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Emotional asymmetries in refractory medial temporal and frontal lobe epilepsy: Their impact on predicting lateralization and localization of seizures☆

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ABSTRACT

Background: Emotional disturbances have been reported in patients with epilepsy. Although conflicting results emanate from relevant studies, depressive symptoms are seen more often in temporal lobe epilepsy (TLE) whereas, hypomanic/manic symptoms usually accompany frontal lobe epilepsy (FLE); the above psychiatric symptoms are especially seen in refractory epilepsy. However, neocortical TLE and medial TLE are considered as distinct epileptic syndromes, and there is limited literature on comparison of affective traits in medial TLE (MTLE) and FLE.
Aim: In the present study, we sought to investigate affective traits among epilepsy surgery candidates suffering refractory left medial TLE (LMTLE), right medial TLE (RMTLE), left FLE (LFLE), and right FLE (RFLE).
Results: Our results revealed that patients with MTLE scored significantly higher than the ones with FLE in depression, anxiety, asthenia, and melancholia as measured by the Symptoms Rating Scale for Depression and Anxiety (SRSDA), while patients with FLE scored significantly higher in mania than those with MTLE. Moreover, patients with MTLE scored significantly higher than their FLE counterparts on the anxiety scale of the State Trait Personality Inventory (STPI)-trait version. When laterality of the seizure focus was taken into account, no differences were found among both patients with MTLE and patients with FLE, with exception for the Trail Making Test part B (TMT-B) in which patients with RMTLE performed significantly worse than patients with LMTLE. Seizure frequency was higher for FLE.
Conclusions: We provide evidence for an anterior-frontal versus a posterior-medial temporal cerebral functional asymmetry with regard to the manifestation of manic and depressive emotional traits in FLE and MTLE, respectively. Our results are mainly discussed within the frame of their contribution in localizing and to a lesser extent in lateralizing seizures foci in epilepsy surgery candidates. We suggest that this is of great importance in the context of preoperative monitoring of epilepsy surgery, especially when neuropsychologists are called upon to provide anatomical information in defining the *functional deficit zone.*

1. Introduction

Although both frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE) may relate to injury or dysfunction in limbic areas associated with mood regulation, depression is more frequently observed and more strongly associated with TLE than other focal epilepsies [1,2]. The well-known shared structural pathology among medial TLE (MTLE) and depression (e.g., hippocampus, amygdale) may probably account for higher incidence of depression in MTLE than in neocortical TLE and extratemporal epilepsies [3].

Mania and hypomania represent rare psychiatric comorbidities in epilepsy, particularly uncommon, following the advent of modern AED's with their known antimanic effects (e.g., carbamazepine and sodium valproate) [4]. Consequently, only a small number of studies have reported differences between patients with FLE and TLE, with the former presenting more manic and hypomanic symptoms [5] during interictal [6], ictal [7], and postictal [8] periods than the latter. With respect to the epileptogenic zone, electroencephalographic evidence links the temporal lobe to states of postictal mania, hypomania, or seizure-related psychological manifestations equivalent to mania (e.g., [8,9]), as well as the frontal lobe [10], while in few circumstances (two cases) multiple lobes may be involved [8]. Single-photon emission

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computed tomography (SPECT) findings suggest a state of hyperperfusion within the right medial prefrontal, frontal polar, and cingulated cortex, as well as the right lateral prefrontal and frontal opercular areas during postictal mania and hypomania respectively [11].

We herewith focused on the comparison between FLE and exclusively MTLE since neocortical TLE and MTLE are considered as distinct epileptic syndromes [12], encompassing different patterns of cognitive and behavioral disturbances. By considering both previous evidence (e.g., [3]) and theoretical accounts (Davidson's valence theory, *see below*) [13], research insights, and limitations, this study seeks to confirm the possible emergence of affective traits among patients with FLE and MTLE. Although numerous studies have detected emotional disturbances in both FLE and TLE, there are limited reports studying emotion in refractory FLE and MTLE with the aim to provide anatomical data (localization and possibly lateralization of emotional dysfunction) to assist neurologists and neurosurgeons in differential diagnosis, whenever making clinical-topographic decisions for epilepsy surgery candidates.

At a neuropsychological level, the still problematic differentiation between patients with FLE and TLE is probably due to the patients' poor cognitive performance, the variety of seizure etiologies, and the lack of highly specialized neuropsychological measures [14,15]. Reciprocal interacting networks between frontal and temporal regions of the brain may frequently account for the overlapping cognitive deficits in TLE and FLE [5,14]. Thus, including measures of depression and mania could provide some additional information to the treating physician or the neuropsychologist in charge of the presurgical cognitive assessment; a possible explanation for the inclusion of emotional measures in the preoperative neuropsychological monitoring is that, at a neural level, affective dimensions of behavior are less susceptible to reorganization than cognitive ones (e.g., due to early disease onset), [16–18] and thus, might be of help in the interpretation of patients' neurocognitive profile. We think that this is of great importance in presurgical assessment for localizing the epileptogenic zone.

