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Alessia Longo[a,b], Marion Houot [c,d,e], Bastien Herlin[a], Marie Méré [f], Marisa Denos[a], Séverine Samson[f,g], Sophie Dupont[a,f,h,i,*]

[a] Rehabilitation Unit, AP-HP, Pitié-Salpêtrière Hospital, Paris, France
[b] Neurosciences Department, Area Del Farmaco E Salute Del Bambino, Firenze, Italy
[c]Clinical Investigation Centre, Institut du Cerveau et de la Moelle épinière (ICM), Pitié-Salpêtrière Hospital Paris, France.
[d]Institute of Memory and Alzheimer's Disease (IM2A), Department of Neurology, AP-HP, Pitié-Salpêtrière Hospital, Paris, France.
[e]Centre of Excellence of Neurodegenerative Disease (CoEN), AP-HP, Pitié-Salpêtrière Hospital, Paris, France.
[f]Epilepsy Unit, AP-HP, Pitié-Salpêtrière Hospital, Paris, France
[g] Univ. Lille, ULR 4072 - PSITEC - Psychologie : Interactions Temps Émotions Cognition, F-59000 Lille, France
[h]Université Paris Sorbonne, Paris, France
[i]Centre de recherche de l'Institut du cerveau et de la moelle épinière (ICM), UMPC-UMR 7225 CNRS-UMRS 975 Inserm, Paris, France

***Corresponding author :**

Pr Sophie Dupont

Epilepsy Unit and Rehabilitation Unit, AP-HP, Pitié-Salpêtrière Hospital, Paris, France; Centre de recherche de l'Institut du cerveau et de la moelle épinière (ICM), UMPC-UMR 7225 CNRS-UMRS 975 Inserm, Paris, France ; Université Paris Sorbonne, Paris, France, sophie.dupont@aphp.fr

ORCID number of the corresponding author: 0000-0003-2080-8253

Abstract

Objective: Lateral temporal lobe epilepsies (LTLE) are poorly characterized heterogeneous epilepsies. As the lateral temporal lobe supports distinct functions, we hypothesized that neuropsychological profiles could differ according to the localization of the seizure focus within the lateral temporal lobe.

Methods: We retrospectively examined the neuropsychological characteristics of 74 consecutive patients with refractory LTLE assessed in the context of a presurgical investigation at the Pitié-Salpêtrière Hospital in Paris between 1998 and 2018. Precise localization of the epileptic focus was correlated with scores on tests of intelligence (Global, Verbal and Performance IQ), working memory, episodic memory (verbal and visual learning and forgetting), executive functions and language abilities.

Results: : We demonstrated an impact of the localization of the epileptic focus within the lateral temporal lobe with worse learning and/or executive performances depicted in the infero-basal and pure pole LTLE groups and greater language difficulties in the posterior LTLE group, Antiepileptic drugs had a greater effect than parameters related to the epilepsy itself as the lesion or the disease duration, and finally as in medial TLE, the age, the education, and the sex influenced some cognitive performances.

Conclusion: Our findings show that the lateral temporal neocortex is also part of the neural substrate for memory processing and executive functions and suggest that this involvement could be related to functions devoted to specific subregions of the temporal lobe (i.e temporal pole, inferior and basal regions) that support language and semantic processing.

Key-words: lateral temporal lobe epilepsy, cognition, memory, executive functions, antiepileptic drugs

Highlights

Patients with lateral temporal lobe epilepsies (LTLE) exhibit distinct cognitive profiles

Memory processing and executive functions are affected in LTLE

Regions that support language and semantic processing are more affected

Anti-epileptic drugs specifically affect cognition

1. Introduction

Lateral temporal lobe epilepsies (LTLE) are still a poorly studied group of conditions [1]. Available descriptions are lacking or often emphasize the absence of typical electro-clinical LTLE syndrome [2] even though specific seizure characteristics, such as auditory auras, aphasic seizures, or a higher propensity to generalize, may help to distinguish lateral temporal lobe epilepsies from medial temporal lobe epilepsies (MTLE) [3,4]. On an anatomical and cognitive point of view, the lateral temporal lobe is large and supports distinct functions. Schematically, it may be divided into five main functional regions [5]: (1) the primary auditory cortex situated on the opercular surface of the temporal lobe (gyrus of Heschl), (2) the auditory association cortex that surrounds the primary auditory cortex and extends to the superior temporal gyrus [6], (3) the infero-basal temporal cortex including the temporal visual association cortex, and the posterior inferior and basal temporal cortices [7] more involved in language and semantic processing (posterior inferior temporal cortex being specifically involved in the transformation of sound-based language codes into modality-independent meaning representations according to Hickok and Poeppel language model [8]), (4) the superior temporal cortex on the upper bank of the superior temporal that includes posteriorly the Wernicke region for language but may also be considered as a polymodal region responding to auditory, visual or somatosensory stimulations, and (5) the temporopolar cortex or temporal pole (area 38 of Brodmann) which has been associated with several high-level cognitive processes such as visual processing for complex objects and face recognition, autobiographic memory, semantic processing or socio-emotional processing [9].

In addition, numerous studies suggest that lateral temporal neocortex could also be part of the neural substrate for episodic memory [10-14] and working memory [15] via semantic processing. A recent fMRI study in healthy volunteers has shown that novelty and subsequent episodic memory responses were observed in prefrontal, lateral, and medial temporal cortices, suggesting that these regions were equally actively engaged in encoding processes [10]. The hypothesis was that lateral temporal cortex could support the encoding of abstract semantic attributes into memory. Similarly, fMRI data obtained during a working memory task have demonstrated increased activation in the posterior left middle and inferior temporal gyri [11]. Here again, the hypothesis was a neural correlate of semantic working memory maintenance.

In front of this multiplicity of functions, a neuropsychological heterogeneity could be suspected but has never been really studied. To better characterize LTLE neuropsychological features, more precise localization of the epileptic focus seems therefore mandatory. In this study, we investigated the neuropsychological profile of consecutive LTLE patients,

candidates to epilepsy surgery according to the exact localization of the epileptic focus within the temporal lobe. We also assessed the effect of other factors known to influence the cognitive abilities of patients with epilepsy such as demographic factors, disease activity, medication, psychiatric history, side of the seizure focus, and lesions (presence/type). We hypothesized that neuropsychological profiles could differ according to the localization of the seizure focus within the lateral temporal lobe reflecting the heterogeneity of LTLE. Precise neuropsychological delineation could further help to guide surgical resections in refractory LTLE who are candidates to surgery.

