

Cerebellar volume is linked to cognitive function in temporal lobe epilepsy: A quantitative MRI study



Sabine Hellwig ^{a,*}, Vladimir Gutmann ^a, Michael R. Trimble ^b, Ludger Tebartz van Elst ^a

^a Department of Psychiatry and Psychotherapy, University Hospital Freiburg, Freiburg, Germany

^b Institute of Neurology, University College London, London, UK

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ABSTRACT

Introduction: Chronic intractable temporal lobe epilepsy (TLE) is associated with certain comorbidities including cognitive impairment. A less common condition among patients with TLE is intermittent explosive disorder (IED), a specific form of aggressive behavior that has been linked to low intelligence and structural pathology in the amygdala. We aimed to identify other neuroanatomical substrates of both cognitive dysfunction and IED in patients with TLE, with special focus on the cerebellum, a brain region known to participate in functional networks involved in neuropsychological and affective processes.

Methods: Magnetic resonance imaging-based volumetric data from 60 patients with temporal lobe epilepsy (36 with and 24 without IED) were evaluated. Cerebellar, hippocampal, and total brain volumes were processed separately. In a total of 50 patients, the relationship between volumetric measurements and clinical and neuropsychological data (full-scale, verbal, and performance intelligence quotients) was analyzed.

Results: Intermittent explosive disorder in patients with TLE was not significantly linked to any of the regional volumes analyzed. However, cognitive performance showed a significant association both with total brain volume and cerebellar volume measurements, whereby the left cerebellar volume showed the strongest association. A deviation from normal cerebellar volumes was related to lower intelligence. Of note, left cerebellar volume was influenced by age and duration of epilepsy. Hippocampal volumes had a minor influence on cognitive parameters.

Conclusion: Our findings suggest that cerebellar volume is not linked to IED in patients with TLE but is significantly associated with cognitive dysfunction. Our findings support recent hypotheses proposing that the cerebellum has a relevant functional topography.

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1. Introduction

Cognitive impairment is a complicating feature in patients with chronic intractable temporal lobe epilepsy (TLE). A multifactorial etiology of cognitive dysfunction has been postulated, whereby anti-epileptic drugs, recurrent seizures, and structural abnormalities of the temporal lobe are suggested to contribute to the underlying neuropathological substrate [1,2]. Recent studies provide evidence for more distributed cognitive and anatomical changes that occur outside the temporal lobe, suggesting that cognitive impairment extends beyond affecting memory function [3]. However, clarifying the origin of these observations remains a challenge.

Interictal episodes characterized by affective aggression are collectively referred to as intermittent explosive disorder (IED), another rare but well-recognized problem in patients with TLE. The amygdala has been identified as a key player in the affective evaluation of multimodal sensory input and the neurobiological mediation of aggressive behavior. Furthermore, amygdala volume was previously found to be related to aggressive behavior and intelligence quotient (IQ) scores alike in patients with TLE [4]. Of note, links between IED, epilepsy, and the cerebellum have been derived from case studies using cerebellar stimulation to treat epilepsy [5,6].

Because of its close connection to the prefrontal cortex and basal ganglia, the cerebellum is thought to play a role in specific aspects of cognition, especially verbal working memory, implicit learning, and temporal information processing as well as shifts in attention and emotion regulation [7–12]. Furthermore, previous research indicates that patients with TLE exhibit cerebellar atrophy compared to healthy controls [13].

Against this background, the aims of the present study were twofold:

1. to investigate the relationship between IED and volumetric measurements of cerebrum (total brain), cerebellum, and hippocampus;

* Corresponding author at: University Hospital Freiburg, Department of Psychiatry and Psychotherapy, Hauptstr. 5, 79104 Freiburg, Germany. Fax: +49 761 270 69170.

E-mail address: sabine.hellwig@uniklinik-freiburg.de (S. Hellwig).

2. to elucidate a potential association between cognitive impairment and the aforementioned regional volumetric measurements.

2. Methods

All procedures were approved by the ethics committee of the National Hospital for Neurology and Neurosurgery. The presented data are part of a larger project on anatomical correlates of psychiatric comorbidity in patients with TLE. A previous paper from this particular project has already been published [4].

