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Diffusion tensor imaging in photosensitive and nonphotosensitive juvenile myoclonic epilepsy

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ABSTRACT

Introduction/background: Juvenile myoclonic epilepsy (JME) syndrome is known to cause alterations in brain structure and white matter integrity. The study aimed to determine structural white matter changes in patients with JME and to reveal the differences between the photosensitive (PS) and nonphotosensitive (NPS) subgroups by diffusion tensor imaging (DTI) using the tract-based spatial statistics (TBSS) method.

Methods: This study included data from 16 PS, 15 NPS patients with JME, and 41 healthy participants. The mean fractional anisotropy (FA) values of these groups were calculated, and comparisons were made via the TBSS method over FA values in the whole-brain and 81 regions of interest (ROI) obtained from the John Hopkins University White Matter Atlas.

Results: In the whole-brain TBSS analysis, no significant differences in FA values were observed in pairwise comparisons of JME patient group and subgroups with healthy controls (HCs) and in comparison between JME subgroups. In ROI-based TBSS analysis, an increase in FA values of right anterior corona radiata and left corticospinal pathways was found in JME patient group compared with HC group. When comparing JME-PS patients with HCs, an FA increase was observed in the bilateral anterior corona radiata region, whereas when comparing JME-NPS patients with HCs, an FA increase was observed in bilateral corticospinal pathway. Moreover, in subgroup comparison, an increase in FA values was noted in corpus callosum genu region in JME-PS compared with JME-NPS.

Conclusions: Our results support the disruption in thalamofrontal white matter integrity in JME, and subgroups and highlight the importance of using different analysis methods to show the underlying microstructural changes.

1. Introduction

Juvenile myoclonic epilepsy (JME) is an idiopathic epilepsy (IGE) syndrome with well-defined clinical and electrophysiological features. Reflex epileptic mechanisms, such as photosensitivity, are also closely related to the nature of JME and are important for understanding JME pathogenesis [1,2].

Routine clinical magnetic resonance imaging (MRI) indicates no focal structural abnormalities that may cause seizures in patients with this common IGE syndrome. On the other hand, with the advanced neuroimaging techniques and statistical tools developed in recent years, microstructural and functional alterations explaining the pathophysiology of JME have been presented, especially cortical and subcortical abnormalities engaged with the frontal and thalamocortical pathways [3–5].

Diffusion tensor imaging (DTI) is an advanced neuroimaging method that provides information about the microstructural integrity and orientation of white matter tracts by measuring the diffusion of water

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molecules in many directions. Water diffusion measured in a single direction varies with the microstructural organization and orientation of nerve fibers in that direction. Therefore, the combined representation of all directional diffusion measurements provides a quantitative expression of cranial white matter structures with parameters such as fractional anisotropy (FA) and mean diffusion [6]. FA images derived from diffusion data provide information on the level of selective diffusion in a given direction for each voxel and could be used in voxel-based analyzes to localize structural changes and degeneration that occur in disease. Tract-based spatial statistics (TBSS) is a widely used voxel-based statistical method for comparing FA maps between subject groups. TBSS employs a standard analysis pipeline, including nonlinear registration of the FA maps to an FA template, generation of skeletal images from the FA maps, their reduction to basic tracts, and use of a nonparametric permutation inference method for group analysis [7]. This method has been one of the most preferred analysis methods in DTI research in recent years because it is insensitive to the smoothing and alignment problems often encountered in DTI analyzes and allows examination of all brain regions, unlike standard region of interest (ROI) approaches.

To date, many studies have been conducted to assess white matter integrity and orientation in subjects with JME using the DTI method. Almost all of these publications have reported that patients with JME have a decrease in FA in many cortical/subcortical structures, such as the longitudinal fasciculus, corticospinal tract, anterior and posterior thalamic radiations, corona radiata, corpus callosum, cingulate gyrus, supplementary motor area, and internal and external capsule [3,8–18]. It is noteworthy that the most consistent differences were observed in the thalamocortical pathways and corpus callosum.

One of the key studies on JME by Vollmar et al. showed that structural changes in the medial frontal region may be responsible for the increased functional connectivity in the pathophysiology of JME. They found increased connectivity between the supplementary motor area and the occipital cortex in patients with a photoparoxysmal response, which may explain the formation of frontocentral dominant generalized epileptiform discharges and seizures in patients with photosensitive JME (JME-PS) [19].

Most DTI studies in JME have not been conducted in homogeneous subgroups separated as PS and non-photosensitive (NPS). Additionally, there are prominent differences in the results of limited DTI studies conducted on JME subgroups. For example, one DTI study revealed decreased FA values in the corpus callosum in JME-PS compared to healthy individuals [20]. Results of another DTI study showed significantly increased FA values in the ascending reticular activating system (ARAS) and ventromedial thalamus in JME-PS compared to JME-NPS and healthy participants [21]. In contrast, one study reported no significant difference between FA values in patients with JME-PS and JME-NPS [18]. Therefore, investigating white matter integrity and microstructural abnormalities in JME, especially in its subgroups, using various statistical methods is important for understanding epileptic mechanisms, which is our main objective in this study.

In this study, we sought to understand the microstructural changes underlying reflex epileptic mechanisms that cause photosensitivity using DTI. We performed whole brain-based TBSS analysis and ROI-based TBSS analysis, and assessed group differences between JME, in well-defined subgroups of JME (JME-PS vs. JME-NPS), and healthy controls (HCs).

2. Methods

2.1. Participants

The patient group was recruited from two epilepsy centers and was consecutively selected from patients aged 16 to 65 years who were followed for at least one year. JME was diagnosed by epileptologists based on clinical and EEG features [22,23].

The control group was recruited from healthy volunteers who matched the patient group in terms of age, gender, and education level. The inclusion criteria for JME were as follows: (i) myoclonic jerks predominantly occurring on awakening, (ii) myoclonic jerks facilitated by sleep deprivation and stress and provoked by visual/light stimuli and praxis or GTCSs preceded by myoclonic jerks, (iii) EEG shows a normal background and at least once interictal generalized spike or poly-spike and waves with some asymmetry allowed with or without myoclonic jerks, (iv) no mental retardation or deterioration, (v) age at onset of between 6 and 25 years, and vi) for those patients with JME-NPS, the criteria were the absence of clinically light/visual stimuli-induced seizures and the absence of a photoparoxysmal response in all EEGs (at least three EEGs had been done before DTI records) [23,24].