2. Material and methods

2.1 Participants

We studied a group of 74 consecutive patients with medically intractable LTLE assessed in the context of a presurgical investigation in the Epilepsy Unit at the Pitié-Salpêtrière Hospital in Paris between 1998 and 2018. Criteria for inclusion were: 1) a well-defined refractory lateral TLE with at least one video-EEG recording of a seizure, 2) a structural MRI, and 3) an extensive comprehensive neuropsychological assessment. Patients with global IQ< 75 were excluded.

LTLE definition implied a localization of the seizure focus within the neocortex (lateral and inferolateral surfaces) with the exclusion of seizures arising from MTL structures (hippocampus, amygdala, and parahippocampal gyrus).

All patients gave their informed written consent at the time of the video-EEG exam for further publication of data related to their epilepsy. This study was conducted according to the French ethical legislation and authorized by CNIL committee (No. 2146842).

Localization boundaries

Based on EEG, neuroimaging (structural MRI, PET, SISCOM, fMRI) and SEEG findings (table 1), we classified LTLE patients according 2 localization approaches:

- A classical anatomical gyral approach that distinguishes 3 subregions [16,17]:
  - The temporal pole, identified as pure pole later on [9]: defined under the lateral sulcus, at the rostral tip of the temporal lobe, inside the most rostral part of the middle cranial fossa. The boundary between the temporal pole and the superior temporal gyrus was located at the lateral bank of the temporopolar sulcus
  - T1-T2 (superior and middle temporal cortex):
    - T1 (superior temporal gyrus): located at the top most aspect of the temporal lobe, lying inferior to the lateral sulcus and superior to the superior temporal sulcus, extending posteriorly from the temporal pole, ending at the temporoparietal junction, and blending with the angular gyrus and supramarginal gyrus of the inferior parietal lobule.
    - T2 (middle temporal gyrus): bounded dorsally by the superior temporal sulcus and superior temporal gyrus and ventrally by the inferior temporal sulcus and inferior temporal gyrus, extending posteriorly from the temporal pole, blending into the parietal and occipital lobes with the

limits defined by an arbitrary line, the lateral parietotemporal line located between the superior and inferior temporal sulci

- T3-T4 (infero-basal temporal cortex):
  - T3 (inferior temporal gyrus): bounded above by the inferior temporal sulcus and below by the lateral occipitotemporal sulcus
  - T4: temporal part of the fusiform gyrus, also known as the lateral occipitotemporal gyrus lying on the basal surface of the temporal and occipital lobes.

- A functional antero-posterior approach that distinguishes an anterior subregion, defined as the most anterior tip of the temporal lobe, located rostrally to the perirhinal cortex [18] (including the whole temporal pole region and the anterior part of T1, T2, T3 and T4 regions) and a posterior subregion (posterior part of T1, T2, T3 and T4 regions).

2.2 Neuropsychological testing

The comprehensive neuropsychological evaluation included a series of tests providing the following measures in different cognitive domains (one measure could involve several cognitive functions):

1. Intellectual function using the Wechsler Adult Intelligence Scales (WAIS-R) providing scores of global IQ, verbal IQ, and performance IQ as well as IQ subtests (block design, similarities, digit span, arithmetic, information, coding, L-N sequencing, picture completion) [19]
2. Verbal learning and memory function using :
   a. An adapted procedure of the verbal learning task from Jones-Gotman et al [20] consisting of learning 13 written abstract words across four successive recall trials (R1, R2, R3, R4) followed by a 24-hr delayed recall test (DR). Three measures were used:
      i. two learning scores: mean average of the four recall trials (R1-R4) and learning between the 1st and the 4th recall trials (R4-R1)
      ii. a forgetting score: R4-DR/R4*100
   b. An adapted procedure of verbal paired associates learning task from the Wechsler Memory Scale (WMS-R) consisting of a learning 10 verbal paired associates across three successive learning trials followed by a 90-min delayed recall providing a forgetting score computed for 6 easy and for 4 difficult paired word associates [21].

3. Non-verbal memory function using the Rey Complex Figure Test (RCFT) [22] which consisted of a copy followed by a 30-min delayed recall of the Figure. We used the non-verbal forgetting score (copy trial - Delayed Recall trial / copy trial).
4. Short term memory using 4 subtests from the WAIS-R and WAIS-III :
    a. The number of digits recalled in the same order (Digit Span Forward)
    b. The number of digits recalled in reverse order (Digit Span Backward), the arithmetic and the letter-number sequencing (WAIS-III) subtests reflecting working memory function [23].
5. Tests sensitive to executive functions:
    a. inhibition and psychomotor speed :
        i. Trail making Test (TMT) using the following score : time required to complete TMT B - Time required to complete TMT A (B-A) (the smaller the score is, the better is the performance) and ratio TMTB/TMTA (B/A) [24,25]
        ii. Stroop Test requiring to 1) name color of small squares, 2) read color words written in black and 3) name the color of the ink in which the color word is written by inhibiting reading the actual word (interference task). The increase in time taken to perform the latter condition compared with to the first one is known as the Stroop interference score[26].
    b. abstract reasoning, concept formation and mental flexibility: the Wisconsin Card Sorting Test (WCST) assesses the ability to sort cards (maximum 128 cards) according to specific categories (color, form, number) in order to achieve a maximum of 6 categories (one category being completed after 10 consecutive good responses). This test allows computing three scores [27,28]:
        i. number of achieved categories
        ii. number of cards/number of achieved categories (the smaller the ratio is, the better is the performance, minimum score= 10)
        iii. number of perseverative errors /number of cards (the larger the ratio is, the higher is the proportion of perseverative errors).
    c. phonological verbal fluency (number of words beginning by the letters P, R, V produced in one minute each)

6. Perceptual motor speed using the coding subtest from the WAIS-R
7. Constructive and visual skills using :
    a. Block design subtest from the WAIS-R
    b. Picture completion subtest from the WAIS-R
8. Language function based on [29]:
    a. lexical search with:
        i. Phonological verbal fluency score (number of words beginning by the letters P, R, V produced in one minute each)
        ii. Semantic verbal fluency score (Animals, fruits, Occupations; one minute each)
    b. Similarities subtest from the WAIS-R
    c. Reading speed from the Stroop test: Condition 2 (time (sec))
9. Handedness was assessed using the Edinburgh test [30]

2.3 Statistical analysis

Demographical and clinical data of the three groups of localization (i.e. pure pole ; T1-T2; T3-T4) were compared using Kruskal-Wallis for continuous variables and Fisher's exact test for categorical variables. Pairwise Mann-Whitney-Wilcoxon tests for continuous variables, and pairwise Fisher's exact tests for categorical variables, both with Benjamini-Hochberg correction were performed for pairwise comparison.

