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Two distinct symptom-based phenotypes of depression in epilepsy yield specific clinical and etiological insights

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ABSTRACT

Depression is common but underdiagnosed in epilepsy. A quarter of patients meet criteria for a depressive disorder, yet few receive active treatment. We hypothesize that the presentation of depression is less recognizable in epilepsy because the symptoms are heterogeneous and often incorrectly attributed to the secondary effects of seizures or medication. Extending the ILAE's new phenomenological approach to classification of the epilepsies to include psychiatric comorbidity, we use data-driven profiling of the symptoms of depression to perform a preliminary investigation of whether there is a distinctive symptom-based phenotype of depression in epilepsy that could facilitate its recognition in the neurology clinic. The psychiatric and neuropsychological functioning of 91 patients with focal epilepsy was compared with that of 77 healthy controls (N = 168). Cluster analysis of current depressive symptoms identified three clusters: one comprising nondepressed patients and two symptom-based phenotypes of depression. The 'Cognitive' phenotype (base rate = 17%) was characterized by symptoms taking the form of self-critical cognitions and dysphoria and was accompanied by pervasive memory deficits. The 'Somatic' phenotype (7%) was characterized by vegetative depressive symptoms and anhedonia and was accompanied by greater anxiety. It is hoped that identification of the features of these two phenotypes will ultimately facilitate improved detection and diagnosis of depression in patients with epilepsy and thereby lead to appropriate and timely treatment, to the benefit of patient wellbeing and the potential efficacy of treatment of the seizure disorder.

This article is part of a Special Issue entitled "The new approach to classification: Rethinking cognition and behavior in epilepsy".

1. Introduction

Depressed mood is the most prominent psychiatric feature of epilepsy [1], with patients 43% more likely to develop unipolar depression than their healthy peers [2]. The stakes surrounding depression in epilepsy, moreover, are high. Not only does it diminish quality of life more so than seizure-related factors [3–5], suicide is also three times more frequent in individuals with epilepsy relative to demographically matched healthy controls [6]. Despite the high rate and impact of depression recognized in clinical research studies, in the busy outpatient clinic, depression in epilepsy quite often goes undiagnosed and is frequently not treated [7,8].

The new approach to classification proposed by the International League Against Epilepsy (ILAE) recognizes the significance of psychiatric comorbidities in epilepsy and positions them as a central consideration in clinical care (see Kanner, this Special Issue [9]). A phenomenological approach is advocated, whereby comorbidities are described according to their behavioral features and grouped into homogenous phenotypes, which has the benefit of being readily applied to clinical practice as well as flexibly updated as our knowledge grows [10]. In the pursuit of uncovering mechanisms for depression in epilepsy, phenotypes also have the presumed benefit of each having distinct etiologies, with the symptom profile giving clues as to what neurobiological systems might be implicated [11]. The explicit reconceptualization of epilepsy as a disease of brain networks by the ILAE [10] raises the possibility that depressive symptoms may stem from the same diseased networks that propagate seizures, with phenotypes providing proximal makers of the distinct brain networks implicated [12].

Abbreviations: AMI, Autobiographical Memory Interview; ESI-55, Epilepsy Surgery Inventory — 55 Items; FACES-IV, Family Adaptability and Cohesion Scale — Fourth Edition; FSIQ, Full-Scale Intelligence Quotient; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition; ILAE, International League Against Epilepsy; NDDI-E, Neurological Disorders Depression Inventory — Epilepsy; PHQ-GAD-7, Patient Health Questionnaire — Generalized Anxiety Disorder — 7 Items; SCID, Structured Clinical Interview for DSM-IV Axis I Diagnoses; WMS-IV, Wechsler Memory Scale — Fourth Edition.

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The current study sought to demonstrate the kinds of clinical and etiological insights that can be gained from extending the new classification approach to psychiatric comorbidity in epilepsy. Data-driven statistical methods were used to define symptom-based phenotypes of depression in patients with focal epilepsy, in order to identify whether there are phenotypes that may expedite the identification of depression in the epilepsy clinic, as well as provide more proximal markers of the underlying network disease. Given the numerous links between mood and memory in the primary depression literature [13] and the high prevalence of memory disorders in people with epilepsy [14,15], it was hypothesized that a predominant phenotype of depression in epilepsy would be characterized by cognitive symptoms and prominent psychometric memory impairments. A final point is as follows: given the relatively small sizes of certain subgroups, these data are preliminary and were designed to illustrate the potential insights to be gained from these new methodologies, as well as to encourage other investigators to replicate and extend the findings.

2. Methods and materials

2.1. Participants

The patient cohort (n = 91) was recruited while undergoing inpatient characterization of focal seizures in the Comprehensive Epilepsy Program of Austin Health, Melbourne between 2010 and 2015 [16]. Inclusion criteria for all participants were the following: (1) aged 18–70, (2) an FSIQ ≥ 70, (3) neurosurgically naïve, and (4) functionally understand English. A consecutive sampling methodology was employed, whereby all individuals who met the preestablished inclusion/exclusion criteria were actively recruited to the study, with all participants who consented to participate included. Of the 91 patients, 76% were diagnosed as having seizures arising from the temporal lobe (46% left hemisphere, 60% lesion-positive) and 24% from extratemporal regions (32% left hemisphere, 73% lesion-positive). Epileptological and demographic features of the patients are summarized in Table 1.