A total of 60 patients, with or without IED, were analyzed in this retrospective study. The following clinical data were obtained from the medical records: age; gender; handedness; duration of epilepsy; frequency of epileptic seizures; history of IED; history of febrile convulsions, encephalitis, or status epilepticus; family history of epilepsy; social history; and outcome of the neuropsychological assessment.

2.1. Patient's assessment

Patients with TLE were recruited from a tertiary referral center (National Hospital for Neurology and Neurosurgery and the associated Chalfont Centre for Epilepsy). The clinical syndrome of interest was defined as complex partial seizures with symptomatology and EEG and magnetic resonance imaging (MRI) findings each compatible with TLE. Neurologists who were not involved in this study made the neurological diagnoses. On the basis of the discharge summaries, patients with TLE with or without a history of IED who were diagnosed according to DSM-IV criteria were identified, contacted, and seen by a psychiatrist (L.T.v.E.) and recruited for the study. Informed consent was obtained from the patients prior to further investigations. Patients with extratemporal or generalized epilepsy were excluded, as were those with a history of mental handicap or psychoses. Neurological examination data and psychiatric history were obtained, and routine EEG and neuropsychological investigations were performed. The frequency and severity of the three main seizure types were documented and rated according to the National Hospital Seizure Severity Scale [14]. Full-scale, verbal, and performance IQs were measured using the revised version of the Wechsler Adult Intelligence Scale [15]. Patients with a full-scale IQ below 65 were excluded from the study to avoid selection bias. In order to assess IED, carers rated the patients according to the Social Dysfunction and Aggression Scale [16,17].

Ten healthy age- and sex-matched volunteers were scanned and measured twice in order to assess the reliability of the volumetric measurements.

2.2. Neuroimaging

2.2.1. Data acquisition

The MR images were obtained at the Chalfont Centre for Epilepsy on a 1.5-T GE Sigma scanner (GE Medical Systems, Milwaukee, WI, USA) using a T1-weighted inversion-recovery-prepared volume acquisition [IRSPGR: TI/TR/TE/flip = 450/15/4.2/20; 124 × 1.5-mm thick contiguous coronal slices; matrix: 256 × 192, 24-cm × 18-cm FOV (field of view) (TI = inversion time; TR = repetition time; TE = echo time)]. MRI data were transferred to a Sun workstation via a network (Sun Microsystems, Mountainview, CA, USA).

2.2.2. Volumetric measurements

Volumetric measurements were performed using the interactive software program Mreg (available on the internet: <http://www.ion.ucl.ac.uk/MRreg.html>) [18,19]. The images were zoomed to a magnification of 4× for outlining the hippocampus, and intensity windowing was monitored consistently. The hippocampi were outlined manually with a mouse-driven cursor according to the established protocol described by Watson and colleagues [20]. The volume of the

delineated structure in each slice ('in-slice volume') was calculated by multiplying the number of voxels contained within each trace (corrected for magnification) by the voxel volume × 10. The total volume of each hippocampus was the sum of all in-slice volumes.

Cerebellar volume was determined by measuring every second slice at a magnification of 2×. Region of interests were anatomically defined by manually tracing the right and left cerebellar hemispheres and the vermis [21]. The brainstem and cerebellar peduncles were excluded from the measurement.

The hippocampal and cerebellar volumes were corrected by dividing each one with the intracranial volume [22]. The total brain volume (TBV) (including the cerebrum, cerebellum, and brainstem superior to the pons) was measured by manually delineating the internal face of the cranium on every 10th slice (original magnification: 2×).

2.3. Data analysis

2.3.1. Reliability

Images of all patients and healthy control participants were mixed, blinding the rater (V.G.) to the identity of the participants. Intrarater reliability figures were calculated from repeated measurements of the subset of 10 healthy controls. The intrarater reliability was assessed by calculation of an intraclass correlation coefficient [23]. We found strong intraclass correlation coefficients between 0.91 and 0.96.

2.3.2. Group stratification

A total of 60 TLE cases (with or without IED) were stratified into three groups based on the volumetric measurements of each analyzed brain structure (cerebellum, hippocampus, and cerebrum): (i) average volume, (ii) below-average volume, and (iii) above-average volume. Average volume was defined as mean volume ± 1 standard deviation (SD) of the control group [24,25].

