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Morphological changes of cerebellar substructures in temporal lobe epilepsy: A complex phenomenon, not mere atrophy

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ABSTRACT

Purpose: To evaluate cerebellar volume changes in temporal lobe epilepsy (TLE) patients in greater detail. We aimed to determine which discrete substructures significantly differ in patients with TLE compared to controls and the nature of this difference. Correlations with age at epilepsy onset, epilepsy duration, seizure frequency, and total number of antiepileptic drugs (AED) in the patient's history were studied. We analyzed the potential association between cerebellar atrophy and epilepsy surgery outcome.
Methods: Study participants were 36 TLE patients; 22 hippocampal sclerosis (HS) only and 38 healthy controls. All patients later underwent temporal lobe resection. All subjects were examined using 1.5T MRI. Cerebellar volume was adjusted for total intracranial volume, age, and gender, and measured using voxel-based morphometry. Cerebellar substructures were defined using the AAL atlas. Data processing was performed automatically. Separate analyses for HS only subset were performed.
Results: Total cerebellar gray matter volume (GMV) appeared non-significantly smaller in epilepsy patients. Within the substructures, the GMV of the selected vermian segments were significantly larger in patients. The GMV of the whole cerebellum and of all individual cerebellar substructures non-significantly decreased with increasing complex partial seizure frequency and total number of AEDs in the patient's history. Total cerebellar GMV was significantly smaller in patients with persistent seizures after epilepsy surgery than in seizure-free patients.
Conclusion: Cerebellar atrophy is a complex phenomenon, the character of changes differs significantly within the cerebellar substructures.
Total cerebellar GMV reduction is associated with worse outcome of temporal lobe resection.

1. Introduction

The role of the cerebellum goes beyond its effect on motor functions. The cerebellum is an important part of the networks involved in cognitive processing, including memory, language, and emotions [1]. The importance of the cerebellum in epileptology is becoming increasingly clear [2]. Cerebellar atrophy is frequently documented in patients with epilepsy [3–7]. The role of the cerebellum in the genesis of seizures is also a subject of discussion. Cerebellar dysfunction has been associated with disinhibition of seizure activity in the cerebral cortex [8–10].

Bilateral reduction of cerebellar GMV regardless of seizure focus in TLE was observed by several authors [11–15]. Lateralized cerebellar changes related to the side of the epileptic focus were reported by Keller et al. [16] Segmented gray and white matter volumes within the cerebellar hemispheres or specific cerebellar subregions were studied with inconsistent findings (McDonald: [11] gray and white matter volumes of the left and right cerebellar hemisphere; Bonilha: [13] GMV of the left and right cerebellar hemisphere; Hagemann: [17] non-differentiated cerebellar volume (gray and white matter together) divided into the midsagittal vermian area, the anterior lobule area, the posterior superior lobule area, and the posterior inferior lobule area; and Oyegbile: [18] gray and white matter volumes of the right and left anterior

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lobes, the superior posterior lobes, the inferior posterior lobes, and the corpus medullare.)

There is conformity in GMV reduction of the whole cerebellum and the posterior cerebellar lobe. There were varying findings for the anterior cerebellar lobe: Oyegbile found an even larger volume of GMV; [18] other authors did not [17]. White matter volume changes appear to be insignificant, whether they negatively correlate with epilepsy duration [19] or not [18].

In the present study, we evaluate cerebellar volume changes in TLE patients and healthy controls in greater detail using the Automated Anatomical Labeling (AAL) atlas (Fig. 1). We aim to determine the character of changes within cerebellar substructures. With regard to previous findings, we hypothesized that whereas total cerebellar volume is reduced in TLE patients, the character of changes might differ within the cerebellar substructures. We expected the difference to depend on the patient age at epilepsy onset, epilepsy duration, number of anti-epileptic drugs (AEDs) in the patient's history, and complex partial seizure (CPS) frequency. Detailed knowledge of the nature of morphological changes could help determine their underlying mechanism.

We focus on the association between cerebellar atrophy and epilepsy surgery outcome as it could contribute to the optimal selection of patients for resective and palliative epilepsy surgery.

2. Methods

2.1. Subjects

Our sample comprised 36 consecutive patients, all with medically intractable focal epilepsies, (25 females, 11 males) ranging in age from 17.7 to 56.9 years (mean age of 36.9 years; median 39 years). All the patients fulfilled the diagnostic criteria for TLE according the ILAE criteria [20]. All patients had a history of at least three AEDs (mean 5.8, max. 13); detailed figures are in Table 1. All the patients had been routinely investigated prior to epilepsy surgery, including long-term semi-invasive video-EEG monitoring (using sphenoidal electrodes), high resolution magnetic resonance imaging (MRI), and neuropsychological testing. The diagnosis of TLE was based on a concordance of history data, ictal and interictal EEG findings, stereoelectroencephalography in selected cases, ictal semiology, neuropsychology, and neuroimaging findings. All patients had been seizure free for $\geq$24 h before the preoperative MRI investigation. All the patients underwent anteromedial temporal resection (AMTR). Hippocampal sclerosis was found in 24 cases (in two patients combined with focal cortical dysplasia), focal cortical dysplasia alone in five patients and seven patients were histopathologically negative. The follow-up interval after epilepsy surgery was at least 12 months (mean 61.1 months, max. 117 months).