2. Materials and methods

2.1. Participants

Our clinical sample consisted of thirty-four patients with pharmacoresistant epilepsy. Seventeen patients (9 men/8 women) suffered from MTLE (hippocampal sclerosis) and seventeen patients (14 men/3 women) from FLE (cortical dysplasia). All the patients were free of other medical (neurological and/or psychiatric) conditions other than symptoms of depression and/or anxiety and had no history of substance abuse. At the time of neurobehavioral assessment, none of the participants was treated with antidepressant or anxiolytic medication. Patients have been found as pharmacoresistant with respect to the International League Against Epilepsy (ILAE*) definition for drug-resistant epilepsy, i.e., all of them were with partial epilepsy diagnoses and continued to have seizures, for more than three years, despite the adequate and informative treatment with at least five antiepileptic drugs (AEDs). All patients were taking AEDs oxcarbazepine, sodium valproate, carbamazepine, lamotrigine, clobazam, phenytoin, phenobarbital, levetiracetam, topiramate, primidone, pregabalin in monotherapy and combination therapy with respect to rational polytherapy general rules.

Patients with MTLE were taking oxcarbazepine = 8, sodium valproate = 3, carbamazepine = 4, lamotrigine = 1, clobazam = 2, phenytoin = 2, phenobarbital = 0, levetiracetam = 10, topiramate = 8, primidone = 0, and pregabalin = 0, while patients with FLE were taking oxcarbazepine = 1, sodium valproate = 6, carbamazepine = 8, lamotrigine = 2, clobazam = 0, phenytoin = 4, phenobarbital = 4, levetiracetam = 4, topiramate = 3, primidone = 0, and pregabalin = 2.

Furthermore, all patients underwent extensive preoperative interictal and ictal video/electroencephalogram (EEG)–electrocorticogram (ECoG) monitoring. Both patients with MTLE and patients with FLE presented circumscribed brain pathologies (hippocampal sclerosis and cortical dysplasia, respectively) as suggested by high-resolution magnetic resonance imaging (MRI). Patients were diagnosed as suffering from either MTLE or FLE on the grounds of their ictal clinical semiology, EEG, and where necessary video-EEG, while all of them underwent neuroradiological (MRI) and neuropsychological assessment. In particular, patients with FLE were evaluated on the basis of long-term video-EEG ictal recordings or by drawing on their motor clinical semiology (asymmetric tonic posturing as the initial clinical sign) suggesting seizures of the supplementary motor area. The Intracarotid Amobarbital Test (IAT) showed that all patients had left-hemisphere language dominance. Neuropsychological assessment was performed once the blood serum levels of the anticonvulsant drugs were within therapeutic ranges. The local Ethical Committee approved the research protocol and patients provided written consent for their participation in the study. The participants were all candidates for epilepsy surgery and were recruited from the 1st Department of Neurosurgery, Epilepsy Surgery Unit, University of Athens, Evangelismos Hospital. Clinical-demographic, emotional, and cognitive data are reported in Table 1a.

2.2. Materials

The Symptoms Rating Scale for Depression and Anxiety (SRSDA) was used to assess the presence of emotional symptoms. The SRSDA includes the Beck-21 item subscale (BDS I-21) and several other clinical subscales, like the 12-item asthenia subscale, the 12-item melancholia subscale, the 14-item anxiety subscale, and the 5-item mania subscale. Trait version of the State Trait Personality Inventory (STPI) was also administrated to assess anxiety and anger.

A study [19] assessing the reliability, validity, and the psychometric properties of the Greek version of the SRSDA found the following optimal cutoff points: Beck Depression Inventory-21 (BDI-21): 14/15, BDI-13: 7/8, Melancholia: 8/9, Asthenia: 9/10, Anxiety: 10/11.

Cognitive measures consisted of a brief neuropsychological battery assessing cognitive speed (Trial Making part A — TMT-A), divided attention (Trial Making part B — TMT-B) [20,21], verbal fluency (phonemic and semantic) [22,23], response inhibition and resistance to interference (Stroop Neuropsychological Screening Test — STROOP) [24], episodic memory (immediate and delayed recall for semantically organized material) (Rivermead Behavioral Memory Test) [25], concept formation, and executive functions (Wisconsin Card Sorting Test-64 cards version-WCST-64) [26].

2.3. Procedure

Preoperatively psychological assessment took place as a part of the routine neuropsychological examination of our clinic. Consent form was obtained by all participants and debriefing took place at the end of the testing.

2.4. Statistical analysis

Between-group (FLE vs MTLE) differences in demographic and clinical variables, as well as in emotional and cognitive variables were tested using nonparametric Mann–Whitney *U* test. Spearman's rho correlation analysis has been implemented to test possible associations between emotional and cognitive performance parameters. Moreover, to test for possible associations among medication number, the overall medication load (mg/day), and emotional and cognitive parameters, the Spearman's rho correlation analysis has been considered.