2.3.3. Group comparisons

Between-group differences were assessed using a chi-square test (nominal data) (two-sided). In the case of multiple group comparisons, the one-factorial analysis of variance (ANOVA) with post hoc Tukey–Kramer HSD test was used. Significance was assigned at $p \leq 0.05$ for all tests. We intentionally used this rather liberal statistical threshold since a comprehensive detection including minor associations was the primary aim of our study. Thus, correction for multiple comparisons was not performed. However, respective findings will have to be tested in future research in order to clarify if or not they might be chance findings. We used the SPSS version 13 software (SPSS Inc.) for all statistical calculations.

3. Results

3.1. Stratification of groups

Based on the volumetric measurements, Supplemental Table S1 summarizes the mean values of the reference group.

3.2. Association between demographic/clinical data and volumetric findings

Analysis of variance revealed a significant relationship between the volume of the left cerebellar hemisphere and the factors age and epilepsy duration. The frequency and severity of seizures had no impact on volumetric measurements (for statistical values, see Table 2). Demographic and clinical characteristics of the study sample are illustrated in Table 1. We did not account for the factor "medication" since 54 out of 60 recruited patients (90%) were undergoing anticonvulsant polytherapy at the time of imaging. Patients were treated as follows: valproic acid ($n = 19$), mean daily dose: 1545 ± 855 mg; phenobarbital (2),

Table 1

Demographic and clinical data of the study sample. Data refer to a pooled group of patients with temporal lobe epilepsy with or without intermittent explosive disorder.

Variable	
Age [range] (years)	32.9 [18–56]
Sex: F/M total group (IED subgroup)	24 (14)/36 (18)
Employment: number unemployed (out of 60)	41
Living: number living independently (out of 60)	30
Income: number on social support (out of 60)	37
Social: number in stable relationship (out of 60)	18
Therapy: monotherapy/polytherapy	6/54
Mean duration of temporal lobe epilepsy [range] (years)	23.7 [4–46]
Mean frequency of seizures per month [range]	16.6 [0.5–190]
Intermittent explosive disorder	36
Birth complications	17
Febrile convulsions	18
Status epilepticus	3
Handedness: right–left–ambidextrous	49–8–3
History of encephalitis	6
Family history of epilepsy	11

120 mg each; gabapentin (14), 1829 ± 1007 mg; topiramate (6), 542 ± 358 mg; primidone (2), 625 ± 177 mg; carbamazepine (38), 1311 ± 464 mg; lamotrigine (15), 260 ± 142 mg; vigabatrin (10), 2650 ± 818 mg; phenytoin (14), 311 ± 74 mg; diazepam equivalent (18), 11 ± 7 mg; haloperidol (1), 10 mg; and fluoxetine (2), 30 or 40 mg.

The factor “gender” significantly influenced the total brain volume, while other volumetric measurements showed no significant association. There was no significant association between the factors handedness and IED and the analyzed volumetric parameters (data not shown). For this reason, all remaining statistical analyses were performed on a pooled group comprising patients with TLE either with or without comorbid IED.

3.3. Association between cognitive function and volumetric measurements

Fifty out of the 60 patients with TLE were included in the association analysis between cognition and volume measurements. Ten patients had to be excluded because of incomplete neuropsychological evaluation. The raw data generated by the cognitive testing are summarized in Supplemental Table S2.

3.3.1. Total brain volume

Total brain volume showed a significant positive association with the following neurocognitive parameters: full-scale IQ ($F(df2) = 5.460, p = 0.007$), verbal IQ ($F(df2) = 3.190, p = 0.049$), vocabulary subtest of verbal IQ ($F(df2) = 4.176, p = 0.022$), performance IQ ($F(df2) = 6.508, p = 0.003$), picture completion subtest of performance IQ ($F(df2) = 3.344, p = 0.044$), and picture arrangement subtest of performance IQ ($F(df2) = 5.077, p = 0.010$).

