of a blocked design and modeled at a single-subject level using a boxcar function for each of the conditions. We created contrast images for each subject to explore the patterns of activation and deactivation in both tasks. For the task-related activations, contrasts comparing the most difficult WM condition with the control task were generated ("2- minus 0-back" and "2-back minus Is-it-bird?"). For task-related deactivations, we used the opposite contrasts ("0- minus 2-back" and "Is-it-bird? minus 2-back"). We excluded 9 patient datasets due to lack of activation.

To explore task-specific effects of LEV at a group level, a full-factorial design with group and LEV treatment as factors was built. All other AEDs, and presence or absence or HS, were entered as covariates of no interest to control for extra variability between groups.

In a post hoc analysis, task-related deactivation patterns were correlated with the daily LEV dose: right TLE median (interquartile range) 2,500 (1,000) mg, left TLE 2,500 (1,000) mg; Mann-Whitney *U* test $p = 0.860$. All patients divided the daily dose into morning (8–10 AM) and evening dose (6–8 AM).

The level for significance was $p < 0.001$ uncorrected with a 20-voxel threshold extent.[7]

Cognitive measures. Standardized frontal lobe tests were administered (table 2). As cognitive outcome variables we used verbal IQ, raw scores for category and verbal fluency, digit span backwards, and Wisconsin Card Sorting Test categories.

Table 1 Demographic and clinical parameters

	Left TLE		Right TLE		Analysis		
Clinical parameters	On LEV (n = 27)	No LEV (n = 26)	On LEV (n = 29)	No LEV (n = 25)	χ^2	*df*	*p*
Female sex	14	14	23	17	6.35	3	0.096
Age, y	38 (19)	40 (20)	39 (15)	40 (22)	0.648	3	0.885
Disease duration, y	17 (22)	16 (26)	16 (23)	17 (20)	1.737	3	0.629
Seizure frequency							
SPS/mo	0 (1.6)	0 (4)	0 (2.5)	0 (8)	1.086	3	0.780
CPS/mo	4 (7)	6 (14)	2.5 (11)	6 (9)	4.250	3	0.236
GTCS/y	0 (1.75)	0 (0)	0 (0)	0 (0.5)	2.144	3	0.543
No. of patients with mesial temporal seizure semiology	20	16	20	14	2.979	3	0.395
No. of current AED	2.5 (2.0)	3.0 (2.0)	3.0 (2.0)	3.0 (3.0)	6.240	3	0.100
No. of previous AED	2 (2)	5 (4.5)	2 (3)	5 (4.5)	16.581	3	0.001

Abbreviations: AED = antiepileptic drugs; CPS = complex partial seizure; GTCS = generalized tonic-clonic seizure; LEV = levetiracetam; SPS = simple partial seizure; TLE = temporal lobe epilepsy.
All variables except sex and semiology are shown as median (interquartile range). χ^2 test was employed for sex and semiology and Kruskal-Wallis test for all other variables. Level of significance: $p < 0.05$. Post hoc group comparisons revealed that the significant difference in number of previous AED is due to patients on LEV having had fewer previous AED than those without LEV (Mann-Whitney $U = 706{,}000$; $p = 0.000$).

Table 2 Kruskal-Wallis test of cognitive performance measures in patients

	Left TLE		Right TLE		Analysis		
Cognitive measures	On LEV, median (IQR)	Without LEV, median (IQR)	On LEV, median (IQR)	Without LEV, median (IQR)	χ^2	*df*	*p*
Verbal IQ	93 (17)	94 (23.5)	93 (19)	99 (21.5)	2.552	3	0.466
Letter fluency	12.5 (6.25)	11.5 (9)	14 (8)	15 (11)	3.680	3	0.298
Category fluency	19 (10)	18 (7)	19 (8)	18 (8)	0.490	3	0.921
Digit span backwards	4 (1)	4 (1)	4 (2)	3.5 (1.75)	0.351	3	0.950
WCST categories	6 (1)	6 (1)	6 (1)	6 (3)	1.404	3	0.705
2-db, % correct	52 (31)	61 (33)	54 (33)	65 (40)	1.983	3	0.576
2-nb, % correct	93.5 (23.75)	98 (14)	97 (15.75)	97 (14)	1.573	3	0.665

Abbreviations: db = dot-back; LEV = levetiracetam; nb = n-back; TLE = temporal lobe epilepsy; WCST = Wisconsin Card-Sorting Test.
Level of significance: $p < 0.05$.

Performance accuracy on the fMRI WM tasks (2–dot-back, 2–n-back) was reported as a percentage.