After surgical resection, 27 patients (75%) were rated as Engel I (seizure free), nine patients (25%) were Engel II–IV (non-seizure free). In the hippocampal sclerosis only (HS) patients, 21 were rated as Engel I, one patient was Engel II–IV. There was no change in Engel classification into group Engel I or group Engel II–IV during the overall follow-up period compared to outcome in the first year after surgery. Significant differences between the Engel groups were detected in epilepsy duration (Mann-Whitney *U* test, $p = 0.032$), which was longer in Engel I group; and in patient age at epilepsy onset (Mann-Whitney *U* test, $p = 0.043$). There was no difference in patient age (Mann-Whitney *U* test, $p = 0.387$), gender (Fisher's exact test, $p = 1$), localization of seizure onset zone (Fisher's exact test, $p = 0.34$), number of AED in medical history (Mann-Whitney *U* test, $p = 0.615$), duration of postoperative follow-up (Mann-Whitney *U* test, $p = 0.914$), or in CPS frequency (Mann-Whitney *U* test, $p = 0.14$). Table 1 provides detailed demographic and medical history data.

The control group consisted of 38 healthy subjects (24 females, 14 males) ranging in age from 18.3 to 56.4 years (mean age of 36.6 years; median 38.2 years). No significant differences in age (Mann-Whitney *U* test, $p = 0.953$) or sex (Fisher's exact test, $p = 0.628$) between the subgroups of patients and controls was detected. The majority of the healthy subjects in the control group were volunteers from the professional sector; no history of neurological or psychiatric disease was presented in any controls.

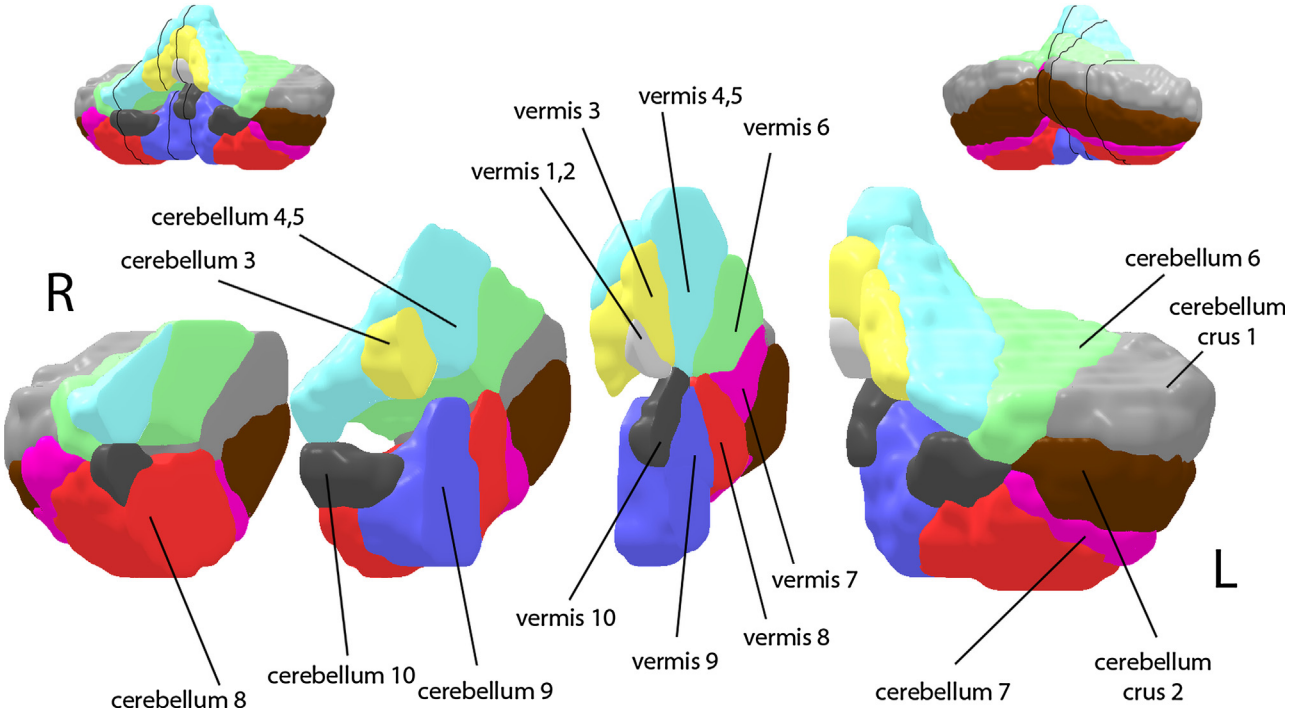

Fig. 1. Cerebellar division according to Automated Anatomical Labeling atlas.