3. Results

Patients with MTLE were significantly more depressed than patients with FLE according to BDS I-21 ($p = 0.002$). A score above 10 indicated mild to moderate, above 20 moderate to severe, and above 30 a severe

Table 1a
Subjects characteristics and neurobehavioral performance per epilepsy type (N = 34).

Epilepsy type			
	MTLE (N = 17)	FLE (N = 17)	p-Value
	M ± sd, N(%)		
Age (years)	33.18 ± 10.06	32.15 ± 10.05	mTLE = FLE (p = 0.767)[a]
Sex (men)	9(52.9)	14(82.4)	mTLE = FLE (p = 0.141)[b]
Education	11.82 ± 3.68	12.53 ± 3.22	mTLE = FLE (p = 0.657) [c]
Onset age	15.32 ± 6.11	15.41 ± 8.97	mTLE = FLE (p = 0.836) [c]
Etiology			
HD	17(100)	17(100)	
FCD			
Seizure frequency	15.76 ± 6.94	32.41 ± 9.28	**mTLE < FLE (p = 0.001)** [c*]
Number of AEDs (antiepileptic drugs)	2.18 ± 0.81	2.29 ± 1.05	mTLE = FLE (p = 0.717) [c]
AED overall load (in milligrams/24 h)	3031.76 ± 2221.96	2104.50 ± 1698.29	mTLE = FLE (p = 0.147) [c]
Beck-depression	14.24 ± 8.76	6.06 ± 4.60	**mTLE > FLE (p = 0.002)**[c*]
Beck-anxiety	10.53 ± 4.94	5.00 ± 4.29	**mTLE > FLE (p = 0.003)**[c*]
Beck-mania	−0.65 ± 1.77	1.24 ± 1.52	**mTLE < FLE (p = 0.003)**[c*]
Beck-asthenia	8.35 ± 4.69	4.94 ± 3.15	**mTLE > FLE (p = 0.031)**[c*]
Beck-melancholia	9.65 ± 6.03	4.29 ± 3.41	**mTLE > FLE (p = 0.004)**[c*]
STPI-anxiety	81.65 ± 17.36	57.65 ± 31.76	**mTLE > FLE (p = 0.033)**[c*]
STPI-curiosity	49.88 ± 25.43	53.88 ± 23.30	mTLE = FLE (p = 0.370)[c]
STPI-anger	83.00 ± 19.28	69.24 ± 30.93	mTLE = FLE (p = 0.162)[c]
STPI-depression	75.88 ± 22.56	55.71 ± 25.45	mTLE>FLE (p = 0.018)[c]
STROOP-Interference score	33.47 ± 11.86	35.65 ± 10.00	mTLE = FLE (p = 0.605)[c]
TMA-Trail Making part A	47.45 ± 19.42	37.09 ± 11.89	mTLE = FLE (p = 0.113)[c]
TMB-Trail Making part B	108.29 ± 41.37	116.53 ± 55.77	mTLE = FLE (p = 0.877)[c]
VF-phonemic fluency	40.47 ± 14.65	44.65 ± 14.30	mTLE = FLE (p = 0.361)[c]
VF-semantic fluency	21.29 ± 9.38	17.65 ± 9.65	mTLE = FLE (p = 0.285)[c]
WCST-number of categories completed	2.29 ± 1.10	2.94 ± 1.39	mTLE = FLE (p = 0.114)[c]
RBMT-story Immediate Recall	6.06 ± 3.08	7.59 ± 2.00	mTLE = FLE (p = 0.052)[c]
RBMT-story Delayed Recall	4.74 ± 2.99	5.32 ± 2.02	mTLE = FLE (p = 0.213)[c]

*Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51: 1069–77.
*p < 0.05, ** p < 0.01.

depression (see Table 1b). Similarly, patients with MTLE scored significantly higher than patients with FLE in anxiety (p = 0.003), asthenia (p = 0.031), and melancholia, (p = 0.004) SRSDA subscales. Furthermore, patients with MTLE showed significantly higher levels of anxiety than patients with FLE based on STPI-anxiety (trait), (p = 0.033). In addition, there was a statistically significant difference between MTLE and FLE with the latter group presenting higher levels of mania than the former (p = 0.003). Seizure frequency was found to be higher for patients with FLE than for patients with MTLE (p = 0.001). The subgroup analysis did not reveal any significant gender effects (p > 0.05).

When the side of epileptogenic zone was taken into account, results showed no evidence of lateralized emotional dysfunction. Only one cognitive discrepancy emerged with regard to a worse right MTLE (RMTLE) performance, as to their left MTLE (LMTLE) counterparts, in selective and divided attention, as well as working memory (TMT-B) [20,21] (see Table 2). Finally, there were no significant correlations among medication number, the overall medication load, and emotional and cognitive parameters (see Tables 3 and 4).