A group of 77 healthy individuals with no neurological or psychiatric history was recruited from the patients' families and broader community to provide a sociodemographically matched control sample (N = 168). Patients and controls were tested separately and asked not to discuss their participation in order to avoid cross-contamination. Participants with epilepsy did not differ from controls in sex, age, or years of education ($P > 0.050$; see Table 1). Controls had a slightly higher mean Full-Scale IQ (FSIQ) than the patients [$t_{(151)} = 2.516$, $P = 0.013$, $\eta^2 = 0.040$, small effect size]; however, mean scores for both groups fell within the 'Average' range (i.e., 90–110). Patients with a comorbid psychiatric diagnosis other than affective disorder (e.g., postictal psychosis) were excluded. The study had approval from the relevant Human Research Ethics Committees, and all participants provided written, informed consent.

Table 1
Demographic and clinical profile of the sample (N = 168).

	Patients with epilepsy (n = 91)	Healthy controls (n = 77)
Age (years), M ± SD	40.850 ± 12.602	45.550 ± 15.749
Range	20–69	21–69
Sex, female (%)	53 (58%)	48 (62%)
Education (years), M ± SD	13.571 ± 3.263	13.974 ± 3.259
Range	5–24	9–21
Full-Scale IQ, M ± SD	101.850 ± 11.327[a]	106.880 ± 12.031[b*]
Range	72–132	71–132
Age of seizure onset (years), M ± SD	22.078 ± 13.520	
Range	1.5–63	
Duration of epilepsy (years), M ± SD	19.150 ± 12.859	
Range	2–52	
Monthly seizure frequency, M ± SD	22.680 ± 52.166	
Range	1–400	
≤1/month	21 (23%)	
Fortnightly (2–3/month)	14 (15%)	
Weekly (4–15/month)	36 (40%)	
More days than not (≥16/month)	20 (22%)	
Side of epilepsy focus		
Left	38 (42%)	
Right	44 (48%)	
Bilateral/unclear	9 (10%)	
Lobar focus		
Temporal	68 (75%)	
Frontal	10 (11%)	
Parietal	6 (7%)	
Other[c]	7 (8%)	
Lesion-positive (%)	58 (64%)	
Antiepileptic drug polytherapy (%)	70 (77%)	
Number of antiepileptic drugs, M ± SD	2.24 ± 0.993	
Range	1–6	

[a] Four cases of missing data.
[b] Eight cases of missing data.
[c] 'Other' comprises four cases with foci localized to the posterior quadrant and three cases with anterior quadrant foci.
* $P < 0.050$.

2.2. Materials

2.2.1. Neuropsychiatric evaluation

In-depth neuropsychiatric evaluation of the patient sample was undertaken using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), the gold standard measure for diagnosing current and past mood disturbance according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition (DSM-IV) [17]. Of particular value, the SCID includes close questioning around atypical symptoms of depression and allows for the diagnosis of minor and unorthodox manifestations of the disorder that some researchers in the field consider to be of special interest to epilepsy. Moreover, patients were carefully questioned about depressive symptoms to ensure that they could not be attributed to changes in antiepileptic medication.

The Neurological Disorders Depression Inventory — Epilepsy (NDDI-E) [18] was administered as a linear self-report measure of current depressive symptoms. Its six items canvass symptoms that do not overlap with commonly comorbid cognitive deficits in epilepsy or the adverse effects of antiepileptic drugs, with each item endorsed on a scale of 1 = never to 4 = always/often. The minimum score is six (no symptoms), and the maximum is 28. Scores for NDDI-E > 15 have been shown to have 90% specificity, 81% sensitivity, and a positive predictive value of 0.62 for a diagnosis of major depression.

The Patient Health Questionnaire — Generalized Anxiety Disorder — 7 Items (PHQ-GAD-7) was developed to assess the severity of current anxiety symptoms in medical populations [19]. Participants assign scores of 0–3 to the response categories of 'not at all', 'several days', 'more than half the days', and 'nearly every day', respectively. Total scores for PHQ-GAD-7 for the seven items range from 0 to 21; scores of 5, 10, and 15 represent cutoffs for mild, moderate, and severe anxiety, respectively.

2.2.2. Psychosocial function and health-related quality of life

The Epilepsy Surgery Inventory — 55 Items (ESI-55) [20] was employed as a measure of health-related quality of life in the patient group. It is reliable and valid and has been used widely in this population.

The Family Adaptability and Cohesion Scale — Fourth Edition (FACES-IV) [21] is a self-assessment of family functioning. It comprises 84 items across six scales, including two that measure healthy dynamics and four 'unbalanced' scales designed to tap low and high cohesion (disengaged and enmeshed) and flexibility (rigid and chaotic). Participants respond on a six-point Likert scale.