Our main objective was to compare the cognitive functioning of the three groups of localization with 27 neuropsychological scores. Nevertheless, we were also interested in testing associations between cognitive functioning and 19 effects as age ; sex ; education ; disease duration ; psychiatric history ; anterior lesion ; posterior lesion ; lesion type (DNET/ganglioglioma, dysplasia, no lesion, others) ; lesion side (left or right) ; antiepileptic drugs (AEDs) number ; taking new AEDs ; taking Sodium Valproate; taking Carbamazepine; taking Topiramate; taking Levetiracetam; taking benzodiazepins; taking Lamotrigine ; taking Oxcarbazepine. AEDS took by less than 10 patients were not selected.

The first step was to pre select variables. For this purpose, we performed one Generalized Linear Model (GLM) for each of the neuropsychological scores with the three groups of localization and each of the 19 other effects as covariates. All effects with $p<0.1$ were included in the final model in addition to the groups of localization.

Type II F-tests were used to test effects. Cohen's f2 were calculated to assess effect sizes. Post-hoc tests on localization group were performed for pairwise comparison. Normality of

residuals and heteroskedasticity were checked visually. Cook's distances and hat values were computed to investigate potential influencers and outliers. Six scores were skewed to the right and were then log transformed (two of the WCST scores: number of cards/ number of achieved categories and number of non-perseverative errors /number of cards ; the two stroop and TMT scores). Three scores were dichotomized due to an over represented value (i.e. the 0 for easy and difficult paired learning tasks ; the 6 for WCST number of categories). Thus, for these three scores, GLMs with Bernoulli family and logit link were used and GLM with gaussian family and identity link for the others. Given the explorative character of the present study, no correction of p values for multiple testing was applied.

Statistical analyses were performed using R 3.6.1. (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

3.Results

3.1 Sample description (Table 2)

The 74 LTLE patients were 33.2±11.1 (mean±sd) years old, with 27 (36.5%) women, 16.0±9.6 years of disease duration and 12.7±2.8 years of education. There were 38 right-side LTLE (51.4%) and 36 left side LTLE (48.6%).

Patients were divided into localization categories based on localising data according to:

- The gyrus localization: pure pole (n= 32, 43.2%), T1-T2 (n=19, 25.7%) and T3-T4 (n=23, 31.1%) (Figure 1)
- The anterior/posterior axis with 43 patients belonging to the anterior group, 31 patients to the posterior group and 7 to both anterior and posterior groups.

- Figure 1 -

Four etiological categories were considered: dysembryoplastic neuroepithelial tumor /ganglioglioma (36.5%), no lesion (25.7%), dysplasia (17.6%), and others (20.3%: glial scars, cavernoma, epidermoid cyst, arteriovenous malformation) (Figure2).

- Figure 2 -

LTLE patients took in average 2 AEDs: 25 patients (33.8%) took only new AEDs and 49 patients (66.2%) took both new and old generation AEDs. The most prescribed AEDs were: Levetiracetam (44.6%), Carbamazepine (41.9%), Lamotrigine (31.1%), and Sodium Valproate (27%), followed by Oxcarbazepine (21.6%), benzodiazepins (18.9%), and Topiramate (13.5%).

20 patients (27. 8%) underwent an intracerebral presurgical evaluation.

63 patients (85.1%) underwent surgery.

No statistical significant differences on demographical and clinical data were noted according to the localization groups.

-insert here table 1-

3.2 Neuropsychological profile

Results on the pre selection variables steps are presented in Table S1 (online resource). Final models were those with effects with p<0.1. Scores stratified by domains are summarized in table 3.

3.2.1 Localization effect

-Figure 3-

A localization effect was found in forgetting score for difficult word lists (Cohen's f2 = 0.18, p=0.003), WCST number of cards/number of achieved categories (Cohen's f2 = 0.11, p=0.031) and phonological verbal fluency score (Cohen's f2 = 0.14, p=0.014).

T3-T4 LTLE patients exhibited worse performances than T1-T2 LTLE patients in paired-associates learning task (forgetting score for difficult word lists, p=0.013).

Pure pole LTLE exhibited worse performances than T1-T2 LTLE patients in two domains: paired-associates learning task (forgetting score for difficult word lists, p=0.041) and executive functions: both WCST (number of cards/number of achieved categories) and phonological verbal fluency (respectively p=0.024 and 0.012)

There was no statistically significant differences between pure pole LTLE patients and T3-T4 patients.

Posterior epileptic focus was selected in 8 final models (out of 27. See Table S1) and remained significant in only two. LTLE patients with posterior epileptic focus exhibited worse performances in similarities IQ subtest (Cohen's f2 = 0.07, p=0.035) and in verbal phonological fluency (Cohen's f2 = 0.07, p=0.040) than those with anterior epileptic focus.

Anterior epileptic focus was selected in 5 final models (out of 27. See Table S1) and did not remain significant in any.

3.2.2 Demographic data effect

As expected, scholar level was significantly associated with numerous neuropsychological scores: global IQ (f2=0.58, p<0.001), verbal and performance IQ (f2= 0.53, p<0.001 and f2=0.19, p=0.001), 5 IQ subtests (arithmetic, similarities, block design, coding, information, respectively f2=0.20 and p=0.001, f2=0.36 and p<0.001, f2=0.07 and p=0.041, f2=0.14 and p=0.005 and f2=0.46 and p<0.001), verbal episodic memory learning (average score, f2=0.23 and p<0.001) and forgetting (paired-associates learning task forgetting score (easy list), f2=0.07 and p=0.043), executive functions (all WCST scores, f2 from 0.09 to 0.16 and p from 0.012 to 0.002) and stroop test subtest (condition 2, f2=0.07 and p=0.035), phonological and semantic fluency scores (f2=0.34 and 0.21 respectively and both p<0.001) with a higher level of education associated to better performances.

As previously described [31], performances improved with age in IQ (global IQ and performance IQ, respectively f2=0.11 and 0.12, p=0.010 and p=0.006) and in 3 IQ subtests: arithmetic, similarities, picture completion (respectively f2=0.07 and p=0.041, f2=0.13 and p=0.006 and f2=0.12 and p=0.006). At the opposite, performances decreased with age in verbal episodic memory forgetting difficult paired-associates learning task (f2=0.10, p=0.010) and in executive tasks (stroop test interference, f2=0.10, p=0.012).
Women with epilepsy exhibited worse performances in arithmetic IQ subtest than men (f2=0.16, p=0.002).

3.2.3 Psychiatric comorbidities effect

The existence of a psychiatric history, including depression, was associated with worse Perceptual motor speed scores using the IQ coding subtest (f2=0.12, p=0.006).