In summary, we found that patients with MTLE scored significantly higher than patients with FLE in depression, anxiety, asthenia, and melancholia as measured by the SRSDA, while patients with FLE scored significantly higher in mania than those with MTLE. Patients with MTLE scored significantly higher on the anxiety scale of the STPI-trait version than their FLE counterparts. In terms of laterality, no differences were found between MTLE and FLE, with exception for the TMT-B test in which patients with RMTLE performed significantly worse than patients with LMTLE. Finally, seizure frequency was higher for patients with FLE.

Table 1b
Rating of the Depression-21 scale (implemented in the study) as appears in the classic version of the Beck Depression Inventory (BDI).

Depression		
Mild	Moderate	Severe
10–20	20–30	>30

4. Discussion

Our results show that depressive symptoms are more often encountered in MTLE than in FLE, which is consistent with previous evidence [3]. In the same line are the results for anxiety symptoms. On the other hand, a strong connection has been observed between FLE and symptoms of mania. It has also been seen that patients with RMTLE performed worse than patients with LMTLE in TMT-B, measuring divided attention, as well as working memory. Finally, we found a higher frequency of seizures occurrence in patients with FLE as compared with that in patients with MTLE. Our findings are in agreement with previous behavioral studies [1,3,24,27–34], while under some aspects somewhat different from recent ones [5].

Although it seems reasonable to assume that epilepsy can precede the development of depressive symptoms and disorders [35], recent research has raised concerns suggesting a possible bidirectional link between epilepsy and depression [36,37]. Regarding the incidence of depression as to the site of the seizure focus, research has delivered inconsistent findings. Some studies support a specific relationship between TLE and depression based on theoretical assumptions on their underlying neurobiological mechanisms [3,38]. By converse, no differences in the incidence of depression were found by others [34,39] between patients with temporal and extratemporal epilepsy. In addition, it has been suggested [2,36] that, not only patients with TLE, but also those with FLE may be at greater risk of developing depressive symptoms.

Early surgical literature has shown that structural lesions of the temporolimbic network may prevent patients with TLE to process certain types of information and impact on the consistency with which the appropriate affective tone will be attributed to particular classes of stimuli or events [40,41]. In fact, the incidence of affective

Table 2
Comparison of patients mean scores based on the side of seizure focus (left/right).