2.2.3. Formal neuropsychological assessment

The semistructured Autobiographical Memory Interview (AMI) [22] was used to assess personal memories from childhood, early adulthood,

and recent life. The Personal Semantic Schedule requires participants to recall personally relevant facts (e.g., former addresses); each of the three timepoints is scored out of 21 (maximum = 63), with a score ≤47 associated with an amnestic syndrome and scores of 48–49 indicative of a probable amnestic syndrome. The Autobiographical Incident Schedule asks participants to recall three episodes from each time period (e.g., a wedding). Episodic memories are scored from 0 to 3 (maximum = 27) based on their richness in detail and how precisely the incident is located in place and time, with a total score ≤12 associated with an amnestic syndrome and scores of 13–15 indicative of a probable amnestic syndrome. Interrater reliability (r) lies between 0.83 and 0.86, with good sensitivity to organic disease.

Neuropsychological evaluation of broader memory functioning was assessed using the Wechsler Memory Scale — Fourth Edition (WMS-IV) [23]. Specifically, auditory–verbal memory was assessed with immediate and delayed recall indices of the Verbal Paired Associates subtest, and visual learning was assessed using the immediate and delayed recall indices of the Design Memory subtest. All subtests were scored according to age-scaled normative data (M = 10; SD = 3), with scaled scores ≤8 considered indicative of impairment.

2.3. Statistical analyses

Analyses were performed using IBM SPSS Statistics (version 22.0), with statistical significance set at $P < 0.050$ (two-tailed). Where data did not meet assumptions for parametric analyses, more conservative alternatives were employed. Given the difference in FSIQ between patients and controls, scatterplots and Pearson product–moment correlations were used to assess the relationships between memory indices and FSIQ. No significant relationships were identified, negating the need to covary for FSIQ in subsequent analyses.

Initial comparison of the demographic, neuropsychological, and psychiatric functioning of the patient cohort with that of the controls was undertaken using chi-squared analyses with Fisher's exact test for categorical variables, independent-sample t-tests for continuous variables, and one-sample t-tests for comparing patient performances on WMS-IV with normative data.

To identify phenotypes of depression in epilepsy, cluster analysis was used to classify patients into groups with shared symptom profiles. Cluster analysis is standard methodology for clinical phenotyping as opposed to (for example) factor analysis, which is more strictly suitable in describing the latent structure of a behavioral measure [24]. The nine binary items describing DSM-IV depressive symptoms on the SCID were selected as the indicator variables, within the '10 cases for every variable' criteria recommended for cluster analysis [24]. Hierarchical cluster analysis using Ward's method was run, with squared Euclidian distances as the similarity measure. Each cluster represents a homogeneous group of patients who share similar responses to the model parameters (i.e., SCID symptoms).

To identify demographic, clinical, psychological, and psychosocial covariates associated with cluster membership, we ran bivariate descriptive analyses comparing the depressive phenotypes or, where power was low, inspected frequency trends across groups. For cognitive measures, performances on the AMI and WMS-IV subscales were converted into z-scores relative to normal performances from healthy controls for ease of comparison.

3. Results

3.1. Elevated rates of psychopathology and disturbed cognition in people with epilepsy

Psychiatric evaluation revealed that 36 patients with epilepsy (40%) met criteria for a lifetime history of Depressive Disorder, and 21 (23%) currently met criteria for a Major Depressive Episode or Depressive Disorder Not Otherwise Specified. This is appreciably higher than the global point prevalence for primary Depressive Disorder of 4.7% (4.4–5.0%) in the general population [25]. Consistent with this, patients with epilepsy endorsed substantially more depressive and anxiety symptoms (NDDI-E: $t_{(151)} = 4.487$, $P < 0.001$, $d = 0.719$, medium–large effect size; PHQ-GAD-7: $t_{(143)} = 2.624$, $P = 0.010$, $d = 0.430$, small–medium effect size; see Fig. 1).

Patients also performed worse on all measures of semantic and episodic autobiographic memory (Total, Personal Semantic Schedule: $t_{(147)} = -4.276$, $P < 0.001$, $d = 0.714$, medium–large effect size; Total, Autobiographical Incident Schedule: $t_{(147)} = -6.276$, $P < 0.001$, $d = 1.057$, large effect size) as well as auditory–verbal and visual forms of immediate and delayed recall (Verbal Paired Associates — I: $t_{(70)} = -2.541$, $P = 0.013$; Verbal Paired Associates — II: $t_{(70)} = -3.625$, $P = 0.001$; Design — I: $t_{(72)} = -2.926$, $P = 0.005$; Design — II: $t_{(71)} = -3.160$, $P = 0.002$).