3.3.2. Hippocampal volume

The right hippocampal volume had a significant influence on the results of the performance IQ subtest picture arrangement ($F(df2) =$

$3.976, p = 0.026$), while in the remaining cognitive tests, no significant association was observed (full-scale IQ: $F(df2) = 1.810, p = 0.175$; verbal IQ: $F(df2) = 1.655, p = 0.202$; performance IQ: $F(df2) = 1.842, p = 0.170$). An association analysis between left hippocampal volume and IQ parameters did not detect any significant effects (full-scale IQ: $F(df2) = 0.823, p = 0.445$; verbal IQ: $F(df2) = 1.656, p = 0.202$; performance IQ: $F(df2) = 0.275, p = 0.761$).

3.3.3. Cerebellar volume

The subtest picture arrangement was significantly influenced by the total cerebellar volume. Full-scale, verbal, and performance IQs remained unaffected (see statistical figures in Table 3). Raw data from the IQ tests (see Supplemental Table S2) illustrate that a deviation from the average cerebellar volume (either below or above) was associated with lower IQ scores. The effect is most pronounced for performance IQ.

3.3.3.1. Left cerebellar volume. Analysis of variance indicated significant associations between left cerebellar volume and the following cognitive measurements (see statistical values in Table 3): full-scale IQ, verbal IQ subtests similarities and digit span, and performance IQ subtests picture arrangement and block design. Analysis of the association between verbal IQ and left cerebellar volume revealed no significance. Fig. 1 shows the scatterplots of the association between left cerebellar volume and full-scale IQ; the aforementioned association between lower IQ scores and both above-average and below-average volume measurements is illustrated.

3.3.3.2. Right cerebellar volume. The volumes of the right cerebellar hemisphere had a significant effect on the subtest picture arrangement. Other parameters of neurocognitive performance did not significantly interact with this volumetric parameter (see Table 3 for statistical values).

4. Discussion

The present study was designed to elucidate a potential association between regional volumetric measurements of total brain, cerebellum, and hippocampus and neuropsychiatric comorbidities (cognitive impairment, IED) in patients with TLE.

In light of the primary study aims, the following results were obtained:

1. No significant association between IED and the aforementioned volumetric parameters was found.
2. Cerebellar volume measurements were significantly associated with cognitive performance in patients with TLE. This association was most prominent in the left cerebellar hemisphere. A deviation in either direction from the average cerebellar volume was associated with lower IQ scores. Left cerebellar volume was influenced by age and duration of epilepsy.
3. Hippocampal volumes had a minor influence on cognitive parameters measured by the Wechsler assessment. Right hippocampal

Table 2

Results of the interaction analysis between demographic parameters, clinical parameters, and volumetric measurements.

Variables	Total brain	Total cerebellum	Left cerebellum	Right cerebellum	Left hippocampus	Right hippocampus
Seizures ^a	F = 0.535 p = 0.589	F = 0.755 p = 0.475	F = 1.298 p = 0.281	F = 0.640 p = 0.531	F = 0.556 p = 0.577	F = 3.094 p = 0.053
Epilepsy duration	F = 1.206 p = 0.307	F = 2.462 p = 0.094	F = 5.246 p = 0.008	F = 1.813 p = 0.172	F = 1.076 p = 0.348	F = 0.643 p = 0.530
Age	F = 0.199 p = 0.820	F = 1.132 p = 0.329	F = 3.235 p = 0.047	F = 0.726 p = 0.488	F = 0.502 p = 0.608	F = 0.532 p = 0.590

Data were analyzed by one-factorial analysis of variance. Significance was assigned for all tests at $p < 0.05$ (bold figures). The degree of freedom (df) for F-statistics is 2.

^a Severity and frequency of seizures are documented and rated according to the National Hospital seizure Severity Scale.

Table 3
Results of the interaction analysis between cerebellar volume measurements and IQ scores.

IQ score	Total cerebellum	Left cerebellum	Right cerebellum
Full-scale	F = 1.698 p = 0.194	F = 3.387 p = 0.042	F = 1.166 p = 0.321
Verbal	F = 0.678 p = 0.513	F = 1.994 p = 0.148	F = 0.419 p = 0.660
Similarities subtest		F = 3.641 p = 0.034	
Digit span subtest		F = 3.549 p = 0.037	
Performance	F = 2.922 p = 0.064	F = 4.385 p = 0.018	F = 2.265 p = 0.115
Picture arrangement subtest		F = 6.221 p = 0.004	F = 3.575 p = 0.037
Block design subtest		F = 3.807 p = 0.030	

Data were analyzed by one-factorial analysis of variance. The degree of freedom (df) for F-statistics is 2. Significance was assigned for all tests at $p < 0.05$ (bold figures). Volume measurements are corrected for total brain volume.

volume was significantly linked to one IQ performance subtest only.