Statistical analysis of clinical, demographic, and cognitive measures. We used SPSS Statistics version 17.0 (SPSS, Chicago, IL) for comparisons across all 4 groups (left/right TLE with/without LEV) and Pearson χ^2 tests for dichotomous data, i.e., sex, semiology, HS frequency. Kruskal-Wallis tests were employed for all other data.

RESULTS **Cognitive measures.** Performances were comparable for all groups (table 2).

fMRI findings. Main effects for task-related activation and deactivation patterns are shown in figure e-2.

We isolated task- and syndrome-specific LEV effects on deactivation patterns (figure 1). Patients on LEV and 28 healthy controls from a previous study[2] showed similar patterns of deactivation. Compared to patients without LEV, those on LEV showed an augmentation of task-related deactivation in the affected temporal lobe, i.e., left mid-temporal gyrus in left TLE during the verbal and right hippocampus in right TLE during the visual-spatial task (figure 1B). The reverse contrast (on LEV > no LEV) showed no effect for either WM paradigm (not shown).

No LEV effect was observed in left TLE during the visual-spatial and or right TLE during the verbal WM task.

We conducted the same analysis in patients treated with CBZ (22 left, 20 right TLE) or LTG (18/17) vs those without CBZ (31/34) or LTG (35/37). No comparable effects were observed.

In a post hoc analysis, a significant dose-dependent LEV effect was demonstrated (figure 1C) in right TLE during the visual-spatial WM task: the lower the LEV dose, the lesser the right hippocampal deactivation. At a less stringent threshold ($p < 0.05$, uncorrected for multiple comparisons), a similar dose effect was observed in left TLE during the verbal task (figure 1C).

DISCUSSION We demonstrate a dose-dependent, task-specific effect of LEV on functional network activations in TLE.

Progressive deactivation of mesial temporal structures during cognitive tasks has been associated with improved performance in healthy controls and patient cohorts.[2,3,8] LEV's dose-dependent facilitation of the deactivation in this study suggests a beneficial drug effect on cognitive networks in TLE. Since WM performance was equal across groups, the observed effect was not influenced by performance.

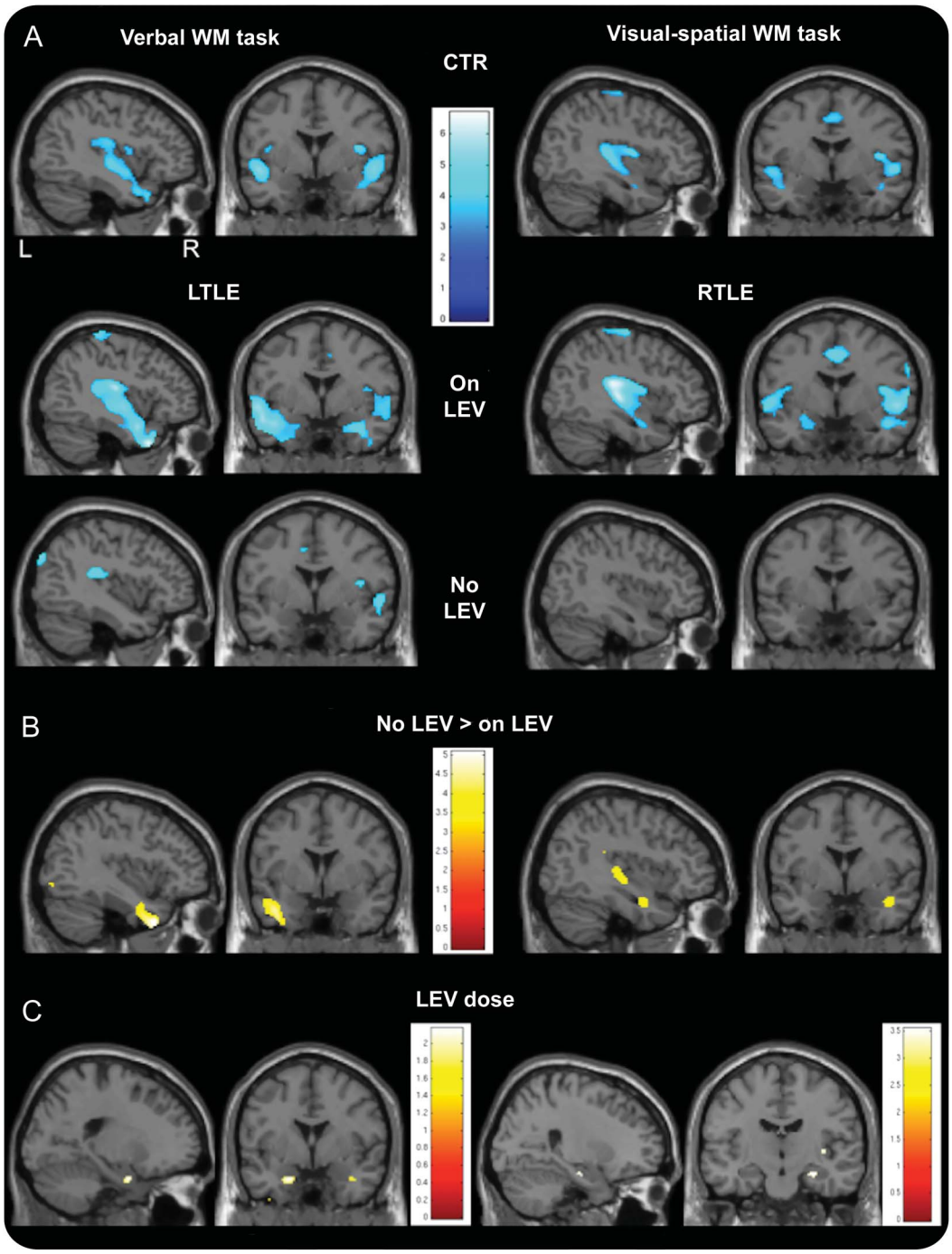
Underlying HS was more frequent in patients with left TLE on LEV than in all other groups, but HS distribution did not differ between patients with right TLE on or without LEV ($\chi^2 = 0.352$, $p = 0.352$). We controlled for the effect of HS diagnosis, which ensures that our findings are not driven by the difference in HS frequencies.