3.2. Two phenotypes of depression in epilepsy

Cluster analysis identified three groups of patients with epilepsy. The largest cluster (n = 70) comprised patients who did not currently meet criteria for depression — a cluster we named 'nondepressed patients'. More interestingly, two distinct phenotypes of depressive symptoms were identified in the 21 currently depressed patients with epilepsy (see Fig. 2 for the dendrogram). We labeled the first, more common cluster 'Cognitive Depression' (n = 15; 71%), as patients endorsed higher rates of cognitive depressive symptoms such as parasuicidal or suicidal thoughts, feelings of worthlessness, and delusions of guilt. They were also more likely to experience dysphoric mood compared with patients in the other cluster and endorsed low rates of somatic symptoms and anhedonia (see Table 2). The base rate of Cognitive Depression in this sample of patients with focal epilepsy was 17%.

We labeled the second, less common cluster 'Somatic Depression' (n = 6; 29%), as these patients were significantly more likely than the group with Cognitive Depression to feel anhedonic and to endorse higher rates of biological symptoms such as appetite change and sleep disturbance. They were also less likely to endorse cognitive symptoms ($P > 0.050$; see Table 2). In the current study, the base rate of Somatic Depression in patients with chronic focal epilepsy was 7%. Both phenotypes endorsed similarly high rates of excessive fatigue and subjective cognitive difficulties ($P > 0.050$), such as difficulties concentrating and indecisiveness.

In terms of clinical epilepsy features, individuals with the Cognitive phenotype were more likely than nondepressed patients to have a left-lateralized seizure focus [$X^2_{(1)} = 4.448$, $P = 0.034$, $\varphi = -0.240$; small–medium effect size]. Neither phenotype differed from nondepressed patients on any other epileptological variables or in anticonvulsant or psychotropic pharmacotherapy ($P > 0.05$ for all comparisons; see Table 3). Between the two depression phenotypes, patients with the Somatic form had more seizures than the Cognitive phenotype (17.5 versus 4 per month on average) and greater variability in their seizure frequency. The two phenotypes were comparable in terms of seizure localization and lateralization.

3.3. Cognitive profiles of the phenotypes of depression

The Cognitive phenotype of depression was characterized by poor memory function (see Supplementary Table A and Fig. 3). Relative to healthy controls, patients with Cognitive Depression exhibited significantly reduced semantic and episodic autobiographic memory across all life periods, including significantly worse overall semantic and episodic recollection. They also showed significantly reduced delayed recall across auditory–verbal ($P = 0.032$) and visual domains ($P = 0.002$) on the WMS-IV subtests, in the context of intact immediate learning ($P > 0.050$). Patients with Somatic Depression showed a more muted and restricted profile of reduced memory, with poorer performances

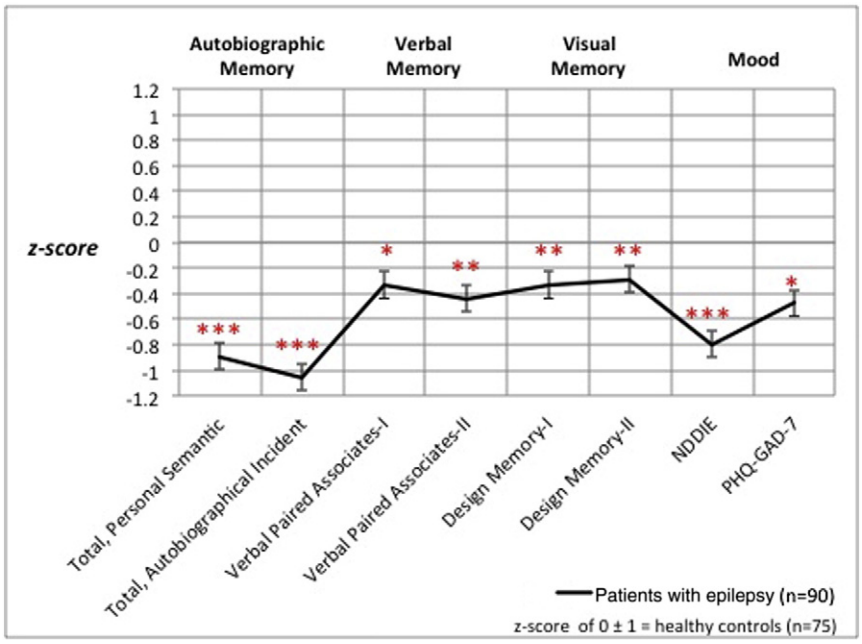


Fig. 1. Patient scores on cognitive and psychological measures converted into z-scores using healthy controls (n = 77) as a baseline of normal task performance, i.e., z-score = 0 ± 1. Scores below zero represent impairments relative to controls, meaning that, in the current study, patients performed worse across all measures of memory and mood functioning. Error bars represent the standard error from the mean. * = P < 0.050, ** = P < 0.010, ***P < 0.001.

than controls on childhood episodic, early adulthood semantic, overall episodic, and delayed visual recall (see Fig. 1). The FSIQ was comparable (P > 0.050; Cognitive Depression = 98.710 ± 9.450; Somatic Depression = 97.750 ± 9.179).