Type	MTLE laterality (N = 17) M ± sd, N(%)			FLE laterality (N = 17) M ± sd, N(%)		
	left (N = 9)	right (N = 8)	p-Value	left (N = 4)	right (N = 13)	p-Value
Age (years)	32.33 ± 7.25	34.13 ± 13.02	LMTLE = RMTLE (p = 0.727)[a]	33.75 ± 13.94	31.65 ± 9.22	LFLE = RFLE (p = 0.728)[a]
Sex (men)	6(66.7)	3(33.3)	LMTLE = RMTLE (p = 0.347)[b]	3(21.4)	11(78.6)	LFLE = RFLE (p = 1.000)[b]
Education	11.00 ± 3.28	12.75 ± 4.10	LMTLE = RMTLE (p = 0.167)[c]	14.00 ± 2.31	12.08 ± 3.40	LFLE = RFLE (p = 0.477)[c]
Onset Age	17.06 ± 6.47	13.38 ± 5.40	LMTLE = RMTLE (p = 0.481)[c]	12.00 ± 7.62	16.46 ± 9.37	LFLE = RFLE (p = 0.549)[c]
Seizure frequency	16.78 ± 9.04	14.63 ± 3.74	LMTLE = RMTLE (p = 0.888)[c]	33.25 ± 7.32	32.15 ± 10.06	LFLE = RFLE (p = 0.956)[c]
Number of AED	2.00 ± 0.71	2.38 ± 0.92	LMTLE = RMTLE (p = 0.606)[c]	2.50 ± 1.29	2.23 ± 1.01	LFLE = RFLE (p = 0.945)[c]
AED average load	2922.22 ± 1855.25	3155.00 ± 2705.25	LMTLE = RMTLE (p = 0.743)[c]	2412.50 ± 1535.35	2009.73 ± 1793.01	LFLE = RFLE (p = 0.703)[c]
Beck-depression	15.33 ± 10.15	13.00 ± 7.39	LMTLE = RMTLE (p = 0.541)[c]	6.25 ± 4.65	6.00 ± 4.78	LFLE = RFLE (p = 0.245)[c]
Beck-anxiety	11.00 ± 6.02	10.00 ± 3.70	LMTLE = RMTLE (p = 0.743)[c]	4.25 ± 4.35	5.23 ± 4.42	LFLE = RFLE (p = 0.296)[c]
Beck-mania	−0.33 ± 1.94	−1.00 ± 1.60	LMTLE = RMTLE (p = 0.743)[c]	2.50 ± 2.38	0.85 ± 0.99	LFLE = RFLE (p = 0.163)[c]
Beck-asthenia	8.22 ± 5.33	8.50 ± 4.21	LMTLE = RMTLE (p = 0.743)[c]	3.75 ± 1.89	5.31 ± 3.43	LFLE = RFLE (p = 0.412)[c]
Beck-melancholia	10.22 ± 7.10	9.00 ± 4.96	LMTLE = RMTLE (p = 0.606)[c]	6.75 ± 4.27	3.54 ± 2.88	LFLE = RFLE (p = 0.060)[c]
STPI-anxiety	85.44 ± 10.14	77.38 ± 23.06	LMTLE = RMTLE (p = 0.167)[c]	69.00 ± 39.56	54.15 ± 29.95	LFLE = RFLE (p = 0.202)[c]
STPI-curiosity	51.44 ± 25.71	48.13 ± 26.76	LMTLE = RMTLE (p = 0.236)[c]	69.50 ± 25.11	49.08 ± 21.45	LFLE = RFLE (p = 0.871)[c]
STPI-anger	89.78 ± 11.29	75.38 ± 24.05	LMTLE = RMTLE (p = 0.606)[c]	87.00 ± 18.67	63.77 ± 32.41	LFLE = RFLE (p = 0.785)[c]
STPI-depression	83.89 ± 14.99	66.88 ± 27.04	LMTLE = RMTLE (p = 0.963)[c]	59.00 ± 30.39	54.69 ± 25.06	LFLE = RFLE (p = 0.956)[c]
STROOP-Interference score	31.44 ± 12.99	35.75 ± 10.85	LMTLE = RMTLE (p = 0.185)[c]	36.00 ± 15.94	35.54 ± 8.35	LFLE = RFLE (p = 0.412)[c]
TMA-Trail Making part A	49.08 ± 21.81	45.63 ± 17.64	LMTLE = RMTLE (p = 0.277)[c]	35.75 ± 4.27	37.50 ± 13.54	LFLE = RFLE (p = 0.296)[c]
TMB-Trail Making part B	111.00 ± 40.94	105.25 ± 44.47	**LMTLE > RMTLE(p = 0.027)**[c]*	151.75 ± 84.63	105.69 ± 42.61	LFLE = RFLE (p = 0.624)[c]
VF-phonemic fluency	36.00 ± 12.44	45.50 ± 16.09	LMTLE = RMTLE (p = 0.743)[c]	40.75 ± 18.46	45.85 ± 13.45	LFLE = RFLE (p = 0.412)[c]
VF-semantic fluency	16.22 ± 7.36	27.00 ± 8.30	LMTLE = RMTLE (p = 0.093)[c]	15.25 ± 13.70	18.38 ± 8.65	LFLE = RFLE (p = 0.202)[c]
WCST-number of categories completed	2.11 ± 0.78	2.50 ± 1.41	LMTLE = RMTLE (p = 0.277)[c]	3.50 ± 1.00	2.77 ± 1.48	LFLE = RFLE (p = 0.079)[c]
RBMT-story Immediate Recall	4.78 ± 2.25	7.50 ± 3.38	LMTLE = RMTLE (p = 0.481)[c]	6.75 ± 1.94	7.85 ± 2.02	LFLE = RFLE (p = 0.703)[c]
RBMT-story Delayed Recall	3.56 ± 1.88	6.06 ± 3.55	LMTLE = RMTLE (p = 0.963)[c]	3.63 ± 2.06	5.85 ± 1.76	LFLE = RFLE (p = 0.477)[c]

*p < 0.05, ** p < 0.01.
[a] Independent sample *t*-test.
[b] Chi-square.
[c] Mann–Whitney *U*.

disorders such as depression according to some studies seems to be higher in TLE than in other focal epilepsies [1,27]. This is especially in those with LTLE [27,28] and possibly hippocampal sclerosis [3].

Serotonin (5-hydroxytryptophan, 5-HT) is known to be involved in the pathophysiology of depression [42,43]. Abnormalities of the 5-HT1A receptors in similar regions have also been reported in TLE, while it has been suggested a binding potential reduction over the epileptogenic temporolimbic structures [44,45]. Moreover, patients with TLE with a current or past history of major depression show greater reduction *^{18}F-FCWAY* binding in hippocampus, temporal neocortex, anterior insula, anterior cingulate, and raphe nuclei than patients with TLE with no such history [46].

Although recently Pizzi and associates [5] did not find any differences with regard to depression between TLE and FLE, our study, by comparing patients with MTLE and FLE, found the former group significantly more depressed than the latter. This finding, taken together with previous research [29–33,35], may probably mirror a temporolimbic involvement in the expression of depression.

Aberrant processing of emotional information has been reported in patients with affective disorders such as bipolar disorder and major depression [47]. Moreover, patients with TLE show selective associative learning impairment for emotional facial expressions, while patients with FLE exhibit associative learning problems for both emotional and neutral faces [48]. A possible explanation of the formers' difficulties might be given by their impaired amygdalar function, a critical structure in emotional processing, and/or the pathogenesis of depression.

Our findings of increased depression rates in MTLE are consistent with those of earlier studies [29–33,35], while somewhat different from those recently documented [5]. In terms of lateralization of emotional dysfunction, we were not able to identify any statistically significant difference between LMTLE and RMTLE, probably because of our small sample sizes, nonparametric statistical analysis, and lack of statistical power.

