

Local thalamic atrophy associates with large-scale functional connectivity alterations of fronto-parietal cortices in genetic generalized epilepsies

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Abstract

Genetic generalized epilepsies (GGEs) are a group of seizure syndromes that start in childhood and adolescence. Although generally viewed as benign, large-scale epidemiological studies suggest that a significant proportion of GGE patients suffer from drug-resistant seizures, cognitive impairment and social problems. This motivates further research into their pathophysiology, which is still incompletely understood. GGE is characterized clinically and on the encephalogram by seizures that seem to involve both hemispheres simultaneously – hence the idea of a ‘generalized’ process. However, findings from experimental animal studies suggest that seizures in GGE arise due to complex functional alterations within a network that involves fronto-parietal cortex and midline thalamus. In line with these results, neuroimaging studies have found metabolic changes in midline frontal and posterior parietal cortices during GGE seizures and atrophy of both frontal lobe structures and thalamus in GGE patients. Pathology of fronto-thalamic networks seems therefore to be a core feature of GGE. It is unknown how alterations of structure and function between different sites of the network influence each other. Given that the thalamus exerts widespread influence on cortical function, we hypothesized that thalamic atrophy in GGE patients would lead to functional impairment in cortical networks. To test this hypothesis, we performed a case–control study on patients with GGE and healthy controls (HCs), using computational neuroanatomical and functional connectivity techniques. Confirming our hypothesis, we found atrophy in midline thalamic regions preferentially connected to midline (pre-) frontal cortex, and correlated functional disconnection between midline frontal and posterior parietal cortex. Of note, we found increased functional connectivity between the left-sided thalamus and the left medial prefrontal cortex, and a decrease in interhemispheric functional connectivity between bilateral parietal cortex in patients compared to HCs. Taken together, our results suggest that even highly localized subcortical structural changes might lead to large-scale network effects in GGE.

Keywords

Epilepsy, genetic generalized epilepsy (GGE), functional connectivity, resting-state fMRI, fMRI, voxel-based morphometry, thalamus

Introduction

Genetic generalized epilepsies (GGEs) are the most frequent type of epilepsy in adolescents, accounting for 20% of all epilepsies. GGEs are currently classified into four sub-syndromes according to the International League Against Epilepsy: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonus epilepsy and generalized tonic clonic seizures. Their common encephalogram

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Table 1. Demographic data of GGE patients and control groups.

| Patients | Gender | Age (years) ^a | Syndrome | Side GSWD ^b | No. GSWD ^b |
|----------|--------|--------------------------|-------------|------------------------|-----------------------|
| No.1 | F | 40 | GGE | Bi | 10 |
| No.2 | M | 46 | GGE | Bi | 3 |
| No.3 | F | 15 | GGE | Bi | 9 |
| No.4 | F | 37 | Unclear/GGE | Bi/L | 8 |
| No.5 | M | 29 | GGE | Bi | 19 |
| No.6 | M | 54 | GGE | Bi | 16 |
| No.7 | M | 53 | GGE | Bi | 23 |
| No.8 | F | 36 | GGE | Bi | 12 |
| No.9 | F | 23 | GGE | Bi | 15 |
| No.10 | M | 30 | GGE | Bi | 16 |
| No.11 | F | 20 | GGE | Bi | 12 |
| No.12 | F | 57 | Unclear | Bi/Occ | 5 |

GGE: genetic generalized epilepsy; M: male; F: female; Bi: bilateral; L: left, Occ: occipital; GSWD: generalized spike-wave discharges; EEG: encephalogram; fMRI: functional magnetic resonance imaging.

^aAt EEG-fMRI examination.

^bDuring EEG-fMRI recording.

(EEG) correlates are generalized synchronous spike-wave discharges (GSWDs) with an average frequency of 3–4 Hz.¹ In GGE, aberrant circuits between the thalamic input and the cortex are facilitating GSWD.^{1–3} While routine magnetic resonance imaging (MRI) examinations are expected to be normal during visual expert analysis, quantitative MRI techniques as voxel-based morphometry (VBM) revealed widespread grey matter changes in the thalamus and cortical structures.^{4,5} Simultaneous EEG-functional MRI (fMRI) studies recorded during absence seizures oder interictal discharges identified characteristic patterns of subcortical (mediodorsal thalamic and striatal) activation followed by a cortical deactivation.^{6–10} Experimental evidence suggests that GSWDs may be generated in the neocortex with subsequent involvement of thalamo-cortical loops.^{11–15}

In this pilot study, we retrospectively analysed 12 patients with GGE to

- i. investigate thalamic grey matter volume changes in GGE and
- ii. investigate a topographic relationship between regional thalamic volume changes and altered connectivity of large-scale networks in the human cortex.