The exclusion criteria for participants were as follows: (i) misdiagnosis of epilepsy syndrome and absence of diagnostic clinical and EEG features for the JME group, (ii) presence of any psychiatric or systemic disease that may affect brain functions, (iii) having visual and/or hearing impairment, (iv) not being literate, (v) presence of metal or any device in the body that is not compatible with MRI scanner, and (vi) having claustrophobia.

The patient group received antiseizure drug treatment throughout the study for ethical reasons.

The study was approved by the Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or the parents of participants under 18 years of age.

2.2. Data acquisition

MRI data were acquired using a 3T scanner (Philips Achieva, Best, The Netherlands) with a 32-channel head coil. During the MRI session, resting-state fMRI sequences were acquired in some participants in addition to diffusion imaging, and the findings regarding functional data were published in a previous study [25]. Diffusion-weighted images were acquired using a single-shot, spin-echo, echo-planar sequence (TR = 10,538 ms; TE = 86 ms; isotropic voxel size of 2 mm; FOV = 240 × 240 mm; 90 axial slices; flip angle = 90°; 32 diffusion directions; b factor = 1000 s/mm^2). T2-weighted anatomic images were acquired with the Turbo Spin Echo sequence (TR = 21,284 ms; TE = 80 ms; voxel size is isotropic 2 mm; FOV = 240 × 240 mm; 90 axial slices; flip angle = 80°).

2.3. Diffusion imaging data preprocessing

Diffusion data were preprocessed using the FSL 6.0 software package (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) [26]. First, a brain extraction tool (BET) was used to remove non-brain tissue from B0 images [27]. Then, the susceptibility-induced field and eddy currents were estimated using the “topup” tool [28]. Eddy currents and head motion distortions were corrected using the eddy current correction tool [29]. Next, a diffusion tensor model was fitted to each voxel using FDT (FMRIB’s Diffusion Toolbox) to generate FA maps.

2.4. Whole-brain TBSS analysis

After fitting the diffusion tensor model, a voxel-wise statistical analysis was performed across all subjects using the TBSS pipeline [7]. First, the FA images were aligned to a standard 1 mm resolution space (FMRIB58_FA) in the nonlinear registration step [30]. Since the registration process moves FA maps into the common space and allows operations between them, the average of all FA images was calculated. A tract skeleton of the mean FA image was created, representing the midline of white matter tracts common to all subjects [7]. The next TBSS step was performed to threshold the mean FA skeletal image at 0.25, and the resulting mask was used for subsequent processes. Subsequently, the FA data were projected onto the mean FA skeleton mask, and these subject-specific skeletonized FA data were used for voxel-wise statistics.

Voxel-wise cross-subject statistics were performed using the FSL randomize tool [31]. The randomize tool was used for nonparametric inference on neuroimaging data [32]. The number of permutations used in the analysis was set to 5000, and threshold-free cluster enhancement (TFCE) was used at $p < 0.05$ at the cluster level for multiple comparisons.

2.5. ROI-based TBSS analysis

Whole-brain TBSS analysis was followed by ROI-based TBSS analysis. Statistical comparisons between groups were performed for the following regions: bilateral anterior corona radiata, bilateral cingulate gyrus, bilateral corticospinal tract, bilateral external capsule, corpus callosum body, corpus callosum genu, corpus callosum splenium, bilateral superior corona radiata, bilateral sagittal stratum, and bilateral superior longitudinal fasciculus.

In ROI-based TBSS analysis, masks were first obtained directly from regions identified in the John Hopkins University DTI White Matter Atlas. Skeletonized FA data obtained from whole-brain TBSS analysis were masked separately for each ROI. Voxel-wise statistics were then performed for each ROI using the FSL randomize tool. FA differences were examined for the JME, subgroups of JME, and HC groups. Finally, for visualization, regions where statistically significant differences were observed were thickened on the skeletonized image.

3. Results

3.1. Demographic and clinical findings

The study included 31 patients with JME (16 JME-PS and 15 JME-NPS) and 41 HCs. The demographic data of the study groups are given in Table 1.

There was no significant difference between the patients and HCs in terms of age [t (70) = 0.608, $p = 0.122$], gender [$X^2(1) = 0.725$, $p = 0.394$], and education level [U (70) = 96.00, $p = 0.825$]. In addition, pairwise comparisons were made between the JME-PS vs. HC, JME-NPS vs. HC, and JME-PS vs. JME-NPS groups, and no significant difference was found (Table 1).

Over half of the patients ($n = 18$) were taking valproate (58.1%) and were under monotherapy [in JME-PS: 81.3% ($n = 13$) /in JME-NPS: 66.7% ($n = 10$)]. There was no difference in terms of seizure control between the subgroups of JME ($p = 0.942$).

3.2. Whole-brain TBSS analysis

In the whole-brain TBSS analysis, performed with a nonparametric approach, no white matter region was found to have a statistically significant FA difference between the groups ($p > 0.05$), as shown in Table 2. Additionally, there were no significant FA differences between females ($n = 19$) and males ($n = 12$) in the patient group when performing a similar whole-brain TBSS analysis with the same nonparametric approach and correction for multiple comparisons across space ($p > 0.05$).

Table 2
Mean fractional anisotropy values of the study groups.

	HC ($N = 41$) Mean ± SD	JME ($N = 31$) Mean ± SD	JME-PS ($N = 16$) Mean ± SD	JME-NPS ($N = 15$) Mean ± SD
FA	0.494 ± 0.02	0.495 ± 0.01	0.490 ± 0.01	0.498 ± 0.01

FA: Fractional anisotropy, JME: Juvenile myoclonic epilepsy, JME-PS: Photosensitive juvenile myoclonic epilepsy, JME-NPS: Non-photosensitive juvenile myoclonic epilepsy, HC: Healthy control, SD: Standard deviation.