- In line with earlier studies, TBV and IQ showed a significant positive association.

4.1. Comparison of results

4.1.1. IED and cerebellar volume

Data describing an association between cerebellar pathology and aggressive behavior in patients with TLE are sparsely available. However, the involvement of the cerebellum in emotional behavior is known (reviewed in [26]). The term cerebellar cognitive affective syndrome describes the dysregulation of affect that occurs when lesions involve the ‘limbic cerebellum’ (vermis and fastigial nucleus) [11]. Remarkably, this neurobehavioral syndrome is characterized by aggression and irritability [27]. Case studies using cerebellar stimulation to treat intractable psychiatric disorders and epilepsy confirmed a role for the cerebellum in behavioral modulation [5,6]. However, we could not detect an association between IED and cerebellar volume measurements. One issue to consider is the chosen technique of cerebellar volumetry. We did not discriminate between

the older vermis and the later-developing cerebellar hemispheres. This could be relevant, since animal studies point towards more distinct anatomical connections between the vermis and its target regions compared to those of the cerebellar hemispheres [28].

Furthermore, there have been studies in other brain regions in patients with TLE with intermittent explosive disorder. In our previous study using the same patients, we found an association between aggressive episodes and amygdala volume loss [4]. An ascending connection between the fastigial nucleus and amygdala has been shown both anatomically and by electrophysiological studies [29–31]. In the cat, cerebellar stimulation produced facilitation as well as inhibition patterns in the amygdala [29]. Thus, cerebellar pathology could potentially affect the physiological function of the amygdala. Ultimately, however, no significant association between IED and each volumetric parameter analyzed was found. Therefore, our results are representative for all patients with TLE regardless of comorbid IED.

4.1.2. Cognition and volume parameters

Numerous studies have reported cerebellar atrophy in patients with TLE. An earlier nonquantitative study reported a 45% incidence of cerebellar atrophy among 78 patients with TLE [32]. A later study using quantitative MRI revealed significant cerebellar atrophy in 25.9% (16.9% TBV corrected cerebellar volume) of 185 patients suffering from pharmacoresistant TLE [33]. Cerebellar atrophy was linked to young age at disease onset [33] as well as a longer duration of epilepsy [13,33] and frequency of tonic-clonic seizures [34]. Nevertheless, there are different hypotheses about the underlying pathophysiological mechanism of cerebellar atrophy. On the one hand, a side effect of chronic anticonvulsant treatment has been postulated [35]. Conversely, a late sequela of recurrent seizures inducing hypoxia and brain edema has also been discussed [36]. Indeed, bilateral projections facilitate a close connection between the hippocampus and cerebellum. The major anatomical substrate of TLE is hippocampal degeneration, which progresses during the course of the disease. Subsequently, it leads to a loss of intrinsic hippocampal connections and promotes regional atrophy of projections to areas such as the cerebellar hemispheres [37].

Ultimately, the idea that underlying etiologies of TLE (i.e., initial precipitating injuries) and generalized tonic-clonic seizures during the course of the disease might affect both the cerebellum as well as other brain regions contributing to cognition needs to be considered. In this light, the association between cerebellar atrophy and cognitive dysfunction is not in itself sufficient to establish cerebellar injury as a cause of cognitive impairment.

Our main finding is the association between cerebellar volume and multiple domains of cognitive performance, which corroborates published data: In a study of 231 children with partial and generalized epilepsy, total cerebellar volume was positively correlated with full-scale IQ scores [38]. A more recent study focused on the characterization of different phenotypes of cognitive impairment in TLE. Remarkably, reductions in both left and right cerebellar hemisphere volumes were related to similar cognitive profiles, revealing deficits in memory, executive function, and speed [39]. Another study reported that reduced total cerebellar volume in patients with chronic TLE was significantly associated with procedural memory performance [40]. Riley et al. reported that changes in the cerebellar white matter ipsilateral to the side of seizure onset in patients with TLE were linked to executive function [41]. Building on available data in the literature, our study addresses two aspects for the first time: First, we performed an association analysis between separate measurements of left and right cerebellum and a comprehensive IQ testing (full-scale, verbal, and performance IQs). Second, we provided evidence that not only reduced but also increased cerebellar volume measurements are associated with lower IQ scores.