We hypothesized that thalamic atrophy associates with altered functional connectivity of large-scale networks within a small sample of GGE patients.

Materials and methods

Subjects

We investigated 12 patients with drug-resistant GGE and frequent GSWD discharges on interictal EEG. Each of the patients underwent resting-state fMRI with simultaneous EEG (EEG-fMRI) and a separate structural T1-weighted

Table 2. Data of GGE patients and control groups for connectivity analysis (control 2).

| Control 2 | Gender | Age (years) |
|-----------|--------|-------------|
| No. 1 | F | 46 |
| No. 2 | F | 21 |
| No. 3 | M | 39 |
| No. 4 | F | 36 |
| No. 5 | M | 34 |
| No. 6 | F | 43 |
| No. 7 | M | 26 |
| No. 8 | M | 41 |
| No. 9 | F | 43 |
| No. 10 | F | 35 |
| No. 11 | M | 39 |
| No. 12 | M | 29 |

GGE: genetic generalized epilepsy; M: male; F: female.

high-resolution MRI included into the routine epilepsy protocol. Average age was 38.7 years (range 15.4–65.1 years, SD 15.4 years, 7 females and 5 males). Ten of 12 patients had a confirmed diagnosis of GGE based on clinical criteria (2 patients had an epilepsy syndrome with generalized seizures and bilateral GSWD and were classified as ‘probable’ GGE).

Visual inspection of the MRI data was normal in all patients (demographic data are summarized in Table 1). Two age- and gender-matched normative control group data sets from an in-house data base were employed for morphometry and functional connectivity analysis. For functional connectivity, 12 healthy controls (HCs) who underwent resting-state EEG-fMRI were used, encompassing 7 females and 5 males (mean age 36.0 years (range 21–46, SD 7.5 years); data are summarized in Table 2). Due to imaging artefacts of the EEG cap in this cohort, we used a second data set that consisted of high-quality T1-weighted high-resolution multiplanar rapid gradient echo sequence

Table 3. Data of GGE patients and control groups for morphological analysis (control I).

| Controls I | Gender | Age (years) |
|------------|--------|-------------|
| No. 1 | M | 31 |
| No. 2 | F | 39 |
| No. 3 | F | 46 |
| No. 4 | F | 33 |
| No. 5 | M | 28 |
| No. 6 | F | 22 |
| No. 7 | F | 17 |
| No. 8 | F | 36 |
| No. 9 | F | 23 |
| No. 10 | M | 46 |
| No. 11 | M | 66 |
| No. 12 | M | 56 |

GGE: genetic generalized epilepsy; M: male; F: female.

(MP-RAGE) images from a separate cohort of 12 age- and gender-matched controls (mean age 36.9 years (range 17–66, SD 14.5), 7 females and 5 males; data are summarized in Table 3).

Data acquisition

All structural and functional data of patients and controls were acquired on the same 3-T scanner (3 T Magnetom Trio TIM system; Siemens Healthineers, Erlangen, Germany). T1-weighted 3D images were acquired using an MP-RAGE with the following parameters: 176 sagittal slices, isovoxel resolution = 1.0 mm, field of view $256 \times 256 \text{ mm}^2$, matrix size = 256×256 and TR/TE/TI = 1950/2.15/900 ms. Resting-state fMRI was acquired using a single-shot echoplanar imaging sequence, TR 1.98 s, 32 slices (interleaved), matrix size 64×64 and voxel size: $3 \times 3 \times 3.75 \text{ mm}^3$. Three hundred acquisitions were recorded in patients and controls. The patients were instructed to keep their eyes closed and relax during the resting-state fMRI examination ('resting state' recording).¹⁶

Data analysis

Overview. Data analysis encompassed two sequential steps: We used VBM to identify regions of grey matter volume change in GGE patients in comparison with HCs. A special focus was set on volume reductions of the thalamus. We employed functional connectivity analysis to test whether regions that exhibited volume change also showed differences in network characteristics. We followed the analysis pipeline as described by Kurth et al.¹⁷