3.3. ROI-based TBSS analysis

ROI-based TBSS analysis comparing the (i) JME and HC groups showed significant FA differences in right anterior corona radiata and left corticospinal tract regions, (ii) JME-PS and HC groups showed significant FA differences in the right and left anterior corona radiata, (iii) JME-NPS and HC groups showed significant FA differences in the right and left corticospinal tracts, and (iv) JME-PS and JME-NPS groups showed significant FA differences in the genu of the corpus callosum (Table 3). For the other ROIs, no white matter regions showed statistically significant FA differences. In Fig. 1, regions of statistically significant FA values were thickened and projected onto the MNI FMRIB58 FA (1 mm) template and mean FA skeleton image.

4. Discussion

In this study, whole brain-based TBSS analysis and ROI-based TBSS analysis were performed together. We could not detect a significant microstructural difference using whole brain- based TBSS, whereas ROI-based TBSS analysis revealed the following substantial white matter differences: (i) in the entire JME group, FA values of the right anterior corona radiata and left corticospinal tract were increased compared to the HC group; (ii) in the JME-PS group, FA values of the bilateral anterior corona radiata were increased compared to the HC group, whereas FA values of the genu of corpus callosum were increased compared to the JME-NPS group; and iii) in the JME-NPS group, FA values of the bilateral corticospinal tract were increased compared to the HC group. Combining whole-brain TBSS analysis with ROI-based TBSS analysis would empower the results of research by examining statistically constrained regions and focusing on hypothesis-based specific

Table 1
The demographic characteristics of the study groups.

	JME-PS ($N = 16$) Mean ± SD (Range)	JME-NPS ($N = 15$) Mean ± SD (Range)	HC ($N = 41$) Mean ± SD (Range)	p
Age (in years)	26.50 ± 6.98 (16–42)	29.47 ± 10.69 (18–54)	32.17 ± 7.36 (16–46)	0.159[a]
Gender (F: M)	12:4	7:8	21:20	0.198[b]
Years of education	10.88 ± 4.60 (2–16)	10.96 ± 4.14 (5–17)	13.26 ± 4.22 (5–22)	0.316[c]
Age of seizure onset (in years)	15 ± 4.60 (10–26)	14.17 ± 4.9 (6–18)	–	0.742[d]
Duration of disease (in years)	12.06 ± 6.59 (1–27)	16.31 ± 12.81 (3–40)	–	0.246[e]

JME-PS: Photosensitive juvenile myoclonic epilepsy, JME-NPS: Non-photosensitive juvenile myoclonic epilepsy, HC: Healthy control, SD: Standard deviation, F: Female, M: Male

[a] One-way analysis of variance (ANOVA)
[b] Pearson Chi-square test.
[c] Kruskal-Wallis H test.
[d] Mann-Whitney U test.
[e] Independent samples t-test.

Table 3
ROI-based TBSS analysis results.

Contrast	White Matter Region	Cluster Index	Voxel Size	Max (x y z)	p[a]
JME> HC	Anterior Corona Radiata R	1	49	64 −144 −88	<0.05
JME> HC	Anterior Corona Radiata R	2	71	68 −163 −68	<0.05
JME> HC	Corticospinal Tract L	3	41	99 −100- 41	<0.05
JME-PS> HC	Anterior Corona Radiata L	1	20	114 −160- 80	<0.05
JME-PS> HC	Anterior Corona Radiata R	2	501	65- 161 −79	<0.05
JME-NPS> HC	Corticospinal Tract L	1	6	95- 100- 42	<0.05
JME-NPS> HC	Corticospinal Tract L	2	14	97 −102- 46	<0.05
JME-NPS> HC	Corticospinal Tract R	3	1	84- 100- 42	<0.05
JME-NPS> HC	Corticospinal Tract R	4	4	80 −101- 44	<0.05
JME-PS> JME-NPS	Genu of Corpus Callosum	1	18	83– 157–80	<0.05

JME: Juvenile myoclonic epilepsy, JME-PS: Photosensitive juvenile myoclonic epilepsy, JME-NPS: Non-photosensitive juvenile myoclonic epilepsy, HC: Healthy control, ROI: Region of interest, TBSS: Tract-based spatial statistics, R: Right, L: Left.
[a] : TFCE-corrected at cluster level for multiple comparisons $p<0.05$,.

pathways, as in our study.

Studies that examined white matter changes in JME mostly used whole-brain TBSS analysis, tractography analysis, or ROI-based analysis [3,14,15,18,33–35]. Table 4 summarizes the results of DTI studies investigating white matter changes in JME.

4.1. White matter abnormalities in juvenile myoclonic epilepsy

The role of thalamocortical networks in the etiopathogenesis of IGEs has been demonstrated in many studies using different modalities [5,36,37]. In our study, increased FA values of the right anterior corona radiata and left corticospinal tract were found in entire JME group compared to the HCs. Supporting our findings, abnormalities in thalamocortical white matter structures have been highlighted in the literature [3,8–10,12,15,16,18,34,38].

The results of DTI studies examining the microstructural white matter changes in JME show variance. For example, von Podewils et al. (2015) reported a decrease in FA values of the lateral geniculate body in JME, whereas Keller et al. (2011) reported an increase in FA values of the putamen and a decrease in thalamocortical networks [9,21]. On the other hand, Vuillemoz et al. reported a decrease in FA values of the supplementary motor area using probabilistic tractography [11]. Deppe et al. found decreased FA values in the anterior thalamic radiation connecting the anterior and medial nuclei of the thalamus with the frontal lobe [8]. Another DTI study using the TBSS method reported decreased FA values in the longitudinal fasciculus, corticospinal tract, anterior and posterior thalamic radiations, corona radiata, corpus callosum, cingulate gyrus, and external capsule [18]. Recently, the ENIGMA-Epilepsy consortium published the results of an aggregate analysis of a large series of patients with epilepsy. The results showed that FA values in most white matter pathways, especially in the genu and body of the corpus callosum, cingulum, and external capsule, were lower in patients with epilepsy than in healthy individuals [39]. Furthermore a subgroup analysis of epilepsy patients was performed. In patients with