Hippocampal atrophy and hippocampal sclerosis are pathophysiological correlates of TLE [42,43] and exert an impact on cognitive performance in patients with TLE [1,44–47]. Of note, there are conflicting

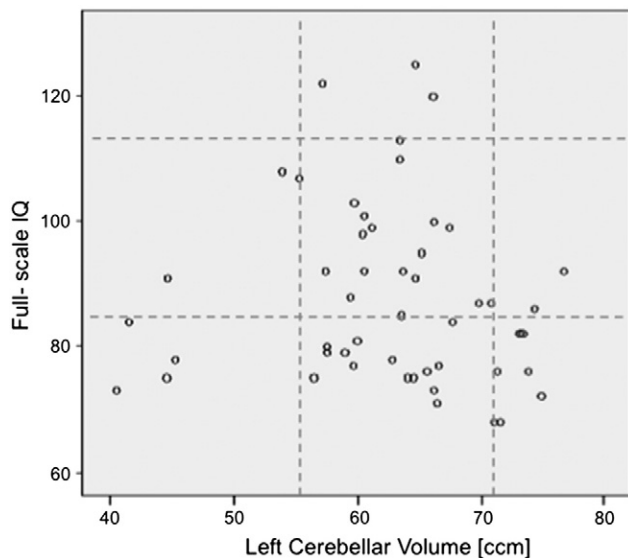


Fig. 1. Scatterplot of the association between full-scale IQ and left cerebellar volume corrected for total brain volume.

data on the actual extent of cognitive dysfunction associated with hippocampal pathology. Additionally, the extent of cognitive abnormality is poorly predicted by disease-related factors (e.g., seizure frequency) [48]. To explain these inconsistencies, it has been assumed that extensive extrahippocampal damage (e.g., frontostriatal system, cerebellum, reduction in cerebral white matter, and thinning of the cortical mantle) may underlie the varied profile of cognitive impairment frequently observed among patients with TLE [49]. Indeed, volumetric abnormalities in some of the aforementioned structures have been linked to cognitive status in TLE [50–52] and have been shown to predict cognitive decline in patients with TLE [52]. The results of the present study are in line with these data, since the hippocampal volume measurements only had a minor influence on cognitive parameters compared to the extrahippocampal regions of interest. Moreover, hippocampal volumes did not appear to affect the neuropsychological parameters in our study because the neuropsychological tests were not designed to pick up hippocampal dysfunction.

Various domains of intelligence require intra- and interhemispheric connectivity. A macroscopic anatomical measurement of connectivity is brain size (reviewed in [53]). Accordingly, a comprehensive meta-analysis (37 studies, 1530 participants) concluded that TBV significantly correlates with IQ, giving a mean correlation value of 0.33. This correlation was stronger for females than for males [54]. Consistent with the latter, we found a significant relationship between TBV and the categorical variable sex. Moreover, our findings are in line with earlier studies indicating a relationship between TBV and IQ in epilepsy [38,42,55–57]. In two more recent studies using quantitative MRI, age [42] and disease duration [57] were shown to affect the TBV of patients with epilepsy. The present study has identified another disease-specific factor, namely, the frequency and severity of seizures, which significantly influenced the TBV.

Finally, the potential role of antiepileptic drugs (AEDs) as a confounding factor should be taken into consideration. First, AED therapy could contribute to cognitive dysfunction in patients with epilepsy [58]. Second, cerebellar function is modified by AEDs, and cerebellar atrophy is a well-known side effect of AEDs [35,59,60]. Third, there is evidence that AEDs are of potential use in the treatment of IED [61]. Despite these points, we chose to omit “medication” as a confounder, given the highly variable pharmacological treatment among those undergoing polytherapy (i.e., 90% of the study sample).