Dose dependence was more apparent in the more demanding nonverbal task. To ensure adequate performance in the 2-back condition of the dot-back task, a greater task-related deactivation may be required. We did not find similar effects for CBZ or LTG, suggesting our findings are LEV-specific.

Longitudinal data are lacking to determine whether LEV led to seizure reduction or improvement of cognitive functions. A further limitation is the number of AED combinations, although distribution was equal for the most commonly prescribed other AEDs.

Our findings in TLE are consistent with previous findings in juvenile myoclonic epilepsy showing a valproate dose-dependent reduction of abnormal motor system coactivation and enhanced WM activations.[1] These effects were not associated with better performance or seizure control, but suggest that AEDs affect epileptogenic and cognitive networks differentially. Our sample included only drug-resistant patients, thus it would be important to establish whether the neural patterns observed here translate

Figure 1 Group comparisons between patients with and without levetiracetam during the 2 working memory functional MRI paradigms



Group maps of areas of task-related deactivation networks in controls and all patients during the left- and right-lateralizing task are demonstrated. Whereas healthy controls and patients on levetiracetam (LEV) show similar patterns of deactivation, patients without LEV show less deactivation in the medial temporal lobe areas than both controls and patients on LEV in either lateralizing task (A). During the verbal working memory (WM) task, patients with left temporal lobe epilepsy (LTLE) without LEV significantly fail to deactivate the left midtemporal gyrus (B; LTLE without LEV > LTLE with LEV, $p < 0.001$, 20-voxel threshold extent). During the right-lateralizing visual-spatial task, patients with right TLE (RTLE) who are not treated with LEV fail to deactivate the right hippocampus (B; RTLE without LEV > RTLE with LEV, $p < 0.001$, 20-voxel threshold extent). A post hoc analysis in patients treated with LEV demonstrated a dose-dependent effect of mesial temporal lobe deactivation through LEV. The lower the LEV dose, the lesser the right hippocampus is deactivated during the visual-spatial WM task (C; $p < 0.001$, 20-voxel threshold extent). A similar dose effect is observed in patients with LTLE during the verbal WM task at a lower level of significance (C; $p < 0.05$, uncorrected). The left > right hippocampus becomes less strongly deactivated with lower LEV dose (C). Inclusively masked for task-related deactivation networks ($p < 0.05$). CTR = healthy controls.

to drug-responsive patients with TLE in a longitudinal study.

AUTHOR CONTRIBUTIONS

Dr. Wandschneider: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. J. Stretton: data acquisition, drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Dr. Sidhu: data acquisition, drafting/revising the manuscript. Dr. Centeno: drafting/revising the manuscript. Dr. Kozák: drafting/revising the manuscript, analysis of data. Dr. Symms: drafting/revising the manuscript, study concept or design, study supervision. Dr. Thompson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Prof. Duncan: drafting/revising the manuscript, study concept, interpretation of data, study supervision, obtaining funding. Prof Koepp: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision, statistical analysis.

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DISCLOSURE

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