Moreover, patients with MTLE scored higher on anxiety subscale than patients with FLE; there is evidence that the risk of anxiety disorders is higher in focal epilepsy, particularly if there is temporal lobe involvement [49]. Experimental studies support that kindling mechanisms and the recurrent epileptic stimulation of the amygdala may predispose patients with epilepsy to interictal anxiety [50].

Instead, mania elevation in our sample with FLE is consistent with the findings of Pizzi and associates [5], indicating higher rates of mania in FLE than in TLE. Again, we did not identify any difference between our patients with left FLE and patients with right FLE. Patients with damage to structures functionally connected to the obitofrontal cortex, mainly in the right hemisphere are likely to present secondary mania [51]. In patients with bipolar disorder, sustained attention deficits characterizing manic states are associated with distractibility that is typical of mania [52]. Moreover, in these patients' manic phases, impulsivity has been linked to response inhibition problems [53], a problem also seen in FLE [14]. Thus, at a cognitive level of analysis, manic symptoms may reflect sustained attention and response inhibition deficits giving raise to dysexecutive problems and related clinical symptoms (e.g., thought acceleration during manic episodes).

In a study describing frontal lobe dysfunction in children with FLE of early onset, Riva and colleagues [54] found selective frontal lobe impairment, (e.g., problems employing mnemonic strategies and complex motor planning). They [54] also reported that these deficits are not side specific, while low performance on some measures of frontal function correlated positively with age at onset and duration of epilepsy, but not with seizure frequency. On the contrary, in a study of adult patients with FLE, Upton and Thompson [55] reported that seizures' frequency and duration are both variables that may affect cognition. Patients experiencing daily seizures seem to be more impaired than those with monthly seizures. Similarly, duration of epilepsy seems to affect specific aspects of executive functions (e.g., animal fluency) [14].

Table 3
Spearman's rho correlation analysis between emotional and cognitive parameters (N = 34).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	14	16	17
1.Beck-depression		0.829**	−0.716**	0.736**	0.868**	0.530**	−0.022	0.419*	0.592**	−0.449**	0.234	0.236	−0.135	−0.179	−0.275	−0.263	−0.190
2.Beck-anxiety			−0.648**	0.764**	0.713**	0.525**	−0.254	0.472**	0.732**	−0.429*	0.216	0.138	−0.158	−0.140	−0.400*	−0.326	−0.253
3.Beck-mania				−0.704**	−0.707**	−0.372*	−0.011	−0.377*	−0.419*	0.311	−0.119	−0.191	0.037	−0.109	0.348*	0.210	0.155
4.Beck-asthenia					0.670**	0.355*	−0.127	0.373*	0.486**	−0.385*	0.069	0.028	−0.103	−0.012	−0.177	−0.171	−0.099
5.Beck-melancholia						0.657**	0.009	0.565**	0.610**	−0.468**	0.223	0.352*	−0.193	−0.210	−0.171	−0.321	−0.319
6.STPI-anxiety							−0.325	0.586**	0.831**	−0.092	0.081	0.221	0.002	−0.050	−0.093	−0.307	−0.431*
7.STPI-curiosity								−0.122	−0.407*	−0.295	0.109	0.213	−0.023	−0.161	−0.103	−0.175	−0.051
8.STPI-anger									0.609**	0.038	−0.090	−0.009	0.105	0.014	−0.369*	−0.167	−0.267
9.STPI-depression										−0.179	0.098	0.148	−0.060	−0.123	−0.178	−0.297	−0.385*
10.STROOP-Interference score											−0.371*	−0.524**	0.512**	0.564**	0.041	0.375*	0.250
11.TMA-Trail Making part B												0.634**	−0.487**	−0.116	−0.065	−0.115	−0.215
12.TMB-Trail Making part A													−0.530**	−0.493**	0.042	−0.158	−0.324
13.VF-phonemic fluency														0.642**	−0.022	0.316	0.397*
14.VF-semantic fluency															0.050	0.326	0.333
15.WCST-number of categories completed																0.086	0.080
16.RBMT-story Immediate Recall																	0.815**
17.RBMT-story Delayed Recall																	

* $p < 0.05$.
** $p < 0.01$.

Considering the dominant role of the frontal lobes, particularly the right, in the control and regulation of arousal, it is expected that injuries on this side may result in a loss of control over arousal. When damaged, the right frontal lobe seems to produce activational disturbances including mania, since it appears to exert bilateral influences on cerebral activation and inhibition. Although men suffering right frontal lesions are probably more likely to develop mania than women, the latter may be similarly affected, particularly if both frontal lobes and the orbital areas have been damaged. [56]; this latter may have impacted lateralization dynamics of emotional performance in the group with FLE. Note that gender effects as well as those of other variables (e.g., side of seizure onset) may remain silent (undetected) because of the implementation of nonparametric analysis (small samples size) in this study, while future studies should target larger clinical samples by applying more sophisticated statistical analyses to make possible effects emerge.