Odds ratio analysis suggested that, compared with patients with Somatic Depression, depressed patients with the Cognitive phenotype were (i) 3.640 times more likely to have a semantic autobiographic memory deficit (i.e., AMI subscale score < 50; 95% CI = 0.162–81.705), (ii) 2.286 times more likely to have an episodic autobiographic memory deficit (i.e., AMI subscale score < 16; 95% CI = 0.316–16.512), (iii) 2.250 times more likely to have significantly impaired immediate verbal learning (i.e., WMS-IV score ≤ 8; 95% CI = 0.252–20.131), (iv) 6.000 times more likely to have significantly impaired delayed verbal recall (95% CI = 0.478–75.347), (v) 5.133 times more likely to have significantly impaired immediate visual learning (95% CI = 0.218–121.108), and (vi) 6.000 times more likely to have significantly impaired delayed visual recall (95% CI = 0.478–75.347).

3.4. Psychosocial and demographic features of the phenotypes of depression

In addition to their distinct cognitive profiles, the Cognitive and Somatic phenotypes had specific demographic, clinical, and psychological features (see Fig. 4). Demographically, inspection of group trends suggested that depressed patients with the Somatic phenotype were more likely to be female (83%) than those with the Cognitive phenotype (47%; see Table 3). The two phenotypes were otherwise comparable in terms of age and relationship status (P > 0.05 for both comparisons).

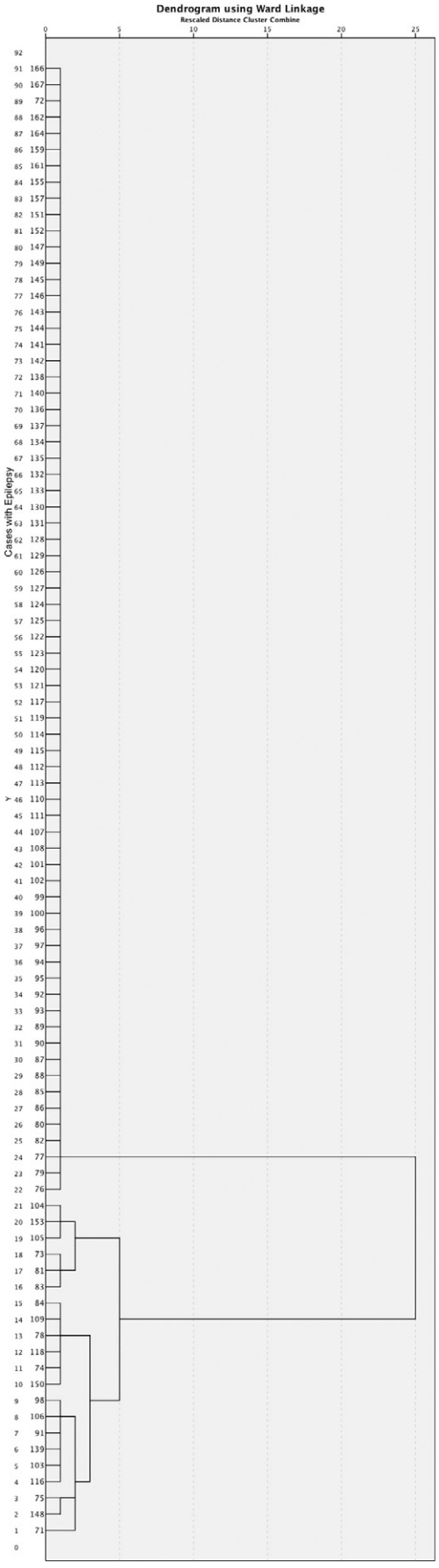
Psychologically, inspection of group trends suggested that the two phenotypes reported a similar level of depressive symptoms on the NDDI-E. However, individuals with the Somatic phenotype reported lower levels of family satisfaction than patients with the Cognitive phenotype and endorsed higher symptoms of anxiety. In contrast, patients with the Cognitive phenotype reported slightly lower epilepsy-related quality of life (see Supplementary Table A). Only five patients with Cognitive Depression (33%) were being actively treated with psychotropic medication; however, their symptoms were better recognized than those with the Somatic Depression phenotype, none of whom were being treated. This is broadly consistent with a recent study showing that only 29.7% of depressed patients with epilepsy were receiving psychological or psychotropic treatment [26].

4. Discussion

By extending the ILAE's new phenomenological approach to classification to psychiatric comorbidity in epilepsy, this pilot study uncovered two clinically distinct, symptom-based phenotypes of depression in focal epilepsy. The first, which we called Cognitive Depression, was more frequent and characterized by cognitive symptoms of depression, dysphoria, and prominent memory deficits. The second, termed Somatic Depression, was typified by vegetative features, anhedonia, elevated anxiety, female gender, onset of frequent seizures as an adult, and unsatisfactory family dynamics. Subjective cognitive difficulties and xcessive fatigue were common to both phenotypes.