AEDs effect

The number of AEDs negatively affected the difficult paired-associates learning task (f2=0.10, p=0.009).
Two AEDs had a deleterious cognitive impact: Sodium Valproate and Topiramate. LTLE patients treated by Sodium Valproate exhibited worse performances in multiple cognitive domains: global IQ (f2=0.08, p=0.035), performance IQ (f2=0.12, p=0.006) and coding sub test IQ (f2=0.11, p=0.012), verbal episodic memory learning (learning score R4-R1, f2=0.13, p=0.003) and executive function (WCST number of cards/number of categories, f2=0.07, p=0.038) than those without Sodium Valproate. LTLE patients treated by Topiramate exhibited worse performances in arithmetic subtest IQ (f2=0.13, p=0.005) and in verbal episodic memory learning (learning score R4-R1, f2=0.06, p=0.042) than those without Topiramate.
At the opposite, two AEDs had a favourable effect on cognition: Lamotrigine and Oxcarbazepine. LTLE patients treated by Lamotrigine had better performances in picture completion subtest IQ (f2=0.10, p=0.013) and in verbal semantic fluency (f2=0.07, p=0.038) than those without Lamotrigine. LTLE patients treated by Oxcarbazepine had better performances in verbal episodic memory learning (average learning score, f2=0.09, p=0.018) and in executive functions (TMT scores, f2=0.09 and 0.08, p=0.015 and p=0.025, TMTB-A and TMTB/A respectively) than those without Oxcarbazepine .

3.2.4 No effect

We failed to find any statistical significant association with: the disease duration, the lesion type, the side of the epileptic focus, the anterior epileptic focus, the presence of new AEDs only or of specific AEDs (Carbamazepine, Levetiracetam, benzodiazepins).

Discussion

Three major results emerge from this study: i) the localization of the epileptic focus within the lateral temporal lobe has an impact on the cognitive profile with worse learning and/or executive performances depicted in the infero-basal and pure pole LTLE groups and greater language difficulties in the posterior LTLE group, ii) AEDs have a greater effect than parameters related to the epilepsy itself as the lesion or the disease duration, and iii) as in MTLE, the age, the education, and the sex may influence some cognitive performances.

4.1 Influence of the localization

Primary or secondary dysfunction?

The question remains whether the episodic memory or executive impairments found in our LTLE patients are related to secondary dysfunction of the medial temporal structures by propagation of the epileptic discharge or whether the lateral temporal lobe belongs to the brain network supporting certain aspects of declarative memory or executive functions. Episodic memory is usually highly related to hippocampal and parahippocampal structures and executive functions are supported by prefrontal cortex but, as mentioned earlier, studies in healthy volunteers suggest that lateral temporal neocortex could also be part of the neural substrate for episodic memory and working memory via semantic processing. Studies in patients also support this hypothesis. A clinical study that examined 21 LTLE patients explored by SEEG found that an half of patients exhibited episodic memory deficits [4] whereas Helmstaedter et al. [15] who addressed the participation of temporomesial and temporolateral structures in different aspects of declarative memory in TLE showed that learning (acquisition and collection processes) and working memory were supported by neocortical temporolateral structures. Lesional studies have also demonstrated that apart from the medial temporal lobe, the lateral temporal region was also responsible for memory processing in humans and that bilateral damage to the lateral temporal lobe sparing the hippocampus could lead to verbal and visual memory impairment [33]. Finally, extracellular recording of neuronal activity during awake neurosurgery suggests that lateral temporal neocortex could be an integral part of the declarative memory network and executive functions. These recordings performed during verbal paired associated learning [34] or during short-term verbal memory testings [13,35] depicted changes in frequency of activity in 55–70% of lateral temporal neurons.

All these findings and our own data support the fact that the temporal lobe regions beyond the hippocampal formation may play a role in memory processing and executive functions.

Deficits according to anatomical subdivisions

The contribution to memory processing, as already discussed, could be related to parallel semantic computations. If so, one may expect lesser performances in patients with epilepsy localized in pure pole, inferior or basal regions, all involved in language processing, object naming or meta-linguistic semantic tasks [9,11].

Our findings support this hypothesis since infero-basal and pure pole LTLE groups had worse performances than T1-T2 group in paired-associates verbal learning task. In a study that addressed more specifically the localization of the recordings within the lateral temporal lobe, Ojemann et al. [36] also found evidence for an anatomic subdivision in human temporal cortical neuronal activity related to recent verbal memory. They showed that inferior lateral and basal cortex (T3-T4 group in our study) were related to all memory stages (encoding, storage, retrieval) whether superior-posterior lateral cortex was more related to implicit and recognition memory. These findings are in agreement with our findings.

Concerning executive functions, we have demonstrated that pure temporal pole group exhibited worse executive performances than T1-T2 group. A study that examined intracerebral electroencephalography recordings in patients with refractory focal epilepsy have underlined the role played by the orbitofrontal cortex and temporal neocortex in processing of executive functions [37]. Our findings could be explained by the direct anatomical pathway connecting the cortex of the temporal pole and the orbitofrontal cortex through the uncinate fascicle.

Finally and logically, posterior LTLE patients exhibited worse language performances. This was an expected finding since the posterior part of the superior and middle temporal gyri are known to be involved in phonological and lexical-semantic processing [38].

In summary, converging evidence show that the lateral temporal neocortex is also part of the neural substrate for memory processing and executive functions. Our findings suggest that this involvement could be related to functions devoted to specific subregions of the temporal lobe (i.e temporal pole, inferior and basal regions) that support language and semantic processing.

4.2 Influence of side

Although a semantic processing is hypothesized to explain our results, we did not evidence a side difference. In healthy volunteers, imaging studies show consistent right hemispheric contribution during language tasks supporting the view that the right hemisphere is also involved in normal language processing. A recent metanalysis of 128 neuroimaging studies evidenced a specific unilateral right temporal involvement during sentence/text linguistic processing tasks [39]. Furthermore, in TLE patients, language-related processing in the right

hemisphere may differ from that with a functionally normal left hemisphere. Patients with seizures originating in the left temporal lobe, for instance, have been shown to have a greater degree of right hemisphere involvement in language [40,41]. The present findings suggest that in LTLE, semantic processing could have a bilateral representation.

4.3 Influence of AEDs

We first found that a higher number of AEDs was associated to worse paired-associates verbal learning task performances. Numerous studies have already underlined that a greater number of AEDs was significantly and negatively associated with cognition in patients with epilepsy, especially in episodic verbal memory (as in our study), working memory and processing speed [42].

Beyond polytherapy, the relative contribution of AEDs to cognitive dysfunction is of relevance. As in our study, most studies agree that some differences exist among the older generation of AEDs with regard to the effects on cognition, and some newer generation molecules may have a better cognitive profile than older AEDs [43].