Early research (Bever 1983, in [57]) on sex differences in functional brain asymmetries reports that adult men and women have different asymmetries, though the classical literature does not clarify on which sex is more lateralized for what. It thus provides a nebulous account about the basis of the behavioral effects on manifest asymmetries of variables as sex and familial handedness. A possible explanation could be that different sexes approach problems differently, which is then reflected in different patterns of manifest laterality. Recent neuroimaging evidence [58] on the effects of gender and age on structural brain asymmetry pointed out that brain asymmetry increases in the anterior–posterior direction starting from the central region onward. Male brains were found to be more asymmetric than female, with gender-related effects being most significantly noticeable in the superior temporal gyrus, Heschl's gyrus, and the adjacent white matter regions in the temporal stem and the knee of the optic radiation, the thalamus, and the posterior cingulate.

Spearman's rho correlation analysis among number of AED, AED overall load, and emotional and cognitive parameters yield no statistical significant associations (see Table 4).

Mental health issues in epilepsy are likely to reflect a multifactorial etiology, with AED effects being only one among many contributing factors. Seizure control/forced normalization in psychosis and GABAergic effects in depression represent two mechanisms through which medication may lead to psychopathology [59].

The occurrence of depressive symptoms is more likely to be associated with the intake of barbiturates, vigabatrin and topiramate, than other AEDs (>10%), and even more so in patients presenting susceptibility (personal or family history of depression). Approximately 7% of treated with high doses of zonisamide seem to develop mood disorders, though evidence is as yet scarce. Monotherapy with slow titration schedules can significantly reduce the incidence of mood disorders in most of cases. Tiagabine, levetiracetam, and felbamate are thought to be intermediate risk medications, since the prevalence of depression is of about 4% or lower. Instead, a low risk for depression (<1%) has been found for phenytoin, ethosuximide, carbamazepine, oxcarbazepine, gabapentin, sodium valproate, pregabalin, and lamotrigine, while several other AEDs are likely to even promote mood [60].

4.1. Implications

Preoperative assessment of affective traits is necessary in patients with refractory epilepsy; depending on mood assessment outcomes, we may possibly provide prognostic information in terms of postoperative depression status prediction, as well as postoperative seizure outcomes. Seizure-free patients usually have lower BDS I-21 scores preoperatively, as well as postoperatively, than patients, who continue having seizure after surgery. The preoperative BDS I-21 score seems to be a significant predictor of postoperative seizure frequency, as well as seizure freedom [61]. However, apart from the above implications,

Table 4
Spearman's rho correlation analysis among number of AED, AED overall load, and emotional and cognitive parameters (N = 34).

	Number of AEDs[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1.AED overall load (in milligrams/24 h)	0.563**																	
2.Seizure frequency	−0.122	−0.312																
3.Beck-depression	0.218	0.284	−0.517**															
4.Beck-anxiety	0.131	0.165	−0.376*	0.829**														
5.Beck-mania	−0.260	−0.252	0.444**	−0.716**	−0.648**													
6.Beck-asthenia	0.174	0.076	−0.216	0.736**	0.764**	−0.704**												
7.Beck-melancholia	0.312	0.294	−0.441**	0.868**	0.713**	−0.707**	0.670**											
8.STPI-anxiety	0.234	0.216	−0.271	0.530**	0.525**	−0.372*	0.355*	0.657**										
9.STPI-curiosity	0.032	0.041	−0.190	−0.022	−0.254	−0.011	−0.127	0.009	−0.325									
10.STPI-anger	0.074	0.213	−0.186	0.419*	0.472**	−0.377*	0.373*	0.565**	0.586**	−0.122								
11.STPI-depression	0.045	0.132	−0.243	0.592**	0.732**	−0.419*	0.486**	0.610**	0.831**	−0.407*	0.609**							
12.STROOP-Interference score	−0.238	−0.116	0.143	−0.449**	−0.429*	0.311	−0.385*	−0.468**	−0.092	−0.295	0.038	−0.179						
13.TMA-Trail Making part B	0.100	−0.076	−0.375*	0.234	0.216	−0.119	0.069	0.223	0.081	0.109	−0.090	0.098	−0.371*					
14.TMB-Trail Making part A	0.027	−0.109	−0.117	0.236	0.138	−0.191	0.028	0.352*	0.221	0.213	−0.009	0.148	−0.524**	0.634**				
15.VF-phonemic fluency	0.089	0.034	−0.008	−0.135	−0.158	0.037	−0.103	−0.193	0.002	−0.023	0.105	−0.060	0.512**	−0.487**	−0.530**			
16.VF-semantic fluency	0.034	−0.082	−0.161	−0.179	−0.140	−0.109	−0.012	−0.210	−0.050	−0.161	0.014	−0.123	0.564**	−0.116	−0.493**	0.642**		
17.WCST-number of categories completed	−0.068	−0.314	0.369*	−0.275	−0.400*	0.348*	−0.177	−0.171	−0.093	−0.103	−0.369*	−0.178	0.041	−0.065	0.042	−0.022	0.050	
18.RBMT-story Immediate Recall	−0.106	−0.265	0.024	−0.190	−0.253	0.155	−0.099	−0.319	−0.431*	−0.051	−0.267	−0.385*	0.250	−0.215	−0.324	0.397*	0.333	0.080

[a] AEDs = antiepileptic drugs.
* $p < 0.05$.
** $p < 0.01$.

preoperative affective assessment may be valuable in a step before surgery: in localizing seizure focus.