Voxel-based morphometry. Every scan was checked for image artefacts and gross anatomical abnormalities. Images were processed with VBM8 (<http://www.neuro.uni-jena.de/vbm/>) using International Consortium for Brain Mapping template tissue priors, modulated normalization, bias

correction and affine registration.¹⁷ Grey matter images of patients and controls were smoothed, using a Gaussian kernel of $10 \times 10 \times 10 \text{ mm}^3$ full-width at half maximum. A region of interest (ROI) mask of bilateral thalamic areas was created using the standard thalamic statistical parametric mapping (SPM) 'Anatomy' toolbox templates.¹⁸

Grey matter volume differences of the thalamus were compared between GGE patients and controls. Morphological differences were estimated with two-sample Student's *t*-tests. Contrasts were set to patients > controls and patients < controls, T contrast vector [1 -1]. Results were visualized using 'Overlap between Structure and Function' in the 'Anatomy' toolbox of MATLAB. Patients < Controls was chosen as the primary contrast, showing areas in which patients have impaired grey substance in thalamus compared to controls. No masking was applied. We used a significance threshold for $p < 0.05$, and family-wise error corrected for multiple comparisons using Gaussian random field theory.¹⁹

Functional connectivity analysis. Functional MRI data were preprocessed using the SPM8 software package in MATLAB (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). The BOLD images were spatially realigned, slice time corrected and spatially smoothed (full-width at half maximum of the Gaussian smoothing 8 mm isotropic) and normalized to standard stereotaxic space. Functional analysis was performed using the CONN Functional Connectivity Toolbox, version 15 (<https://www.nitrc.org/projects/conn/>) in MATLAB. Preprocessed, smoothed and normalized T1-weighted images were used for anatomy and preprocessed fMRI data for functional overlay. For artefact removal, we first implemented segmented grey matter, white matter and cerebrospinal fluid (CSF) images of patients and controls. For region-wise analysis, we overlaid ROIs encompassing (i) the default mode network (DMN; CONN template, medial prefrontal cortex (mPFC), posterior cingulate cortex, left and right lateral parietal cortex) and (ii) areas that displayed a significant thalamic volume reductions in the VBM analysis separately for left and right side.²⁰ Patients and controls were segregated into two groups. Data were bandpass filtered (0.01–0.1 Hz) to reduce the effect of high- and low-frequency physiological noise. Confounders (six motion parameters, CSF, white matter and effect of rest) were removed to reduce non-neuronal BOLD fluctuations and the effect of head movement. A ROI-to-ROI and seed-to-voxel-based statistical analysis comparing patients and controls was performed to investigate the functional connectivity distribution map for patients and controls. We evaluated the contrasts patients > controls and controls > patients connectivity using a two-sided *t*-test.