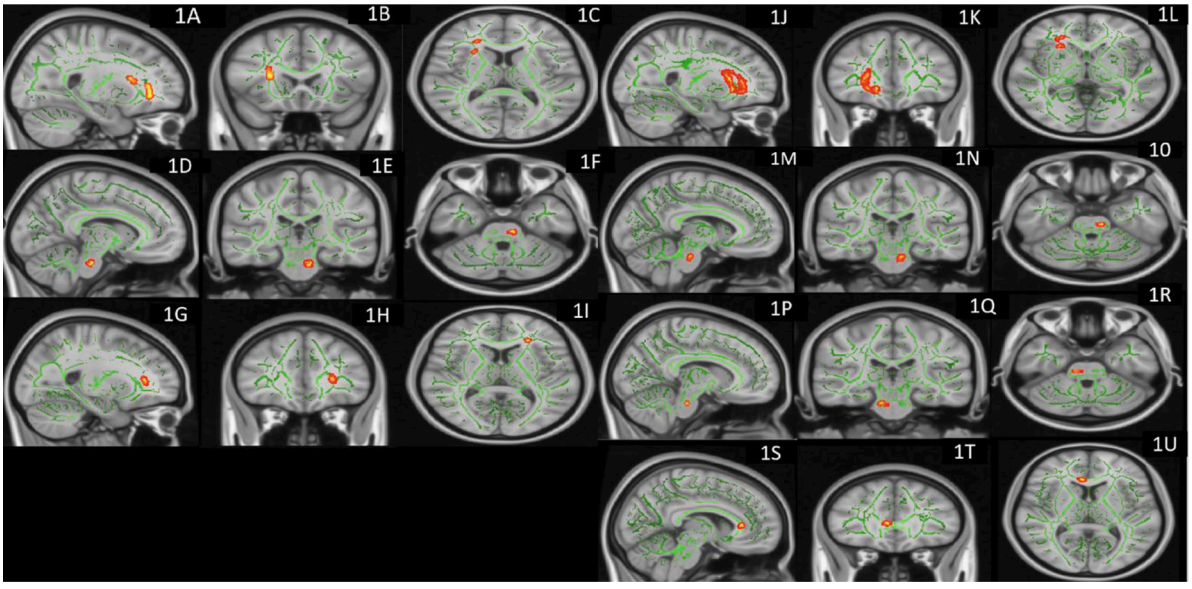

Fig. 1. A-B-C: Projection of the areas showing significantly higher FA value in the right anterior corona radiata in juvenile myoclonic epilepsy group compared to healthy control group; Fig. 1D-E-F: Projection of the areas showing significantly higher FA value in the left corticospinal tract in juvenile myoclonic epilepsy group compared to healthy control group; Fig. 1G-H-I: Projection of areas showing significantly higher FA value in the left anterior corona radiata in photosensitive juvenile myoclonic epilepsy group compared to healthy control group; Fig. 1J-K-L: Projection of areas showing significantly higher FA value in the right anterior corona radiata in photosensitive juvenile myoclonic epilepsy group compared to healthy control group; Fig. 1M-N-O: Projection of the areas showing significantly higher FA value in the left corticospinal tract in non-photosensitive juvenile myoclonic epilepsy group compared to healthy control group; Fig. 1P-Q-R: Projection of the areas showing significantly higher FA value in the right corticosoinal tract in non-photosensitive juvenile myoclonic epilepsy group compared to healthy control group; Fig. 1S-T-U: Projection of the areas showing significantly higher FA value in the genu of the corpus callosum in photosensitive juvenile myoclonic epilepsy group compared to non-photosensitive juvenile myoclonic epilepsy group on the MNI FMRIB58 FA (1 mm) template and mean FA skeleton, sagittal, coronal and axial planes from left to right, respectively.

Table 4
Reported white matter alterations in juvenile myoclonic epilepsy.

Study	Participants	Method	Findings
Deppe et al. (2008)	10 JME & 67 HC	ROI-based	Decreased FA in the anterior thalamus and prefrontal cortex pathways in the JME group compared to the HC group
Keller et al. (2011)	10 JME & 59 HC	ROI-based	Decreased FA in the frontal lobe and thalamocortical networks in the JME group compared to the HC group Decreased FA in putamen in the JME group compared to the HC group
O'Muircheartaigh et al. (2011)	28 JME & 30 HC	TBSS	Decreased FA in splenium and body of the corpus callosum in JME group compared to HC group
Kim et al. (2015)	18 JME & 22 HC	TBSS	Decreased FA in frontal white matter tracts and corpus callosum of JME group compared to HC group
Kim et al. (2012)	25 JME & 30 HC	TBSS	Decreased FA in bilateral anterior and superior corona radiata, corpus callosum genu, corpus callosum body, and frontal white matter tracts in JME compared to HC group
Du et al. (2014)	8 JME-PS & 16 HC	TBSS	Decreased FA in corpus callosum of JME group compared to HC group
Focke et al. (2014)	12 JME&44 HC	TBSS	Decreased FA in corpus callosum, corticospinal tract, superior longitudinal fasciculus, and frontal white matter tracts of JME group compared to HC group
von Podewils et al. (2015)	8 JME-PS & 10 JME-NPS & 27 HC	ROI-based	Increased FA in ARAS and ventromedial thalamus of JME-PS group compared to JME-NPS and HC groups Decreased FA in lateral geniculate of JME group compared to HC group
Ekmekçi et al. (2016)	24 JME & 28 HC	ROI-based	Decreased FA in dorsolateral prefrontal cortex, thalamus, posterior cingulate cortex, corpus callosum, and corona radiata of JME group compared to HC group
Gong et al. (2017)	26 JME & 25 HC	TBSS	No difference in JME and HC groups
Domin et al. (2018)	12 JME-PS & 19 JME-NPS & 27 HC	TBSS	Decreased FA in longitudinal fasciculus, corticospinal tract, anterior and posterior thalamic radiations, corona radiata, corpus callosum, cingulate gyrus, and external capsule in JME group compared to HC group No difference in JME subgroups
Current study	16 JME-PS &15 JME-NPS & 41 HC	TBSS ROI-based	No difference in JME and HC groups Increased FA in right anterior corona radiata and left corticospinal tract in JME compared to HC group Increased FA in genu of corpus callosum in JME-PS compared to JME-NPS group Increased FA in bilateral corticospinal tract in JME-NPS compared to HC group Increased FA in bilateral anterior corona radiata in JME-PS compared to HC group

JME: Juvenile myoclonic epilepsy, JME-PS: Photosensitive juvenile myoclonic epilepsy, JME-NPS: Non-photosensitive juvenile myoclonic epilepsy, HC: Healthy control, FA: Fractional anisotropy, ROI: Region of interest, TBSS: Tract-based spatial statistics.

