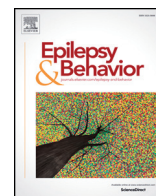




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## Microstructural white matter changes and their relation to neuropsychological deficits in patients with juvenile myoclonic epilepsy

Susanne Knake<sup>a,1</sup>, Christine Roth<sup>a,1</sup>, Marcus Belke<sup>a,2</sup>, Jens Sonntag<sup>a</sup>, Tobias Kniess<sup>b</sup>, Soeren Krach<sup>c,3</sup>, Andreas Jansen<sup>d,e</sup>, Jens Sommer<sup>e</sup>, Frieder M. Paulus<sup>c,3</sup>, Barbara Carl<sup>f</sup>, Felix Rosenow<sup>a,4</sup>, Anke M. Hermsen<sup>a,4</sup>, Katja Menzler<sup>a,\*</sup>

<sup>a</sup> Epilepsy Center Hessen, Department of Neurology, Philipps-University Marburg, Marburg, Germany

<sup>b</sup> Clinic of Neurology, Bad Neustadt, Germany

<sup>c</sup> Department of Child and Adolescent Psychiatry, Philipps-University Marburg, Marburg, Germany

<sup>d</sup> Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Marburg, Germany

<sup>e</sup> Core-Unit Brainimaging, Faculty of Medicine, Philipps-University Marburg, Marburg, Germany

<sup>f</sup> Epilepsy Center Hessen, Department of Neurosurgery, Philipps-University Marburg, Marburg, Germany

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### ABSTRACT

**Objective:** Juvenile myoclonic epilepsy (JME) is the most common idiopathic generalized epilepsy syndrome. Neuropsychological, electrophysiological, and neuroimaging studies have led to the hypothesis that JME is related to dysfunction of frontal brain regions and mainly frontal thalamocortical networks.

**Methods:** We investigated possible microstructural white matter abnormalities of 20 patients with JME as compared with 20 healthy control subjects using diffusion tensor imaging (DTI). We analyzed whole-head DTI scans without an a-priori hypothesis using Tract-Based Spatial Statistics (TBSS). To analyze associated gray matter changes, we applied voxel-based morphometry (VBM) to a 3D T1 magnetization prepared rapid gradient echo (MPRAGE) sequence. Neuropsychological testing and personality trait tests were performed to bridge the gap between structure and function.

**Results:** In patients, DTI revealed microstructural white matter changes in anterior parts of the Corpus callosum, anterior parts of the cingulate gyrus, and widespread frontal white matter bilaterally as well as in anterior parts of the right thalamus, which were not accompanied by gray matter changes in VBM. Microstructural changes in the cingulum correlated with personality traits. Neuropsychological test results showed impaired attention and executive functions and reduced short-term memory in the patient group. Also, there was a tendency toward alexithymia and significantly higher scores on depression.

**Significance:** The present study results showed neuropsychological deficits including frontal lobe cognitive performance and a tendency toward alexithymia as well as accompanying microstructural neuroimaging changes in patients with JME, which all point to alterations in frontal brain regions and frontal thalamocortical networks in these patients.

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### 1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common idiopathic generalized epilepsy syndrome, accounting for 5–10% of all epilepsy cases and 26% of idiopathic generalized epilepsies [1]. The patients typically present with myoclonic jerks, generalized tonic-clonic seizures, and less frequently absence seizures, which mainly occur in the morning hours after waking [1–3]. Patients with JME commonly show certain personality traits such as impulsivity and emotional instability and deficits in frontal lobe cognitive performance. These include deficits in attention, executive functions, and mental flexibility and decreases in processing speed. The results resemble those observed in patients with frontal lobe epilepsy [2,4].

\* Corresponding author at: Center of Brain Imaging, Epilepsy Center Hessen, Philipps-University Marburg, Department of Neurology, Baldingerstrasse, 35043 Marburg, Germany.

E-mail address: [hattermer@med.uni-marburg.de](mailto:hattermer@med.uni-marburg.de) (K. Menzler).

<sup>1</sup> Equal contribution.

<sup>2</sup> Department of Neurology, Centre of Neurology and Neuropsychiatry, Landschaftsverband Rheinland Klinikum Düsseldorf, Heinrich-Heine-University Düsseldorf.

<sup>3</sup> Department of Psychiatry and Psychotherapy, Social Neuroscience Lab, University of Lübeck, Lübeck, Germany.

<sup>4</sup> Epilepsy Center Frankfurt Rhine-Main, Center of Neurology and Neurosurgery, Goethe University, Frankfurt am Main, Germany.

Electroencephalography (EEG) shows generalized 3- to 6-Hz (poly-)spike-wave activity with a frontocentral predominance [1]. More recent studies suggest that these epileptic discharges originate in orbitofrontal, mesiofrontal, and temporal regions [5]. Furthermore, thalamocortical networks were shown to contribute to the generation of these discharges [6].

Routine magnetic resonance imaging (MRI) studies do not show any abnormalities related to JME on visual inspection [1]. However, advanced neuroimaging methods revealed subtle structural abnormalities in widespread frontal areas and frontal thalamocortical networks and suggested a dysfunction of frontal thalamocortical networks [1,6–17].

The present study investigated changes in white matter microstructure and gray matter volume in patients with JME. Additionally, we performed extensive neuropsychological and personality testing in order to investigate the neural correlates of potential neuropsychological and behavioral changes.

## 2. Patients and methods

The study was approved by the local institutional review board. All subjects provided written informed consent to participate in this study. The study is in accordance with the Declaration of Helsinki.