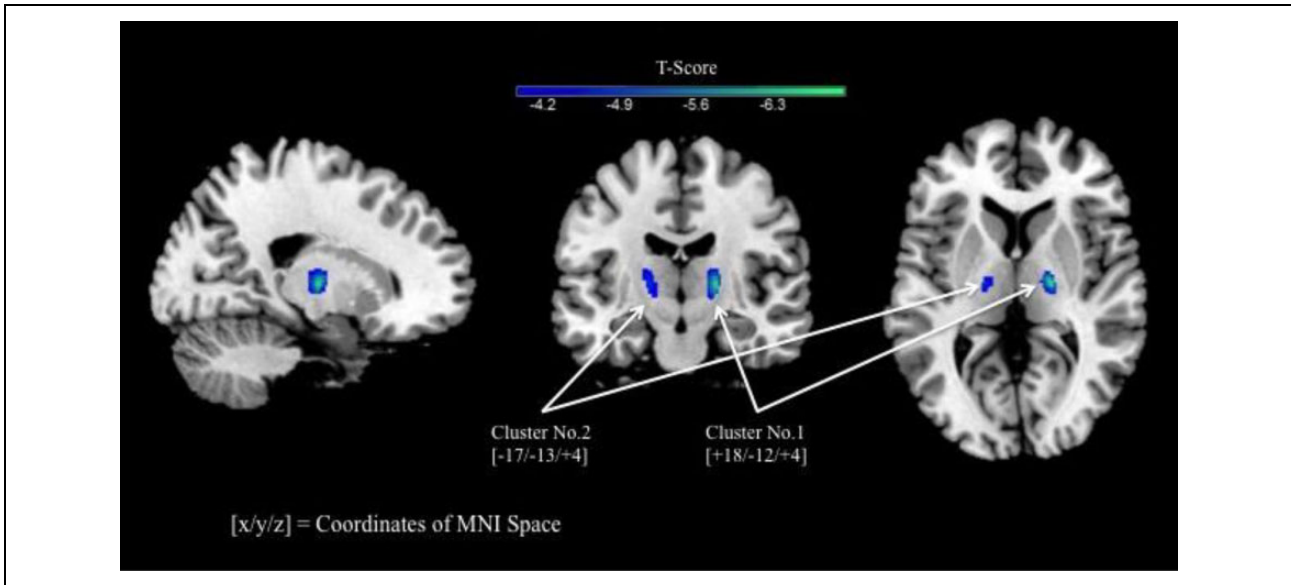


Figure 1. VBM of thalamus. VBM: voxel-based morphometry.

Table 4. VBM results of the thalamus.

| Cluster | Coordinates (MNI) | Anatomy | nVox | T value |
|---------|-------------------|---|------|---------|
| No. 1 | [+18/-12/+4] | Th. Premotor 43.3% T: 3.26 Th. Prefrontal 38.4% T:1.46 Th. Motor 13.8% T:1.31 | 235 | 3.98 |
| No. 2 | [-17/-13/+4] | Th. Premotor 41.7% T:3.07 Th. Prefrontal 61.5% T:2.17 Th. Motor 4.1% T:0.4 | 111 | 3.98 |

VBM: voxel-based morphometry; MNI: Montreal Neurological Institute; nVox: number of voxels; No: number; Th.: thalamus.

Results

VBM of thalamus

Patients with GGE showed decreased grey matter volume in the thalamus bilaterally (Figure 1). A nearly symmetrical cluster in corresponding areas of three nuclei of thalamus was detected. Areas in the premotor and prefrontal nuclei, as well as the motor nucleus, were primarily affected (Table 4). We did not find areas of increased grey matter volumes in patients.

T-score maps (threshold at $p\text{-FWE} = 0.05$) generated by VBM8 analysis were projected over a standard T1-weighted MPR brain image for visualization. Clusters in the bilateral thalamus indicated areas of decreased volume in patients with GWE in comparison with controls. Clusters are color-coded, green colour indicates a lower T-contrast and blue colour indicates a higher T-contrast (at an inferior threshold of 4.0).

Functional connectivity analysis

Areas of decreased thalamic grey matter volume were selected as seed regions for functional connectivity analysis

on resting-state fMRI data. Functional connectivity maps of both the patients and the controls showed a significant positive correlation along both thalami, indicating inter-thalamic connectivity. However, no significant correlation was observed along other brain areas, neither for patients nor for controls. ROI-to-ROI functional connectivity increases between GGE patients and controls were detected between the left-sided thalamus and the left mPFC. Decreased connectivity was observed between both parietal cortices, respectively (Figure 2).

In this table, significant functional connectivity differences between GGE patients and HCs (threshold at $p\text{-FDR} = 0.05$) are displayed. Compared to control subjects, patients showed increased connectivity between the left thalamus and the left mPFC (contrast = patients > controls). Patients showed a decrease in connectivity between bilateral parietal cortex (contrast = patients < controls); $t = t\text{-values}$, $\beta\text{-values} = \text{Fisher-transformed correlation coefficient values}$.

Discussion

Here, we used brain morphometry and functional connectivity analysis to investigate grey matter abnormalities in