AEDs negative effects

We demonstrated that two AEDs had a deleterious cognitive impact: Sodium Valproate and Topiramate.

A detrimental influence of Sodium Valproate was already noted in healthy volunteers [44] and in PWE who exhibited cognitive problems such as memory, speech, attention or psychomotor slowing and overall more attentional problems than with Ethosuximide or Lamotrigine [45].

Concerning Topiramate, negative effects on memory, verbal and executive functions was demonstrated in healthy volunteers [46] whereas early clinical studies in PWE reported concentration and memory problems (as in our study) in up to 10% of subjects [47]. Further studies demonstrated that Topiramate could also selectively affect language functions even with very low dosages [48].

AEDs positive effects

At the opposite, positive effects of Lamotrigine on cognitive function epilepsy have already been reported in PWE [49]. Lamotrigine has also been shown to have a favourable cognitive profile in comparison with other AEDs [50]. As in our study, better performances were noted with Lamotrigine for verbal fluency scores but also for inhibition/attention measures. Several studies have also pointed out the beneficial effect of Lamotrigine on alertness and arousal that could partly explain the cognitive improvement due to Lamotrigine [51].

Studies have indicated no deterioration in learning, memory or attention in patients treated with Oxcarbazepine but to our knowledge, only one study documented improvement in an information processing speed task in patients with focal epilepsy [52].
We confirmed in this study that particular AEDs may have greater potential for negative or beneficial impacts on cognition in epilepsy.

4.4 Influence of other factors

Psychiatric co-morbidity

In this study, we demonstrated that a personal psychiatric history, including depression, was associated to worse perceptual motor speed in LTLE. A meta-analysis already revealed significant moderate cognitive deficits in executive function, memory and attention in patients with depression relative to controls [53] highlighting the association between cognition and psychiatric comorbidities in general. To explain this association, contemporary models, such as the cognitive neuropsychological model of depression, propose a causal role of the cognitive impairment that could drive and maintain depressive symptoms [54]. Another hypothesis suggests that their coexistence may be the consequence of confounding shared genetic risk factors causing both independently [55]. As suggested by our results, the epilepsy itself could also be considered as another confounding shared factor.

Age

We found that ageing worsens verbal episodic memory performances and executive tasks. This finding has already been reported in both healthy volunteers [56] and PWE [31,57]. Even if these results may highlight a normal ageing phenomenon, we did not find a worsening of another cognitive domains with age reinforcing the implication of temporal lobe neocortex in declarative memory and executive functions.
As previously assessed [31], we found that IQ scores (global IQ and performance IQ) improved with age in LTLE patients. The improvement of intellectual abilities with age has already been reported in another studies that addressed the evolution of IQ over time in adult patients with TLE [58,59] and would need further confirmation.

Sex

LTLE women exhibited worse performances in arithmetic IQ subtest than LTLE men. Studies that have already addressed the gender effects in arithmetic across countries in healthy volunteers suggested that educational context may play a role in sex differences in mathematics [60]. Consistent with this explanation, Bedard and Cho [62] demonstrated that

countries that practice tracking in upper grades are more likely to reveal sex differences in high school math achievement. This trend may reflect differences in boys' and girls' educational experiences resulting from a higher proportion of boys placed in advanced classes and we can speculate here the same hypothesis for boys and girls with epilepsy.

4.5 Limitations of the study

Although the sample size of the patient groups was reasonably large compared to other neuropsychological studies in the domain, limitations of the sample size may have threatened our statistical power. Another limitation is that auditory cognition, socio-emotional processing, and autobiographic memory that are known functions of the lateral temporal lobe were not tested. The strength of our study is the inclusion of well-characterized LTLE patients with distinct localizations within the temporal lobe who all underwent an overall complete comprehensive neuropsychological assessment.

4. Conclusion

Our findings show that the lateral temporal neocortex is also part of the neural substrate for memory processing and executive functions and suggest that this involvement could be related to functions devoted to specific subregions of the temporal lobe (i.e temporal pole, inferior and basal regions) that support language and semantic processing. This specific neuropsychological delineation could further help to guide surgical resections in refractory LTLE who are candidates to surgery.

Declarations

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Conflicts of interest/Competing interests

On behalf of all authors, Sophie Dupont states that there is no conflict of interest.

Availability of data and material

Anonymized data will be shared by request from any qualified investigator.

Code availability

Text and cover letter: Microsoft word

Figures : TIFF format

Ethics approval

The study was conducted in accordance with the ethical standards of the AP-HP according to the declaration of Helsinki and authorized by CNIL committee (No. 2146842).

References

1. Michelucci R, Pasini E, Nobile C. Lateral temporal lobe epilepsies: Clinical and genetic features. Epilepsia. 2009;50(Suppl. 5): 52–54. https:// doi: 10.1111/j.1528-1167.2009.02122.x
2. Walczak TS. Lateral Temporal Lobe Epilepsy: Characterizing the Syndrome. Epilepsia, 1995; 36(7):633435. https:// doi: 10.1111/j.1528-1157.1995.tb01658.x
3. Kennedy JD, Schuele SU. Clin Neurophysiol. 2012;29: 366–370. https:// doi: 10.1097/WNP.0b013e31826bd78b
4. Pacia SV, Devinsky O, Perrine K, Ravdin L, Luciano D, Vazquez B, et al. Clinical features of neocortical temporal lobe epilepsy. Ann Neurol. 1996;40(5):724-30. https:// doi: 10.1002/ana.410400508
5. Nieuwenhuys R, Voogd J, van Huijzen C. The human central nervous system : A Synopsis and Atlas. 4th ed. Springer 2008; 611-617.
6. Moore JK, Linthicium FH. Auditory system. In: Paxinos G, Mai JK (eds) The Human nervous system, 2nd ed. Elsevier, Amsterdam 2004; 1241-1279.
7. Lüders H, Lesser RP, Hahn J, Dinner DS, Morris HH, Wyllie E, et al. Basal temporal language area. Brain. 1991;114 (Pt 2):743-54. https:// doi: 10.1093/brain/114.2.743
8. Hickok G, Poeppel D. Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. Cognition. 2004; 92: 67–99. https:// doi: 10.1016/j.cognition.2003.10.011
9. Herlin B, Navarro V, Dupont S. The temporal pole: From anatomy to function-A literature appraisal. J Chem Neuroanat. 2021;113:101925. https:// doi: 10.1016/j.jchemneu.2021.101925
10. Kirchhoff BA, Wagner AD, Maril A, Stern CE. Prefrontal–Temporal Circuitry for Episodic Encoding and Subsequent Memory J. Neurosci. 2000; 20(16):6173–6180. https:// doi: 10.1523/JNEUROSCI.20-16-06173.2000
11. Fiebach CJ, Friederici AD, Smith EE, Swinney D. Lateral inferotemporal cortex maintains conceptual-semantic representations in verbal working memory. J Cogn Neurosci. 2007;19(12):2035-49. https:// doi: 10.1162/jocn.2007.19.12.2035
12. Perrine K, Devinsky O, Uysal S, Luciano,D, Dogali M. Left temporal neocortex mediation of verbal memory. Neurology.1994; 44:1845–1850. https:// doi: 10.1212/wnl.44.10.1845