IGE, without subgroup analysis for JME, the most pronounced effect size differences were detected in FA of the corpus callosum and external capsule and FA/MD of the bilateral anterior corona radiata [39,40]. Although the results of this important analysis strongly highlighted the decreased FA values in crucial white matter pathways in IGE, the subgroup analysis for JME has not been reported.

The anterior corona radiata is part of the limbic–thalamo–cortical circuit and contains thalamic radiations that extend from the internal capsule to cortical structures, including the prefrontal cortex [41,42]. The corticospinal tract is the major motor pathway from the cerebral cortex to the spinal cord, which originates from the primary motor cortex, premotor cortex, supplementary motor area, somatosensory cortex, parietal lobe, and cingulate gyrus. It passes through the posterior part of the internal capsule and extends to the brain stem and spinal cord [43]. Given these neuroanatomical connections, myoclonic seizures in JME may be associated with disruptions in the main white matter pathways.

Impairments in white matter integrity and changes in cortical organization have been shown in DTI studies conducted in patients with JME [3,10,15,16]. It has been reported that JME is mainly associated with the disruption of thalamofrontal connections [3,8,14,15,18,33,41]. Furthermore, in studies with neuropsychological evaluations of JME patients, the results of tests related to frontal lobe functions such as attention, memory, learning, verbal fluency, and executive functions were also supportive of this disruption [12,13,44–47]. Although, in the current study, cognitive functions were not evaluated with neuropsychological tests, the shown white matter changes in thalamofrontal connections support the neuroimaging correlation of the already known interictal cognitive function deficits in JME patients.

The decrease in the diffusion parameter FA is explained by axonal destruction in white matter tracts and disruption of white matter integrity [12]. Reduced FA in neurodegenerative diseases has often been associated with white matter degeneration, demyelination, reduced gliosis, or gray matter loss [12,48,49]. However, the increase in FA values in whole-brain TBSS analysis and ROI-based TBSS analysis should also be considered a critical finding. For example, a combined diffusion tensor and histology-based study showed FA increase in cortical regions in a rat model of traumatic brain injury [50]. In addition, some authors suggested that FA is associated more with axonal bundle density and less with myelination [51]. On the other hand, it has been reported that motor units, which are the basic structural and functional units innervated by spinal motor neurons, are larger in patients with JME than in healthy individuals using the motor unit number estimation method [16,52–54]. Some studies have reported that large motor neurons might be normal in density in JME patients [52,53]. Since JME patients may show genetic-based differences in motor neuron level, it is difficult to make inferences about axonal impairments and white matter integrity of cortical motor neurons. Supporting the FA increase in our study, increased FA values have been shown in some studies conducted in patients with IGE, including JME patients [21,55]. Interpretation of the results of the DTI analysis should be done with caution. The increase in FA values in our study may reflect a different kind of disruption in white matter integrity and may be important in understanding the pathogenesis of JME.

4.2. White matter abnormalities in photosensitive and nonphotosensitive juvenile myoclonic epilepsy

White matter alterations have been reported only in a limited number of DTI studies in homogeneous subgroups of JME, such as JME-PS and JME-NPS [15,20,21]. In a TBSS study conducted by Du et al. (2014), FA values of the corpus callosum were found to be decreased in the JME-PS group compared to healthy individuals [20]. On the other hand, in the study by Domin et al. (2018), no difference was observed in the FA values of JME-PS and JME-NPS subgroups [18]. Indeed, when the mean FA values of the JME-PS and HC groups were compared with the whole-brain TBSS method, no significant difference was observed in our study. However, in ROI-based TBSS analyzes, in which TBSS analysis was conducted in restricted areas, the mean FA values of bilateral anterior corona radiata tracts were found to be increased in the JME-PS

group compared to HCs. Additionally, FA values of the corpus callosum genu were increased in our JME-PS group compared to JME-NPS. On the other hand, in an ROI-based tractography analysis conducted by von Podewils et al. increased FA values in the ARAS, and ventromedial thalamus and decreased FA values in the internal capsule were found in JME-PS compared to JME-NPS and healthy individuals. In addition, the authors reported that FA values of the lateral geniculate body decreased in JME. They suggested that the lateral geniculate body, ARAS, and thalamocortical networks are critical in the ictogenesis of JME in terms of light-induced and awakening seizures. The microstructural changes observed in these regions may explain the electroclinical characteristics of JME and its subgroups [21]. Supporting the role of ARAS in the ictogenesis of JME, a recent fMRI study conducted in our laboratory, the predecessor of this DTI study, revealed altered connectivity of mesencephalic reticular formation and locus coeruleus in JME and its subgroups [25].

The genu of the corpus callosum is one of the critical interhemispheric commissural fibers connecting the prefrontal, premotor, and supplementary motor areas [56]. In our study, a significant difference in the genu of the corpus callosum indicates the microstructural white matter alterations in frontal pathways, which might be associated with the inability to prevent the propagation of the photoparoxysmal response between the hemispheres.

In our ROI-based TBSS analysis, the JME-NPS group showed increased FA values in the bilateral corticospinal tracts compared to the HCs. However, in the DTI study conducted by von Podewils et al. no significant difference in FA was reported for JME-NPS and healthy individuals using the ROI analysis approach [21]. On the other hand, in JME studies, without regarding subgroups, the corticospinal tract is a region where microstructural changes were observed [15,18]. These changes in FA values obtained in the corticospinal tracts may indicate that patients with JME-NPS are structurally separated from those with JME-PS. JME studies performed with larger samples and subgroups that are homogeneously separated, as in our study, will help us obtain further information in terms of JME phenotypes. Considering our study and the results of previous research, there are probably individual differences that affect white matter integrity in JME in different ways that we cannot explain with our current knowledge.