Some of the standard techniques used in defining the epileptogenic zone are those of functional MRI (fMRI), neuropsychological assessment, conventional EEG, intracranial-EEG recording, and Wada test. The inherent nature of epilepsy as well as the complex interplay among epidemiologic, clinical, developmental, and neurobehavioral factors under many instances may render seizures localization and lateralization problematic. In such cases, we believe that the inclusion of emotional measures, along with other techniques, in the preoperative assessment protocol (*scales of depression, anxiety, and mania*) may be of aid to epileptologists and neurosurgeons, to make a decision on where to operate.

A famous traditional cortical centered theory (*among other frontal asymmetry models*) in the domain of affective and social neuroscience is the *valence model* for behavioral expression of emotion, suggesting a frontal asymmetrical representation of emotions. In 1978, Davidson published a paper bearing on the rapport between emotional experience and differentiation of patterns of asymmetrical frontal brain organization (*for a review see* [62]). Davidson provided for the first time EEG evidence on the role of the left and right prefrontal cortex (PFC) in the processing positive and negative motions, respectively. This theory views fear, anger, disgust and sadness as negative emotions, and happiness and surprise as positive ones [63], and along with the approach/withdrawal hypotheses have received strong support from many studies in the last decades [64]. Davidson's "frontal lateralization model" has been extensively investigated and offered insights to the development of alternative theories of frontal lateralization (*for a review see* [62]).

Although our results on left to right emotional asymmetries did not reach statistical significance, because of small samples sizes, they show a pattern of anterior-frontal (manic) to posterior-medial temporal (depressive) brain asymmetry. This latter is consistent with previous evidence suggesting functional rapports between depression and mania, and medial temporal (mostly left) and frontal (mostly right) lobes respectively (see above); in this case, a possible source of bias may be represented by the well-known effects of seizure propagation from medial temporal to frontal territories and vice versa (e.g., [65,66]), thus affecting both emotional and cognitive performance. In particular, Lieb and associates showed that medial temporal seizures spread to the ipsilateral frontal lobes [67].

We are therefore tempted to indulge in speculation that beyond the predicted frontal emotional asymmetry (valence model), patients' emotional performance may be further represented along a frontal to medial temporal dimension. Future research should further develop and confirm these preliminary findings by considering wider and more balanced samples with respect to gender and side of seizure onset.

A limiting factor of our study is the small size of both patient samples with FLE and MTLE, since it poses a limit as to what kind of sophisticated analyses can be done. Thus, it is meaningless to run dozens of correlational analyses or multivariate analyses controlling for x factors, as significant results for confounders are very unlikely considering the power restrictions**.** Consequently, we were not able to analyze neither the differential contribution of a multifaceted intrahemispheric lesion site nor the effect of seizures onset hemispheric side in terms of their emotional impact. Consequently, the small sample and subsamples size prevented us from discovering possible effects in support to the valence model *(attributing to the two hemispheres different processing modalities, with the right and left hemispheres, the frontal areas in particular, subserving negative and positive emotional processing, respectively)* [13,63], which formed part of our initial working hypothesis on emotional asymmetries.

Another limitation of the present study is the lack of a sufficient number of female patients in our samples, particularly in FLE. It is well-known however, that symptomatic localization-related epilepsy appears to be more frequent among men than women, possibly

reflecting differences in risk or structural damage to the brain and subsequent seizures [68].

Our preliminary results might be further supported by future studies with larger samples of patients with FLE and patients with MTLE and more balanced as to the sex variable, to enable researchers perform parametric analysis and consequently provide a more detailed account for possible interactions among clinical variables and emotional dimensions. It is possible that future studies with larger sample sizes and subgroups matched for gender will provide evidence of a further left to right asymmetry (*as predicted by the valence model*), and hopefully of an additional frontal to medial temporal one, as suggested by our preliminary data.

5. Conclusions

Mood assessment should be included in the routine neuropsychological assessment of epilepsy surgery candidates, since there is evidence that depressive and manic symptoms, as measured by the SRSDA, may be of topical-localizing and hopefully lateralizing value. Our findings are consistent with an anterior-frontal to posterior-medial temporal asymmetry of emotional performance, suggesting that, in addition to neuropsychological measures, SRSDA depressive and manic symptoms in FLE and MTLE respectively may provide clinical hints when interpreting patients' preoperative neurocognitive profiles. Consequently, we suggest that assessing emotional along with cognitive dimensions may be of help in the context of preoperative monitoring of epilepsy surgery, especially when neuropsychologists are called upon to provide anatomical information in defining the *functional deficit zone*.

Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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