13. Ojemann GA, Creutzfeldt OD, Lettich E, Haglund MM. Neuronal activity in human lateral temporal cortex related to short-term verbal memory, naming and reading. Brain. 1988; 111: 1383–1403. https:// doi: 10.1093/brain/111.6.1383
14. Ojemann GA. Organization of short-term verbal memory in language areas of human cortex: evidence from electrical stimulation. Brain Lang. 1978;5: 331–340. https:// doi: 10.1016/0093-934x(78)90030-5
15. Helmstaedter C, Grunwald T, Lehnertz K, Gleissner U, Elger CE. Differential involvement of left temporolateral and temporomesial structures in verbal declarative learning and memory: evidence from temporal lobe epilepsy. Brain Cogn. 1997; 35:110–31. https:// doi: 10.1006/brcg.1997.0930
16. Kiernan JA. Anatomy of the temporal lobe. Epilepsy Research and Treatment. 2012 ; 176157. https:// doi: 10.1155/2012/176157
17. Sindou M, Guenot M. Surgical anatomy of the temporal lobe for epilepsy surgery. Adv Tech Stand Neurosurg. 2003;28:315-43. https:// doi: 10.1007/978-3-7091-0641-9_6.
18. Wong C, Gallate. The function of the anterior temporal lobe: a review of the empirical evidence. J. Brain Res. 2012;1449:94-116. https:// doi: 10.1016/j.brainres.2012.02.017
19. Wechsler D. The Wechsler adult intelligence scale-Revised. New York: The Psychological Corporation. 1981.
20. Jones-Gotman M, Zatorre RJ, Olivier A, Andermann F, Cendes F, Staunton H, et al. Learning and retention of words and designs following excision from medial or lateral temporal-lobe structures. Neuropsychologia. 1997 ; 35:963–73. https:// doi: 10.1016/s0028-3932(97)00024-9
21. Wechsler, D. Echelle clinique de Mémoire de Wechsler forme révisée MEM-R. 1991 ; Paris: Les éditions du centre de psychologie appliquée.
22. Osterrieth, P. A. Test of copying a complex figure: Contribution to the study of perception and memory. Archives de Psychologie. 1944 ; 30:286–356.
23. Wechsler, D. WAIS-III Echelle d'intelligence de Wechsler pour adultes (3ème ed.). 2000 ; Paris: Les éditions du centre de psychologie appliquée.
24. Army Individual Test Battery. Manual of Directions and Scoring. Washington DC: War Department, Adjutant General's Office.1944.
25. Strauss E, Sherman EMS, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary (3rd ed.). 2006; Oxford University Press, New York.

26. Stroop JR. Studies of interference in serial verbal reaction. Journal of Experimental Psychology. 1935; 18:643–662.
27. Grant DA, Berg E. A behavioral analysis of degree of reinforcement and ease of shifting to new responses in Weigl-type card-sorting problem. Journal of Experimental Psychology. 1948; 38:404–411. https:// doi: 10.1037/h0059831
28. Milner B. Effects of Different Brain Lesions on Card Sorting : The Role of the Frontal Lobes. Arch Neurol. 1963; 9(1):90-100.
29. Cardebat D, Doyon B, Puel M, Goulet P, Joanette Y. Évocation lexicale formelle et sémantique chez des sujets normaux Performances et dynamiques de production en fonction du sexe, de l'âge et du niveau d'étude. Acta Neurol Belg. 1990; 90(4) : 207-217.
30. Oldfield RC.The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia. 1971 ; 9: 97-113. https:// doi: 10.1016/0028-3932(71)90067-4
31. Phuong TH, Houot M, Méré M, Denos M, Samson S, Dupont S. Cognitive impairment in temporal lobe epilepsy: contributions of lesion, localization and lateralization. J Neurol. 2021;268(4):1443-1452. https:// doi: 10.1007/s00415-020-10307-6
32. Jackson RL, Bajada CJ, Rice GE , Cloutman LL, Lambon RMA. An emergent functional parcellation of the temporal cortex. Neuroimage. 2018;170:385-399. https:// doi: 10.1016/j.neuroimage.2017.04.024
33. Cheung MC, Chan AS. Memory impairment in humans after bilateral damage to lateral temporal neocortex. NeuroReport. 2003;14(3):371-4. https:// doi: 10.1097/00001756-200303030-00015
34. Weber P, Ojemann GA. Neuronal recordings in human lateral temporal lobe during verbal paired associates learning. Neuroreport. 1995; 6: 685–689. https:// doi: 10.1097/00001756-199503000-00025
35. Haglund MM, Ojemann GA, Schwartz TW, Lettich E. Neuronal activity in human lateral temporal cortex during serial retrieval from short term verbal memory. J. Neurosci. 1994;14:1507–1515. https:// doi: 10.1523/JNEUROSCI.14-03-01507.1994
36. Ojemann GA, Schoenfield-McNeill J, Corina DP. Anatomic subdivisions in human temporal cortical neuronal activity related to recent verbal memory. Nat Neurosci. 2002;5(1):64-71. https:// doi: 10.1038/nn785
37. Rusnáková S, Chládek J, Jurák P, Halámek J, Daniel P, Rektor I. The executive functions in frontal and in temporal cortices. A flanker task intracerebral recording

study. J Clin Neurophysiol. 2011;28(1):30-5. https:// doi: 10.1097/WNP.0b013e31820512d4