Another point of debate is that the presence or absence of photosensitivity in JME may be merely quantitative rather than qualitative given the marginal differences in our DTI study. Frequency of photosensitivity is around 40% of patients with JME in most of the studies, whereas Appleton reported a much higher prevalence (90%) which may be related to both the duration of intermittent photic stimulation (IPS) and also the age at which the procedure is undertaken [57–59]. To separate the non-PS group effectively, we conducted at least three EEG recordings with the appropriate standardized IPS protocol using repeated photic stimulation sessions, applying higher light intensity, lower background illumination, longer duration, as suggested in the relevant literature [60].

A recent study introduced a new prognostic stratification for JME. Being woman with both absence seizures and stress-related precipitants was found to be a bad prognostic risk factor for drug resistance in JME, whereas no such prognostic inference could be made for those women with photosensitivity. In addition, the study highlights photosensitivity as a potential predictor among others and emphasizes a circuit-based risk assessment for seizure control [61]. While our study did not examine prognostic factors, we did underscore the potential significance of photosensitivity in the context of brain circuits in JME.

There are some limitations of this study. First, the study sample was relatively small, and larger studies are needed to increase the sensitivity of the statistical analysis. However, the mean FA values of the participants were examined for each participant in the whole-brain TBSS and ROI-based TBSS analyzes, and it was observed that the mean FA values were within normal ranges and no outliers were detected. The fluctuating nature of photosensitivity and its variations based on age and sex could potentially introduce bias into our results. However, our data demonstrated the current understanding of the differentiation between photosensitive and non-photosensitive subjects, with no statistically significant differences observed between the groups in terms of age and sex. Last but not least, even though the majority of patients were under monotherapy and taking valproate, the use of antiseizure medications may be considered one of the major limitations of the current study.

In conclusion, the use of combined analysis methods in this study demonstrated widespread structural white matter alterations in patients with JME, with an emphasis on the corpus callosum and thalamocortical pathways. The widespread structural changes we detected suggest that further investigation is essential, especially focusing on specific pathways from the visual cortex to the motor cortex may provide important contributions to the mechanism of photosensitivity. Considering that there are few DTI studies on JME subgroups, ROI-based TBSS analysis conducted in well-defined JME subgroups and healthy individuals, as in our study, will obviously add more to our understanding of microstructural changes in PS vs. NPS.

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request

CRediT authorship contribution statement

Dilan Acar: Conceptualization, Funding acquisition, Formal analysis, Writing – original draft. **Emel Ur Ozcelik:** Conceptualization, Funding acquisition, Formal analysis, Writing – original draft. **Betül Baykan:** Conceptualization, Writing – original draft, Writing – review & editing. **Nerses Bebek:** Funding acquisition, Formal analysis, Writing – review & editing. **Tamer Demiralp:** Conceptualization, Writing – review & editing. **Ali Bayram:** Conceptualization, Funding acquisition, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None of the authors have any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

[1] Baykan B, Wolf P. Juvenile myoclonic epilepsy as a spectrum disorder: a focused review. Seizure 2017;49:36–41. https://doi.org/10.1016/j.seizure.2017.05.011.
[2] Wolf P, Yacubian EMT, Avanzini G, Sander T, Schmitz B, Wandschneider B, et al. Juvenile myoclonic epilepsy: a system disorder of the brain. Epilepsy Res. 2015; 114:2–12. https://doi.org/10.1016/j.eplepsyres.2015.04.008.
[3] Kim SH, Lim SC, Kim W, Kwon OH, Jeon S, Lee JM. Extrafrontal structural changes in juvenile myoclonic epilepsy: a topographic analysis of combined structural and microstructural brain imaging. Seizure 2015;30:124–31. https://doi.org/10.1016/j.seizure.2015.06.009.
[4] Lin K, Carrete H, Lin J, Peruchi MM, De Araújo Filho GM, Guaranha MSB, et al. Magnetic resonance spectroscopy reveals an epileptic network in juvenile myoclonic epilepsy. Epilepsia 2009;50(5):1191–200. https://doi.org/10.1111/j.1528-1167.2008.01948.x.
[5] Anderson J, Hamandi K. Understanding juvenile myoclonic epilepsy: contributions from neuroimaging. Epilepsy Res 2011;94(3):127–37. https://doi.org/10.1016/j.eplepsyres.2011.03.008.
[6] Tae WS, Ham BJ, Pyun SB, Kang SH, Kim BJ. Current clinical applications of diffusion-tensor imaging in neurological disorders. J Clin Neurol 2018;14(2): 129–40. https://doi.org/10.3988/jcn.2018.14.2.129.
[7] Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data.