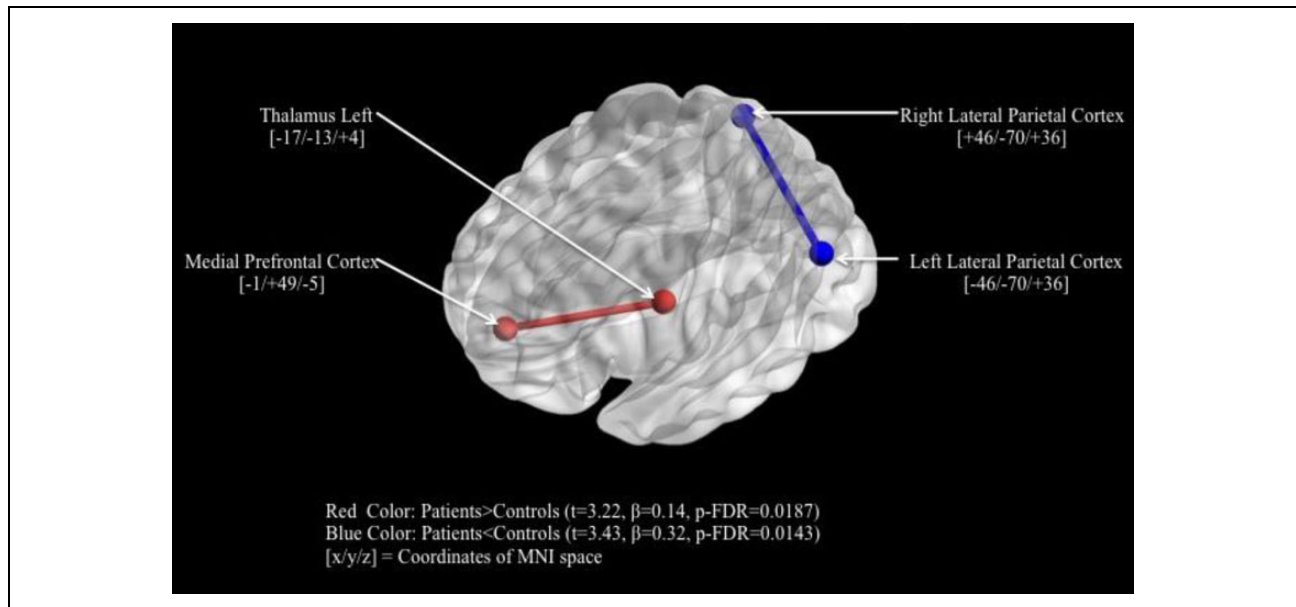


Figure 2. ROI-to-ROI functional connectivity analysis. ROI: region of interest.

the thalamus and its influence on brain network connectivity in patients with GGE. Our results indicate that significant bilateral thalamic atrophy is associated with functional changes in the anterior and posterior areas of the DMN. Specifically, stronger thalamus-to-mPFC connectivity was offset by loss of bilateral connectivity between the right and the left posterior parietal cortices.

Structural alterations

Compared to HCs, patients showed decreased grey matter volumes bilaterally in the thalamus. These results largely replicate previous findings in studies of VBM analysis, which also demonstrated bilateral grey matter loss in the thalamus and cortical structures.^{4,5} Our results corroborate these findings, yet refine them by using a detailed neuroanatomical atlas. We correlated grey matter alterations within thalamic regions that have a high (structural) connection probability to areas of premotor, prefrontal and motor areas.²¹ This is in line with a number of clinical and neuroimaging studies, indicating that the frontal lobes are important in GGE pathophysiology.²² For instance, recent neuropsychological investigations in GGE patients have shown that they suffer from a variety of deficits that are commonly attributed to frontal lobe dysfunction, that is, impairments in non-verbal reasoning, verbal generativity, attention and working memory.²³ Indeed, recent meta-analyses have shown that these deficits are quite pervasive, as could be expected from the ‘supra-modal’ control that the frontal lobes exert on other, more specific cognitive domains.²⁴ One might therefore hypothesize that alterations of thalamo-frontal interactions, given their dense reciprocal connectivity, could be one of the mechanisms behind these deficits.²⁵ Furthermore, Bernhardt et al. have

shown that cortical thickness is reduced in GGE patients in motor and midline prefrontal cortex and that the degree of thickness reduction is commensurate with thalamic volume changes (as well as disease duration and poor seizure control).⁵ O’Muircheartaigh et al. have shown that white matter tracts from anterior thalamus to midline frontal cortices are abnormal in patients with GGE and that their frontal targets show pathological activation to a word generation task, supporting the findings of the neuropsychological studies cited above.²⁶ These authors also showed that atrophy of bilateral mPFC is associated with concomitant alterations in white matter of the corpus callosum connecting these prefrontal areas and that these alterations, again, correlate with neuropsychological deficits.²⁷ Overall, our study is in line with previous observations that structural alterations of thalamo-cortical circuits are detectable in GGE.