38. Choi YH, Park HK, Paik NJ. Role of the posterior temporal lobe during language tasks: a virtual lesion study using repetitive transcranial magnetic stimulation. Neuroreport. 2015;26(6):314-9. https:// doi: 10.1097/WNR.0000000000000339
39. Vigneau M, Beaucousin V, Hervé PY, Jobard G, Petit L, Crivello F, et al. What is right-hemisphere contribution to phonological, lexico-semantic, and sentence processing? Insights from a meta-analysis. Neuroimage. 2011;54(1):577-93. https:// doi: 10.1016/j.neuroimage.2010.07.036
40. Brazdil M, Zakopcan J, Kuba R, Fanfrdlova Z, Rektor I. Atypical hemispheric language dominance in left temporal lobe epilepsy as a result of the reorganization of language functions. Epilepsy Behav. 2003; 4: 414–9. https:// doi: 10.1016/s1525-5050(03)00119-7
41. Liegeois F, Connelly A, Cross JH, Boyd SG, Gadian DG, Vargha-Khadem F, et al. Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. Brain. 2004; 127: 1229–36. https:// doi: 10.1093/brain/awh159
42. Javed A, Cohen B, Detyniecki K, Hirsch LJ, Legge A, Chen B, et al. Rates and predictors of patient-reported cognitive side effects of antiepileptic drugs: an extended followup. Seizure. 2015;29:34–40. https:// seizure.2015.03.013
43. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. Lancet Neurol. 2012;11: 792–802. https:// doi: 10.1016/S1474-4422(12)70153-9
44. Thompson PJ, Trimble MR. Sodium valproate and cognitive functioning in normal volunteers. Br. J. Clin. Pharmac. 1981; 12: 819-824. https:// doi: 10.1111/j.1365-2125.1981.tb01313.x
45. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D. et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med. 2010; 362: 790–799. https:// doi: 10.1056/NEJMoa0902014
46. Aldenkamp, A. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. Neurology. 2000; 54: 271–272.
47. Ben-Menachem E, Henriksen O, Dam M, Mikkelsen M, Schmidt D, Reid S, et al. Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. Epilepsia. 1996; 37: 539–543. https:// doi: 10.1111/j.1528-1157.1996.tb00606.x

48. Mula M, Trimble M, Thompson P, Sander J. Topiramate and word-finding difficulties in patients with epilepsy. Neurology. 2003; 60: 1104–1107. https:// doi: 10.1212/01.wnl.0000056637.37509.c6
49. Placidi F, Marciani MG, Diomedi M, Scalise A, Pauri F, Giacomini P, et al. Effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions in focal epilepsy. Acta Neurol Scand. 2000; 102: 81–86. https:// doi: 10.1034/j.1600-0404.2000.102002081.x
50. Lee SA, Lee HW, Heo K, Shin DJ, Song HK, Kim OJ, et al. Cognitive and behavioral effects of lamotrigine and carbamazepine monotherapy in patients with newly diagnosed or untreated partial epilepsy. Seizure. 2011; 20: 49–54. https:// doi: 10.1016/j.seizure.2010.10.006
51. Uvebrant P, Bauzienè R. Intractable epilepsy in children. The efficacy of lamotrigine treatment, including non-seizure-related benefits. Neuropediatrics. 1994;25(6):284-9. https:// doi: 10.1055/s-2008-107304
52. Donati F, Gobbi G, Campistol J, Rapatz G, Daehler M, Sturm Y, et al. Effects of oxcarbazepine on cognitive function in children and adolescents with partial seizures. Neurology. 2006; 67: 679–682. https:// doi: 10.1212/01.wnl.0000230138.46508.5b
53. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med. 2014;44 (10):2029-2040. https:// doi: 10.1017/S0033291713002535
54. Halahakoon DC, Lewis G, Roiser JP. Cognitive Impairment and Depression-Cause, Consequence, or Coincidence? JAMA Psychiatry. 2019;76(3):239-240. https:// doi: 10.1001/jamapsychiatry.2018.3631
55. MacKenzie LE, Uher R, Pavlova B. Cognitive performance in first-degree relatives of individuals with vs without major depressive disorder: a meta-analysis. JAMA Psychiatry. 2019;76(3):297-305. https:// doi: 10.1001/jamapsychiatry.2018.3672
56. Scott H, Fraundorf KL, Hourihan RA, Peters BAS. Aging and recognition memory: A meta-analysis. Psychol Bull. 2019; 145: 339–371. https:// doi: 10.1037/bul0000185
57. Samson S, Moncomble C, Méré M, Vasseur R, Dupont S. Getting older with chronic temporal lobe epilepsy: What memory profile? Rev Neurol (Paris). 2020;176:439–443. https:// doi: 10.1016/j.neurol.2020.04.011
58. Selwa LM, Berent S, Giordani B, Henry TR, Buchtel HA, Ross DA. Serial cognitive testing in temporal lobe epilepsy: longitudinal changes with medical and surgical therapies. Epilepsia. 1994; 35:743–9. https:// doi: 10.1111/j.1528-1157.1994.tb02505.x

59. Holmes MD, Dodrill CB, Wilkus RJ, Ojemann LM, Ojemann GA. Is partial epilepsy progressive? Ten-year follow-up of EEG and neuropsychological changes in adults with partial seizures. Epilepsia. 1998; 39:1189–93. https:// doi: 10.1111/j.1528-1157.1998.tb01310.x
60. Shen C, Vasilyeva M, Laski EV. Here, but not there: Cross-national variability of gender effects in arithmetic. J Exp Child Psychol. 2016;146:50-65. https:// doi: 10.1016/j.jecp.2016.01.016
61. Bedard K, Cho I. Early gender test score gaps across OECD countries. Economics of Education Review. 2010; 29, 348–363.

Tables

Table 1 Localisation methodologies

Table 2 Demographical and clinical data comparison between the 3 groups of localization.

Table 3 Pvalues from final Generalized Linear Models with pre selected effects

Table S1(online resource). Pvalues from Generalized Linear Models with neuropsychological scores as dependent variables (in line) and each of the 19 effects and groups of localization as independent variables.

Table 1 Localisation methodologies

localisation methodologies	pure pole	T1-T2	T3-T4
total number	32	19	23
video EEG	32	19	23
MRI lesion	21	14	20
PET	17	5	9
SISCOM	14	7	6
SEEG	11	4	5
language fMRI	5	6	5
memory fMRI	1	0	0
Wada test	2	0	1

MRI=magnetic resonance imaging, PET= positron emission tomography, SISCOM= Subtraction Ictal SPECT Co-registered to MRI, SEEG= stereoelectroencephalography, fMRI = functional MRI

Table 2. Demographic and clinical data comparison between the 3 groups of localization.