4.1. Cognitive and Somatic phenotypes of depression in other populations

This delineation of Cognitive and Somatic phenotypes supports the longstanding observation that depression in epilepsy is not a homogenous condition with a canonical presentation. While some psychiatrists have felt that depression in epilepsy has a heterogeneous presentation not well-captured by hegemonic psychiatric criteria [27], there has been scant quantitative evidence to either prove or disprove this. Symptom clusters with predominantly somatic or cognitive features are also found in psychiatric outpatients, community samples, and medical cohorts with coronary disease [28–32]. The ubiquity of the Somatic and Cognitive phenotypes illustrates that, while the clinical presentation of depression is heterogeneous, it is not random. Unique to this cohort of focal epilepsy, however, is the finding that the Somatic phenotype was far less common. This is the inverse to what is seen in psychiatric populations [29] and may contribute to the low rate of recognition and diagnosis of depression in epilepsy. Given the higher frequency of the Cognitive phenotype in this preliminary investigation (base rate of 17%), it could be argued that the etiology of depression in epilepsy is more strongly linked to dysfunction in distinct cognition-related networks than is typical of primary depression. Supporting this, there is a predominance of nonsomatic depressive symptoms in



patients who have suffered a stroke [33], potentially pointing to common mechanisms underlying depression across neurological diseases that can selectively impact large-scale cognitive brain networks.

4.2. Phenotypes and their underlying brain networks

Psychiatry has long used phenotyping of presenting symptoms to systematically classify mental disorders, to validate observational diagnoses and, more recently, to infer their neurobiological mechanisms [11]. In the current study, Cognitive and Somatic phenotypes of depression likely provide differential markers of brain network dysregulation. Epilepsy seems to have a predilection for the networks that regulate mood and cognition. There is a growing belief that a fundamental neurological feature of epilepsy is hypersynchronous engagement of large-scale cognitive networks, leading to the cognitive deficits commonly seen in patients, as well as in relatives without seizures [34]. This is consistent with EEG–fMRI evidence that cognition-related networks can be coactivated during epileptogenic discharges [35] and, over time, alter their functioning and connectivity [36].

Recent research shows that symptoms of primary unipolar depression also arise from failed regulation of large-scale cognition-related brain networks, with different depressive symptoms reflecting different network substrates [37]. In the psychiatric literature, the distorted self-related cognitive processing and memory disturbance that were common to our Cognitive phenotype have been shown to reflect dysregulation of the cognitive control network (CCN) and autobiographic memory network (AMN), two networks that neuroimaging suggests function abnormally in focal epilepsy [38,39]. In brief, the CCN is important for goal-directed behavior and includes the dorsolateral prefrontal cortex (PFC), dorsal anterior cingulate cortex, and parietal regions. The AMN is anticorrelated to the CCN and is considered central to self-reflection through personal life memories, comprising the orbitomesial PFC and mesial temporal and posterior cingulate cortices, as well as the precuneus [40]. In unipolar depression, the AMN becomes chronically hyperactivated, leading to pathological introspective brooding and rumination. It also suppresses the CCN, leading to diminished performances on goal-directed tasks, rigid thinking, and distorted information processing [37]. This behavioral profile is entirely consistent with the presentation of the Cognitive phenotype described here and may implicate similarly altered regulation of the CCN and AMN in people with depression and epilepsy.

In contrast, the Somatic profile of depression in epilepsy appears to index dysregulation of networks that support emotional processing and visceral monitoring, such as the affective network (AN) and the salience network (SN) [41,42]. The physiology of these networks overlaps in part with both the AMN and CCN and includes the subgenual and pregenual cingulate cortices, orbitofrontal PFC, and connected regions of the amygdala, entorhinal cortex, hypothalamus, anterior insula, and nucleus accumbens. These corticosubcortical regions support appetite, libido, sleep, reward processing, and vigilance, disturbance to which underpins the vegetative and anhedonic symptoms of depression that are predominant in the Somatic phenotype [40,41]. Although speculative, the link between the Somatic profile and more frequent seizures may suggest involvement of the piriform cortex, which is both exquisitely epileptogenic and a key region in hedonic processing [43].

To date, symptom diversity has likely hindered the progress of research into the causal mechanisms and treatment of patients with both depression and epilepsy. The current findings highlight that

Fig. 2. Dendrogram produced by hierarchical cluster analysis of the nine DSM-IV symptoms of depression using Ward linkage, showing a clear three-cluster solution. The topmost cluster comprises nondepressed patients (cases 22–91), while the middle of the three clusters represents Somatic Depression (cases 16–21), and the bottom cluster represents Cognitive Depression (cases 1–15).

Table 2
Two phenotypes of depression in epilepsy.