### 2.1. Subjects

Twenty patients with JME based on clinical and EEG criteria participated in the study. Patients were included if they had myoclonic jerks predominantly in the morning hours with or without additional generalized tonic-clonic seizures or absence seizures and generalized 3- to 6-Hz (poly-)spike-wave activity in the EEG. Exclusion criteria were any neurological or psychiatric disorders beside JME, and any known structural brain abnormalities and contraindications for MRI. Twenty healthy controls without a history of neurological disorders, matched for sex, age, and years of education served as control group.

### 2.2. Neuropsychological tests

Standardized neuropsychological tests were used. We tested verbal learning and memory using the standardized German version of the American verbal learning and memory task (VLMT) and visual/figural learning and memory using a German test called Diagnostikum für Cerebralschädigung (diagnostic test for cerebral damage, DCS). Patients and control subjects performed 5 test runs in the VLMT and 6 test runs in the DCS trying to remember verbal or figural items. Also, in the VLMT, they performed an additional test run after a fixed time interval for delayed recall.

We evaluated executive functions and attention with the D2 attention test and the Trail Making Test (TMT) A (digits only) and B (alteration of letters and digits). Short-term and working memory was evaluated using digit and block span forward and backward from the Wechsler Memory Scale (WMS), which is also influenced by attention. We also included the Word Fluency Test (WFT) to evaluate semantic and lexical verbal fluency and finding similarities from the Hamburg-Wechsler intelligence test for adults (HAWIE) to evaluate the capability of verbal abstraction. Alexithymia was evaluated using the Toronto Alexithymia Scale (TAS). The Beck's Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), and NEO five factor inventory (NEO FFI) were used to explore depression, anxiety, and personality traits.

Statistical analysis was computed with IBM SPSS Statistics 22® (SPSS, IBM Company, Chicago, Illinois).

For statistical analysis of the cognitive tests, a general linear model (GLM) was computed at the group-level (mANOVA) to compare the neuropsychological performance in the JME and the healthy control group. The tests were the dependent variables, group was the two-staged between-subject factor ("JME" vs. "controls"). If group variances were

nonhomogenous (according to Levene's test of variance homogeneity), degrees of freedom were adjusted.

Differences in the questionnaires for alexithymia, depression, anxiety, and personality traits were evaluated in an exploratory analysis using *t*-tests for unpaired groups.

We also correlated neuropsychological test results with disease duration, duration of seizure freedom, and neuroimaging results using Pearson's correlation coefficient.

### 2.3. Magnetic resonance imaging

#### 2.3.1. MRI acquisition

Diffusion tensor imaging (DTI) was used to quantify microstructural white matter changes. DTI is based on the measurement of molecular diffusion and its directionality which is influenced by the surrounding brain tissue, cell membranes, or myelin sheaths [18]. The DTI scans were collected on a 3 T MRI (Tim Trio Siemens Medical Solutions, Erlangen, Germany), using a circular polarized head array coil. We performed a single shot echo planar sequence with a twice-refocused spin echo pulse, optimized to minimize eddy current-induced image distortions, with the following parameters: TR/TE = 10,700/104 ms, flip angle = 90°,  $b = 1000 \text{ s/mm}^2$ , diffusion directions = 30,  $256 \times 256 \text{ mm FOV}$ , and voxel size  $2.0 \times 2.0 \times 2.4 \text{ mm}$ . One T2 b0 image and 30 diffusion weighted b1000 images were collected during one scan. We acquired a 3D T1 magnetization prepared rapid gradient echo sequence (MPRAGE sequence, image parameters: TR/TE = 1900/2.52 ms,  $256 \times 256 \text{ mm FOV}$ , flip angle = 9°, voxel size  $1.0 \times 1.0 \times 1.0 \text{ mm}$ ) during the same session. Subtle gray matter changes were analyzed in this sequence using voxel-based morphometry (VBM). These imaging and analysis methods have been applied successfully to several neurodegenerative disorders, providing insight in the underlying pathophysiology of these conditions [19–21].

We investigated all images to be free of motion or ghosting, high frequency, and/or wrap-around artifacts at the time of image acquisition.

#### 2.3.2. MRI analysis

For DTI and VBM calculations, we used programs published by the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) [22–25].

##### 2.3.2.1. DTI

**2.3.2.1.1. DTI preprocessing and analysis.** Image preprocessing was performed as described previously [26]. Diffusion volumes were motion-corrected and averaged using the FMRIB's Linear Image Registration Tool (FLIRT) with mutual information cost function to register each direction to the minimally eddy current distorted T2-weighted b0 DTI volume that had no diffusion weighting. We computed eigenvalues ( $\lambda_1, \lambda_2, \lambda_3$ ) and eigenvectors of the diffusion tensor matrix for each voxel from the DTI volumes for each patient and control subject on a voxel-by-voxel basis using conventional reconstruction methods. These tools are included in the FreeSurfer package (FreeSurfer version 4.2.0; <http://surfer.nmr.mgh.harvard.edu/>).

**2.3.2.1.2. Fractional anisotropy and diffusivity map calculation.** Brain tissue integrity was assessed using DTI measures of fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) as described previously [26]. The primary measure acquired from the DTI data was the FA, a scalar metric unit describing the directionality of water diffusion. Fractional anisotropy is dependent on the orientational coherence of the diffusion compartments within a voxel and reflects the degree of tissue organization or alignment [18]. Fractional anisotropy was calculated using the standard formula defined previously [27]. To further characterize tissue organization, measures of AD ( $\lambda_1$ ) and RD ( $(\lambda_2 + \lambda_3) / 2$ ) were examined. Axial diffusivity measures the diffusivity along the primary diffusion direction, RD represents the diffusivities along directions that are orthogonal to the primary diffusion direction. While all these metric parameters might be influenced by several factors including myelination,

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