4.2. Pathophysiological interpretation

A functional topography of the cerebellum has been postulated based on previous functional MRI studies [12,62,63]. Cognitive impairment occurs when posterior lobe lesions disrupt the cerebellar modulation of cognitive loops with cerebral association cortices. Neuropsychiatric disorders manifest when vermis lesions deprive cerebrocerebellar limbic loops of cerebellar input [62]. A more detailed analysis of cognitive cerebellar functions revealed lateralized activation patterns in distinct cognitive domains [12]. It has been assumed that the right cerebellar hemisphere is engaged in language and executive function (e.g., verbal generation task) [12,64], whereas the contralateral side contributes to visuospatial tasks [12,65–67]. Memory tasks seem to involve both hemispheres [12,64]. Our data confirm the proposed topography of the cerebellum, since the left cerebellar volume was linked to subtests of the verbal IQ (picture arrangement, block design), which require visuospatial abilities such as mental rotation. Remarkably, language functions were also positively correlated with left cerebellar hemispheric volume. Taking into account the dominance of the left cerebral hemisphere in language, the contribution of the right hemisphere to semantic processing is still a matter of debate. A recent metaanalysis found that the right hemisphere hosts no phonological representation per se, but the right frontal area participates in the recruitment of additional executive processes such as selective attention and/or the manipulation of working memory in terms of verbal material [68]. Given the convincing evidence

for compensatory laterality shifts in lateralized brain functions in patients with Alzheimer's disease, one may also speculate that such a shift could take place in patients with TLE [69]. Likewise, the recently established ‘scaffolding theory of aging and cognition’ postulates that this laterality shift occurs as a compensatory response in the normal aging brain [70]. In this context, it seems to be relevant that 30 out of the 60 patients analyzed presented with a left-sided epileptogenic focus or MRI pathology.

It was previously reported that increased white matter volume of the vermis in men with schizophrenia is associated with an executive dysfunction and deficits in verbal memory [71,72]. The authors hypothesized that volumetric abnormalities could point towards anomalous connectivity, a theory which could also pertain to the present study sample of patients with TLE. The neurodevelopmental signaling protein Reelin plays a key role in the pathophysiology of both TLE and schizophrenia [73]. One may speculate that disease-dependent changes in Reelin expression contribute to structural abnormalities in the brain. However, further studies are needed to ascertain the substrate and mechanisms underlying abnormal cerebellar volume.

4.3. Methodological issues

4.3.1. Sample selection

All patients suffered from treatment-refractory TLE that was diagnosed at a tertiary referral center. Patients with an IED that was clearly defined by DSM-IV criteria were recruited to obtain a homogeneous study sample in terms of psychopathology. The two groups (with or without IED) were homogeneous in terms of demographic background and clinical features relating to the epilepsy [4]. To control for a neuropsychological selection bias, patients with a mental handicap and IQ below 65 were excluded. To avoid selection bias, the main inclusion criteria were the clinical diagnoses of TLE and IED, regardless of the underlying brain pathology. Imaging and neuropsychological data were obtained after inclusion.

4.3.2. Quantitative MR imaging

Former studies indicate the sensitivity of quantitative MRI in the detection of cerebral and cerebellar volume changes [33,37,38,40,42,43,74–77]. Our data confirm the reliability of this method.

Different measures can be chosen as markers of total brain volume: either the intracranial volume as an indicator of brain size at its peak adult volume or the different measures of actual total brain size. In epilepsy, different factors such as seizure frequency, the disease process itself, or anticonvulsant medication may affect brain size and lead to a generalized total or focal loss of brain volume in such a way that it is difficult to assess. Therefore, we chose intracranial volume as the reference point to which cerebral subvolumes were corrected because we felt that this is a more clear and less compromised measure.

In summary, this study rules out an association between cerebellar volume and IED in patients with TLE. In contrast, cerebellar volume was significantly associated with cognitive functions, thus supporting the notion that distinct cognitive domains have a functional topographical organization in the cerebellum. Further research should address the question of whether cerebellar volume alterations might serve as a surrogate marker of neuropsychological dysfunction in temporal lobe epilepsy.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.yebeh.2013.04.020>.

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