NeuroImage 2006;31(4):1487–505. https://doi.org/10.1016/j.neuroimage.2006.02.024.
[8] Deppe M, Kellinghaus C, Duning T, Möddel G, Mohammadi S, Deppe K, et al. Nerve fiber impairment of anterior thalamocortical circuitry in juvenile myoclonic epilepsy. Neurology 2008;71(24):1981–5. https://doi.org/10.1212/01.wnl.0000336969.98241.17.
[9] Keller SS, Ahrens T, Mohammadi S, Möddel G, Kugel H, Bernd Ringelstein E, et al. Microstructural and volumetric abnormalities of the putamen in juvenile myoclonic epilepsy. Epilepsia 2011;52(9):1715–24. https://doi.org/10.1111/j.1528-1167.2011.03117.x.
[10] Liu M, Concha L, Beaulieu C, Gross DW. Distinct white matter abnormalities in different idiopathic generalized epilepsy syndromes. Epilepsia 2011;52(12):2267–75. https://doi.org/10.1111/j.1528-1167.2011.03313.x.
[11] Vulliemoz S, Vollmar C, Koepp MJ, Yogarajah M, O'Muircheartaigh J, Carmichael DW, et al. Connectivity of the supplementary motor area in juvenile myoclonic epilepsy and frontal lobe epilepsy. Epilepsia 2011;52(3):507–14. https://doi.org/10.1111/j.1528-1167.2010.02770.x.
[12] Kim JH, Suh SI, Park SY, Seo WK, Koh I, Koh SB, et al. Microstructural white matter abnormality and frontal cognitive dysfunctions in juvenile myoclonic epilepsy. Epilepsia 2012;53(8):1371–8. https://doi.org/10.1111/j.1528-1167.2012.03544.x.
[13] O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, et al. Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy. Neurology 2011;76(1):34–40. https://doi.org/10.1212/wnl.0b013e318203e93d.
[14] O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, et al. Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. Brain 2012;135(12):3635–44. https://doi.org/10.1093/brain/aws296.
[15] Focke NK, Diederich C, Helms G, Nitsche MA, L.erche H, Paulus W. Idiopathic-generalized epilepsy shows profound white matter diffusion—Tensor imaging alterations. Hum Brain Mapp 2014;35(7):3332–42. https://doi.org/10.1002/hbm.22405.
[16] Ertekin C, Araç N, Bilgin S, Ediboğlu H, Ertaş M. Subclinical anterior horn cell involvement in juvenile myoclonic epilepsy. Epilepsia 1994;35(2):322–7. https://doi.org/10.1111/j.1528-1157.1994.tb02438.x.
[17] Gong J, Chang X, Jiang S, Klugah-Brown B, Tan S, Yao D, et al. Microstructural alterations of white matter in juvenile myoclonic epilepsy. Epilepsy Res 2017;135:1–8. https://doi.org/10.1016/j.eplepsyres.2017.04.002.
[18] Domin M, Bartels S, Geithner J, Wang ZI, Runge U, Grothe M, et al. Juvenile myoclonic epilepsy shows potential structural white matter abnormalities: a TBSS study. Front Neurol 2018;9:509. https://doi.org/10.3389/fneur.2018.00509.
[19] Vollmar C, O'Muircheartaigh J, Symms MR, Barker GJ, Thompson P, Kumari V, et al. Altered microstructural connectivity in juvenile myoclonic epilepsy: the missing link. Neurology 2012;78(20):1555–9. https://doi.org/10.1212/wnl.0b013e3182563b44.
[20] Du H, Xie B, Lu P, Feng H, Wang J, Yuan S. Impaired white-matter integrity in photosensitive epilepsy: a DTI study using tract-based spatial statistics. J Neuroradiol 2014;41(2):131–5. https://doi.org/10.1016/j.neurad.2013.06.002.
[21] von Podewils F, Runge U, Krüger S, Geithner J, Wang ZI, Khaw AV, et al. Diffusion tensor imaging abnormalities in photosensitive juvenile myoclonic epilepsy. Eur J Neurol 2015;22(8):1192–200. https://doi.org/10.1111/ene.12725.
[22] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:512–21. https://doi.org/10.1111/epi.13709.
[23] Kasteleijn-Nolst DGT, Schmitz B, Janz D, Delgado-Escueta AV, Thomas P, Hirsch E, et al. Consensus on diagnosis and management of JME: from founder's observations to current trends. Epilepsy Behav 2013;28(1):S87–90. https://doi.org/10.1016/j.yebeh.2012.11.051. E&BSuppl.
[24] Verrotti A, Tocco AM, Salladini C, Latini G, Chiarelli F. Human photosensitivity: from pathophysiology to treatment. Eur J Neurol 2005;12(11):828–41. https://doi.org/10.1111/j.1468-1331.2005.01085.x.
[25] Özçelik EU, Kurt E, Şirin NG, Eryürek K, Yıldız ÇU, Harı E, et al. Functional connectivity disturbances of ascending reticular activating system and posterior thalamus in juvenile myoclonic epilepsy in relation with photosensitivity: a resting-state fMRI study. Epilepsy Res 2021;171:106569. https://doi.org/10.1016/j.eplepsyres.2021.106569.
[26] Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 2004;23:S208–19. https://doi.org/10.1016/j.neuroimage.2004.07.051.
[27] Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17(3):143–55. https://doi.org/10.1002/hbm.10062.
[28] Andersson JL, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. NeuroImage 2003;20(2):870–88. https://doi.org/10.1016/s1053-8119(03)00336-7.
[29] Andersson JL, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. NeuroImage 2016;125:1063–78. https://doi.org/10.1016/j.neuroimage.2015.10.019.
[30] Andersson JL, Jenkinson M, Smith S. Non-linear registration, aka spatial normalisation fmrib technical report TR07JA2, 2. FMRIB Analysis Group of the University of Oxford; 2007. p. e21. https://www.fmrib.ox.ac.uk/datasets/techrep/tr07ja2/tr07ja2.pdf.
[31] Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. NeuroImage 2014;92:381–97. https://doi.org/10.1016/j.neuroimage.2014.01.060.
[32] Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002;15(1):1–25. https://doi.org/10.1002/hbm.1058.
[33] Gilsoul M, Grisar T, Delgado-Escueta AV, de Nijs L, Lakaye B. Subtle brain developmental abnormalities in the pathogenesis of juvenile myoclonic epilepsy. Front Cell Neurosci 2019;13:433. https://doi.org/10.3389/fncel.2019.00433.
[34] Groppa S, Moeller F, Siebner H, Wolff S, Riedel C, Deuschl G, et al. White matter microstructural changes of thalamocortical networks in photosensitivity and idiopathic generalized epilepsy. Epilepsia 2012;53(4):668–76. https://doi.org/10.1111/j.1528-1167.2012.03414.x.
[35] Kim JH, Kim JB, Suh SI, Kim DW. Subcortical grey matter changes in juvenile myoclonic epilepsy. NeuroImage Clin 2018;17:397–404. https://doi.org/10.1016/2Fj.nicl.2017.11.001.
[36] Moeller F, Maneshi M, Pittau F, Gholipour T, Bellec P, Dubeau F, et al. Functional connectivity in patients with idiopathic generalized epilepsy. Epilepsia 2011;52(3):515–22. https://doi.org/10.1111/j.1528-1167.2010.02938.x.
[37] Holmes MD, Quiring J, Tucker DM. Evidence that juvenile myoclonic epilepsy is a disorder of fronto-temporal corticothalamic networks. NeuroImage 2010;49:80–93. https://doi.org/10.1016/j.neuroimage.2009.08.04.
[38] Pulsipher DT, Seidenberg M, Guidotti L, Tuchscherer VN, Morton J, Sheth RD, et al. Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. Epilepsia 2009;50(5):1210–9. https://doi.org/10.1111/j.1528-1167.2008.01952.x.
[39] Sisodiya SM, Whelan CD, Hatton SN, Huynh K, Altmann A, Ryten M, ENIGMA Consortium Epilepsy Working Group.. The ENIGMA-Epilepsy working group: mapping disease from large data sets. Hum Brain Mapp 2020;43(1):113–28. https://doi.org/10.1002/hbm.25037. Advance online publication.
[40] Hatton SN, Huynh KH, Bonilha L, Abela E, Alhusaini S, Altmann A, et al. White matter abnormalities across different epilepsy syndromes in adults: an ENIGMA-Epilepsy study. Brain A J Neurol 2020;143(8):2454–73. https://doi.org/10.1093/brain/awaa200.
[41] Catani M, Howard RJ, Pajevic S, Jones DK. Virtual *in vivo* interactive dissection of white matter fasciculi in the human brain. NeuroImage 2002;17(1):77–94. https://doi.org/10.1006/nimg.2002.1136.
[42] Wakana S, Jiang H, Nagae-Poetscher LM, Van Zijl PC, Mori S. Fiber tract–based atlas of human white matter anatomy. Radiology 2004;230(1):77–87. https://doi.org/10.1148/radiol.2301021640.
[43] Welniarz Q, Dusart I, Roze E. The corticospinal tract: evolution, development, and human disorders. Dev Neurobiol 2017;77(7):810–29. https://doi.org/10.1002/dneu.22455.
[44] Devinsky O, Gershengorn J, Brown E, Perrine K, Vazquez B, Luciano D. Frontal functions in juvenile myoclonic epilepsy. Neuropsychiatry Neuropsychol Behav Neurol 1997;10(4):243–6.
[45] Sonmez F, Atakli D, Sari H, Atay T, Arpaci B. Cognitive function in juvenile myoclonic epilepsy. Epilepsy Behav 2004;5(3):329–36. https://doi.org/10.1016/j.yebeh.2004.01.007.
[46] Piazzini A, Turner K, Vignoli A, Canger R, Canevini MP. Frontal cognitive dysfunction in juvenile myoclonic epilepsy. Epilepsia 2008;49(4):657–62. https://doi.org/10.1111/j.1528-1167.2007.01482.x.
[47] Knake S, Roth C, Belke M, Sonntag J, Kniess T, Krach S, et al. Microstructural white matter changes and their relation to neuropsychological deficits in patients with juvenile myoclonic epilepsy. Epilepsy Behav 2017;76:56–62. https://doi.org/10.1016/j.yebeh.2017.08.031.
[48] Concha L, Gross DW, Wheatley BM, Beaulieu C. Diffusion tensor imaging of time-dependent axonal and myelin degradation after corpus callosotomy in epilepsy patients. NeuroImage 2006;32(3):1090–9. https://doi.org/10.1016/j.neuroimage.2006.04.187.
[49] Assaf Y. Can we use diffusion MRI as a bio-marker of neurodegenerative processes? Bioessays 2008;30(11–12):1235–45. https://doi.org/10.1002/bies.20851.
[50] Budde MD, Janes L, Gold E, Turtzo LC, Frank JA. The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: validation in the rat using Fourier analysis of stained tissue sections. Brain 2011;134(8):2248–60. https://doi.org/10.1093/brain/awr161.
[51] Winston GP. The physical and biological basis of quantitative parameters derived from diffusion MRI. Quant Imaging Med Surg 2012;2(4):254. https://doi.org/10.3978/j.issn.2223-4292.2012.12.05.
[52] Ertaş M, Uludağ B, Araç N, Ertekin C, Stålberg E. A special kind of anterior horn cell involvement in juvenile myoclonic epilepsy demonstrated by macro electromyography. Muscle Nerve 1997;20(2):148–52.
[53] Goker I, Baslo B, Ertas M, Ulgen Y. Large motor unit territories by scanning electromyography in patients with juvenile myoclonic epilepsy. J Clin Neurophysiol 2010;27(3):212–5. https://doi.org/10.1097/wnp.0b013e3181e0b228.
[54] Altindag E, Baslo B, Baykan B, Bebek N, Ertas M. Reduced axon number in juvenile myoclonic epilepsy demonstrated by motor unit number estimation analysis. Clin EEG Neurosci 2007;38(3):127–31. https://doi.org/10.1177/155005940703800307.
[55] Luo C, Xia Y, Li Q, Xue K, Lai Y, Gong Q, et al. Diffusion and volumetry abnormalities in subcortical nuclei of patients with absence seizures. Epilepsia 2011;52(6):1092–9. https://doi.org/10.1111/j.1528-1167.2011.03045.x.
[56] Park HJ, Kim JJ, Lee SK, Seok JH, Chun J, Kim DI, et al. Corpus callosal connection mapping using cortical gray matter parcellation and DT-MRI. Hum Brain Mapp 2008;29(5):503–16. https://doi.org/10.1002/hbm.20314.