Functional abnormalities

Connectivity within the DMN is pivotal for normal brain function. In fact, alterations of its intrinsic connectivity have been described in a number of neuropsychiatric disorders, for example, autism, depression, and Alzheimer’s disease, supporting its importance in neurological disease.^{28,29} In GGE, multiple studies have described fMRI deactivation of the DMN in response to GSWD,^{29,30} and this seems to coincide with periods of loss of consciousness in these patients.³¹ Three previous studies have shown aberrant functional connectivity within the DMN, mostly concerning prefrontal nodes. Luo et al. found globally reduced connectivity within the prefrontal and the bilateral parietal regions of the DMN and a negative correlation between fronto-parietal connectivity and disease

duration.³² Similarly, McGill et al. identified a negative correlation between connectivity of medial frontal cortex and medial parietal cortex and disease duration, as well as global reductions of within-DMN connectivity.³³ Both studies, however, did not record EEG simultaneously with fMRI and thus could not account for the effects of concurrent GSWD. This was refined in a study by Kay et al. who used simultaneous EEG-fMRI to assess DMN connectivity in the context of drug resistance in GGE.³⁴ This work confirmed the results of the two aforementioned studies and additionally reported that DMN connectivity reductions were more pronounced in antiepileptic drug (AED)-resistant patients. Of note, a qualitative overview of all three studies indicates that (posterior) parietal connectivity of the DMN was predominantly reduced compared to frontal connectivity; this is in line with our observations of reduced biparietal connectivity. The role of the thalamus in these connectivity alterations has not been investigated in detail so far, although the thalamus is known to play a crucial role in GSWD pathophysiology.¹ Our results suggest that, paradoxically, thalamic atrophy is associated with selectively increased functional connectivity from thalamus to mPFC. The main difficulty in interpreting these findings is that our cross-sectional study design does not allow disentangling the direction of causality between morphological changes and functional connectivity alterations. One hypothesis might be that changes in thalamic volumes are an endophenotype of GGE that predates the onset of seizures and that functional connectivity alterations ensue once the disease is established. Evidence for this hypothesis comes from very recent data that show that thalamic anatomy is altered in children with absence epilepsy (a GGE syndrome) already at the onset of the disorder and even ahead of AED treatment.³⁵ In this scenario, a loss of thalamo-cortical excitatory afferents to inhibitory cortical interneurons could putatively lead to a facilitation of cortico-thalamic excitatory efferents and thus to increased influence of cortex on thalamic output.³⁶ However, the fMRI connectivity analyses we performed are not directional and have only a tenuous relationship to underlying cellular mechanisms. The mechanisms behind prefrontal–thalamic connectivity alterations must therefore remain speculative.

Limitations

Our findings have to be interpreted in the light of the following limitations. In particular, our sample sizes were small, and we used two heterogeneous subgroups of controls. This limits the generalizability of our findings and increases the risk of false-positive results. An additional threat to generalizability is the fact that all patients were selected from a tertiary epilepsy centre; this inherently biases our sample towards more severe cases and/or those with unusual presentations. Indeed, we were not able to definitively ascertain the GGE diagnosis in two cases (although alternative syndromes were unlikely). Another

limitation is the potential confound of AED treatment, which we did not investigate in the present study. Recent fMRI studies suggest that common AEDs – such as valproic acid, levetiracetam or carbamazepine – have spatially extended effects on network connectivity and activation, both at rest and under cognitive stimulation.^{37,38} It will therefore be essential to assess the effects we found in drug-naïve cohorts or larger samples in which patients could be stratified according to AED use. Despite these shortcomings, it is remarkable that we were able to recover patterns of alterations that are very much concordant with the literature; this could indicate that thalamo-cortical alterations are not subtle, as they can stand out even in small-scale (and potentially noisy) studies such as ours. Finally, we note that a cross-sectional study such as the present one cannot provide causal evidence on the relationship between atrophy and functional alterations; larger longitudinal studies will be needed to establish whether atrophy and functional impairments indeed show parallel alterations over time.

Conclusions

We show that bilateral thalamic atrophy affects subcortico-cortical and cortico-cortical connectivity in specific thalamo-prefrontal circuits in patients with GGE. Our findings underscore the network hypothesis of epilepsy³⁹ and emphasize how affections of critical nodes – in this case, medio-lateral thalamus – can have disruptive brain-wide effects.


Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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