DSM-IV symptoms of depression		**Depression subtype**		Sig.	X^2	Effect size (ϕ)[a]
		Cognitive n = 15	**Somatic n = 6**			
Affective symptoms	Dysphoria	**93%**	50%	^	5.219	0.499
	Anhedonia	13%	**83%**	**	9.450	0.671
Somatic symptoms	Appetite changes	27%	**100%**	**	9.240	0.663
	Sleep changes	13%	**83%**	**	9.450	0.671
	Psychomotor agitation	13%	**33%**		1.112	0.230
	Fatigue	60%	67%		0.081	0.062
Cognitive symptoms	Worthlessness and guilt	**93%**	50%	^	5.219	0.499
	Subjective cognitive difficulties	87%	100%		0.884	0.205
	Suicidality	**67%**	33%		0.304	0.304

^P = 0.053 (trend); **P < 0.010; X^2 degrees of freedom = 1.
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition; Sig. = significance level.
The defining symptomatic features of each phenotype are in bold.
[a] Measure of effect size where 0.1 is considered a small effect, 0.3 a medium effect, and 0.5 a large effect.

Table 3
Demographic, clinical epilepsy, and psychosocial profile of depression phenotypes in epilepsy, relative to nondepressed patients.

	Cognitive Depression n = 15	Somatic Depression n = 6	Nondepressed n = 70
Age (years), M ± SD	38.47 ± 11.76	34.33 ± 7.53	41.91 ± 12.995
Range	23–57	27–42	20–69
Sex, female (%)	7 (47%)	5 (83%)	41 (59%)
Relationship status, single (%)	6 (40%)	3 (50%)	21 (30%)
Full-Scale IQ, M ± SD	98.71 ± 9.45	97.75 ± 9.18	102.72 ± 11.733
Range	92–113	84–103	72–132
Age of seizure onset (years), M ± SD	20.73 ± 11.56	21.25 ± 14.40	22.442 ± 13.996
Range	8–41	9–37	2–63
Childhood/adolescent onset (n, %)	8 (53%)	2 (33%)	36 (51%)
Adult onset (n, %)	7 (47%)	4 (67%)	34 (49%)
Duration of epilepsy (years), M ± SD	17.53 ± 10.5	12.92 ± 13.29	20.04 ± 13.257
Range	6–41	2–18	3–52
Average monthly seizure frequency, median	4	17.5	7
Range	1–75	1–200	1–400
Lobar focus, temporal (%)	11 (73%)	4 (67%)	53 (76%)
Side of epilepsy focus			
Left (%)	10 (67%)	3 (50%)	25 (36%)
Right (%)	4 (27%)	3 (50%)	37 (53%)
Bilateral/unclear (%)	1 (7%)	0	8 (11%)
Number of AEDs, M ± SD	2.46 ± 0.990	2.20 ± 1.862	2.19 ± 0.906
Range	1–4	1–6	1–4
No. of patients prescribed with different AEDs (%)			
Levetiracetam	8 (53%)	3 (50%)	38 (54%)
Topiramate	7 (47%)	2 (33%)	12 (17%)
Carbamazepine	6 (40%)	3 (50%)	29 (41%)
Lamotrigine	5 (33%)	2 (33%)	18 (26%)
Sodium valproate	3 (20%)	0	16 (23%)
Lacosamide	3 (20%)	0	14 (20%)
Oxcarbazepine	2 (13%)	0	3 (4%)
Clobazam	1 (7%)	1 (17%)	2 (6%)
Phenytoin	0	1 (17%)	5 (7%)
Clonazepam	0	1 (17%)	9 (13%)
Midazolam (prn)	0	1 (17%)	0
Phenobarbital	0	0	1 (1%)
Zonisamide	0	0	2 (3%)
Vigabatrin	1 (7%)	0	0
Pregabalin	0	0	2 (3%)
Gabapentin	1 (7%)	0	0
Diagnosis of depression (%)			
Major Depressive Disorder	6 (40%)	4 (66.7%)	
Dysthymic Disorder	4 (27%)	0	
Minor Depressive Disorder	5 (33%)	2 (33%)	
Psychotropic medication, yes (%)	5 (33%)	0	10 (14%)
NDDI-E score, M ± SD	15.92 ± 2.91	14.25 ± 4.99	11.97 ± 3.196
Range	12–20	9–19	6–20
PHQ-GAD-7 score, M ± SD	8.83 ± 5.73	11 ± 5.72	4.65 ± 4.106
Range	1–18	6–19	0–17
ESI-55 overall QOL, M ± SD	45.00 ± 13.37	53.00 ± 16.14	63.639 ± 14.727
Range	25–75	50–77.5	27.50–100.00
FACES-IV family satisfaction, M ± SD	59.29 ± 22.11	38.80 ± 27.85	61.17 ± 28.833
Range	13–92	10–71	10–99

AED = antiepileptic drug; ESI-55 = Epilepsy Surgery Inventory — 55 Items; FACES-IV = Family Adaptability and Cohesion Scale — Fourth Edition; NDDI-E = Neurological Disorders Depression Inventory — Epilepsy; PHQ-GAD-7 = Patient Health Questionnaire — Generalized Anxiety Disorder — 7 Items.

phenotypes may provide more precise, individualized insights into the neurobiological underpinnings of depression in epilepsy, whereby different phenotypes have different etiologies. The role of different neurocognitive and affective brain networks should therefore be directly investigated using task-based neuroimaging paradigms in patients with different phenotypes of depressive disorder relative to euthymic patients and controls. Confirmation of the role of different networks in different syndromes could give more nuanced insights into what anatomical, neurochemical, and functional systems should be targeted by pharmacotherapy or psychotherapy. For instance, dampening of CCN activation in unipolar depression has been shown to dysregulate the mesostriatal dopamine system [44], potentially providing insights into region-specific neurotransmitter systems that may be targeted in the development of future medical treatments.