[57] Appleton R, Beirne M, ve Acomb B. Photosensitivity in juvenile myoclonic epilepsy. Seizure 2000;9(2):108–11. https://doi.org/10.1053/seiz.1999.0376.
[58] Kasteleijn-Nolst Trenité DG, de Weerd A, Beniczky S. Chronodependency and provocative factors in juvenile myoclonic epilepsy. Epilepsy Behav 2013;28(1): S25–9. https://doi.org/10.1016/j.yebeh.2012.11.045.
[59] Poleon S, Szaflarski JP. Photosensitivity in generalized epilepsies. Epilepsy Behav 2017;68:225–33. https://doi.org/10.1016/j.yebeh.2016.10.040.
[60] Kasteleijn-Nolst Trenité D, Rubboli G, Hirsch E, Martins da Silva A, Seri S, Wilkins A, et al. Methodology of photic stimulation revisited: updated European algorithm for visual stimulation in the EEG laboratory. Epilepsia 2012;53(1): 16–24. https://doi.org/10.1111/j.1528-1167.2011.03319.x.
[61] Shakeshaft A, Panjwani N, Collingwood A, Crudgington H, Hall A, Andrade DM, et al. Sex-specific disease modifiers in juvenile myoclonic epilepsy. Sci Rep 2022; 12(1):2785. https://doi.org/10.1038/s41598-022-06324-2.