	all N=74	Pure pole (a) N=32 (43.24%)	T1-T2 (b) N=19 (25.68%)	T3-T4 (c) N=23 (31.08%)	p ‡
disease duration (*years*)	15.00 [8.00, 20.75]	12.00 [6.75, 18.25]	17.00 [13.00, 22.00]	15.00 [7.50, 21.50]	0.124
age (*years*)	30.00 [25.00, 41.00]	27.50 [24.00, 40.25]	35.00 [26.50, 42.00]	27.00 [25.00, 42.50]	0.683
gender (*female*)	27 (36.49%)	9 (28.12%)	11 (57.89%)	7 (30.43%)	0.089
laterality					1.000
right handed	67 (90.54%)	29 (90.62%)	17 (89.47%)	21 (91.30%)	
left handed	3 (4.05%)	1 (3.12%)	1 (5.26%)	1 (4.35%)	
ambidextrous	4 (5.41%)	2 (6.25%)	1 (5.26%)	1 (4.35%)	
scholar level (*years*)	12.00 [11.00, 14.00]	12.50 [11.00, 14.00]	12.00 [11.50, 14.00]	12.00 [10.00, 16.50]	0.986
focus side (*right*)	38 (51.35%)	13 (40.62%)	13 (68.42%)	12 (52.17%)	0.164
anterior ¥	50 (67.57%)	32 (100.00%) b,c	10 (52.63%) a	8 (34.78%) a	<0.001*
Posterior ¥	31 (41.89%)	0 (0.00%) b,c	13 (68.42%) a	18 (78.26%) a	<0.001*
history of febrile seizures	4 (5.41%)	1 (3.12%)	2 (10.53%)	1 (4.35%)	0.692
history of head trauma	15 (20.27%)	5 (15.62%)	4 (21.05%)	6 (26.09%)	0.659
familial history of epilepsy	8 (10.81%)	1 (3.12%)	3 (15.79%)	4 (17.39%)	0.150
history of depression	11 (14.86%)	5 (15.62%)	2 (10.53%)	4 (17.39%)	0.845
monthly frequency of seizures	7.25 [3.00, 12.00]	8.00 [4.00, 13.50]	7.00 [3.00, 17.38]	5.00 [2.00, 10.00]	0.354
AEDs number	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	3.00 [2.00, 3.00]	0.627
new AEDs only	25 (33.78%)	11 (34.38%)	6 (31.58%)	8 (34.78%)	1.000
lesion type					0.231
DNET	27 (36.49%)	10 (31.25%)	4 (21.05%)	13 (56.52%)	
dysplasia	13 (17.57%)	5 (15.62%)	4 (21.05%)	4 (17.39%)	
no lesion	19 (25.68%)	11 (34.38%)	5 (26.32%)	3 (13.04%)	
others	15 (20.27%)	6 (18.75%)	6 (31.58%)	3 (13.04%)	
SEEG	20 (27.78%)	11 (35.48%)	4 (21.05%)	5 (22.73%)	0.483
surgery	63 (85.14%)	28 (87.50%)	16 (84.21%)	19 (82.61%)	0.924

Notes. Data are given as median [first quartile, third quartile] for continuous variables and as count (percentages) for categorical variables.

‡ Kruskal-Wallis was used to compare groups for continuous variables and Fisher's exact test for categorical variables. Pairwise Mann-Whitney-Wilcoxon tests for continuous variables, and pairwise Fisher's exact tests for categorical variables, both with Benjamini-Hochberg correction were performed for pairwise comparison.

¥ since all pure pole belonged to the anterior category, the statistical analysis was significant to differentiate the 3 gyrus localization groups, some patients could belong to both anterior and posterior groups

Abbreviations: AED = antiepileptic drugs ; DNET = dysembryoplasic neuroepithelial tumor, N= number; SEEG= stereoelectroencephalography (intracerebral presurgicalevaluation).

Table 3 Pvalues from final Generalized Linear Models with pre selected effects

Cognitive domains and scores ((one score may involve several cognitive functions)	group of localisation	age	gender	disease duration	scholar level	history of psychiatric disease	anterior	posterior	lesion type	AEDs number	new AEDs	VPA	CBZ	TPM	LTG	OXCBZ	side
Intellectual function																	
GIQ	0.955	**0.010***			**<0.001***			0.148		0.759		**0.035***					
VIQ	0.458				**<0.001***	0.163		0.059									
PIQ	0.976	**0.006***			**0.001***		0.377	0.964		0.259		**0.006***					
information IQ subtest	0.093				**<0.001***	0.196		0.141									
L-N sequencing IQ subtest	0.978				0.066												
QI.arithmetic	0.218	**0.041***	**0.02***	0.188	**0.001***									**0.005***			
Similarities IQ subtest	0.161	**0.006***			**<0.001***	0.056		**0.035***									
picture completion IQ subtest	0.407	**0.006***					0.107								**0.013***		
Block design IQ subtest	0.338				**0.041***			0.306	0.140	0.335							0.274
coding IQ subtest	0.903		0.068		**0.005***	**0.006***					0.856	**0.012***		0.068	0.285		
Digit span forward	0.865	0.059								0.072							
Digit span backward	0.697																
Verbal learning and memory function																	
Forgetting score for easy word lists ¥	0.401		0.139		**0.043***			0.051									
Forgetting score for difficult word lists ¥	**0.003***	**0.010***							0.098	**0.009***							
Jones-Gotman.learning score (R1-R4)/4	0.118		0.117		**<0.001***											**0.018***	
Jones-Gotman.learning score(R4-R1)	0.083											**0.003***		**0.042***			
Jones-Gotman.forgetting score	0.236				0.071												
Non-verbal memory function																	
RCFT forgetting score	0.694			0.090													
Executive functions																	
WCST.nb_of achieved categories ¥	0.135				**0.005***												
WCST.nb_of cards/nb of achieved categories‡	**0.031***				**0.002***							**0.038***					
WCST.nb of perseverative errors/nb of cards ‡	0.172				**0.012***												

stroop.condition2 ‡	0.429	0.106	**0.035***	0.384			0.210	0.599		0.490		
stroop.interference score ‡	0.590	**0.012***										
TMT.B-A A‡	0.255	0.084		0.152								**0.015***
TMT.B/A‡	0.130			0.059								**0.025***
Language functions												
phonological fluency	**0.014***		**<0.001***		**0.040***	0.108	0.186	0.158	0.503	0.147		
semantic fluency	0.192		**<0.001***				0.606	0.608		**0.038***	0.128	

‡ log transformed variables
¥ GLMs with Bernoulli family and logit link
VPA = sodium valproate, CBZ=carbamazepine, TPM=topiramate, LEV=levetiracetam, BZD=benzodiazepins, LTG=lamotrigine, OXCBZ=oxcarbazepine
GIQ=global IQ, VIQ=verbal IQ, PIQ= performance IQ
RCFT= Rey Complex Figure Test
WCST = Wisconsin Card Sorting Test
TMT= Trail making test
Nb=number

Figures

Figure 1 : Number of patients according to the gyrus localization

Figure 2 : Examples of lesions

Figure 3 : Estimated marginal means and post hoc comparison of group localization, extracted from GLMs. Only scores with significant effect of group localization.