4.3. Clinical implications

Despite increasing recognition of the significant impact of depression in epilepsy, the paucity of currently depressed patients receiving medical treatment (only 33% here and ~30% in other studies) [26] indicates that its management requires a shift in thinking among clinicians. Recognition of symptom subtypes constitutes such a shift that might improve diagnosis and treatment. For instance, the Somatic phenotype is characterized by symptoms that overlap with the side effects of seizures and antiepileptic drug use, potentially leading to an incorrect attribution of depressive symptoms such as sleep disturbance and weight gain to medical effects. Recognition that the features of depression in epilepsy may mimic the cognitive or vegetative correlates of seizures and antiepileptic medications could serve as a prompt for more detailed questioning, particularly around the emergence of cardinal diagnostic symptoms such as anhedonia and dysphoria.

The ubiquity of subjective memory complaints across the two phenotypes of depression may also hold immediate clinical utility. Rather than indexing objective cognitive ability, this characteristic feature may be better viewed as a sensitive marker of mood disturbance in epilepsy. This is commensurate with strong evidence that bitter memory complaints offered by people with epilepsy commonly reflect depression and anxiety, with formal neuropsychological assessment able to help differentiate between psychological and neurocognitive underpinnings and inform treatment decisions [45,46]. Moreover, the lack of a proconvulsant effect of newer generation antidepressant medications should reassure clinicians of their safety for use in people with epilepsy [47].

Correct classification of psychopathology remains a key goal, so that clinical features that reliably cluster together can be used to precisely predict the prognosis and treatment response of individuals [11,28]. In other populations, patients with different phenotypes of depression may be at

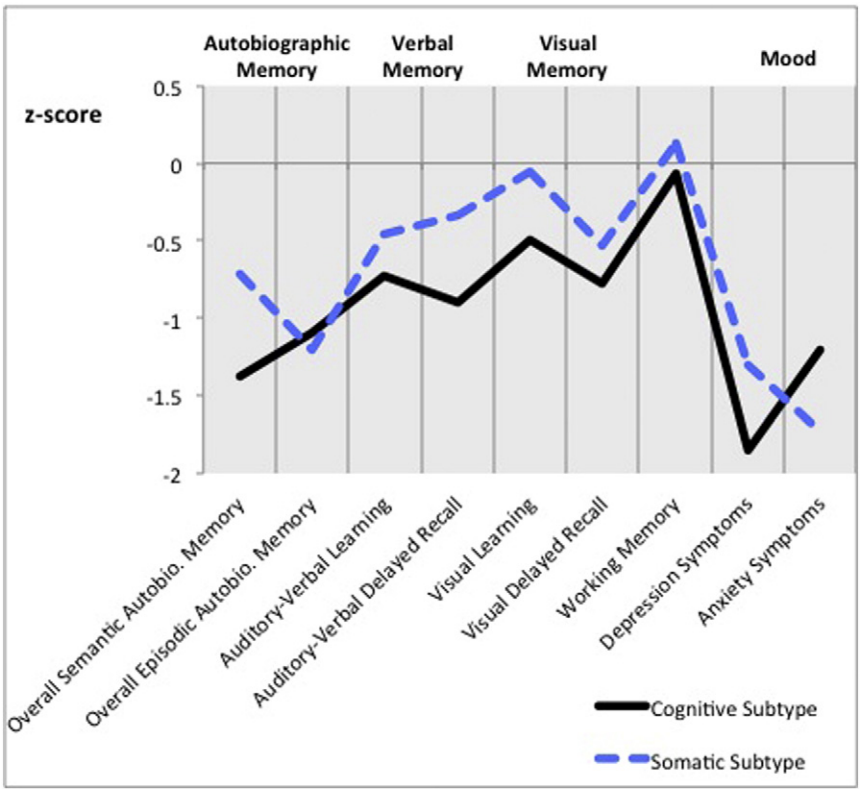


Fig. 3. Reduced neuropsychological functioning of the two depression phenotypes relative to a baseline of normal task performance provided by the control group (z-score = 0 ± 1). Patients with the Cognitive phenotype perform worse than those with the Somatic phenotype across the majority of memory measures. Patients with the Somatic phenotype endorsed increased symptoms of anxiety.

risk of different long-term health outcomes. In particular, somatic forms are considered cardiotoxic [30–32] and have been strongly linked to poor outcome after psychotropic treatment (N = 811) [48], suggesting that Somatic Depression may require more aggressive treatment. A priority for future investigation should be replication of these phenotypes in other populations with epilepsy (e.g., community-based) as well as exploration of the negative health outcomes associated with each of the phenotypes of depression in epilepsy. This encompasses neurological outcomes such as seizure intractability, suitability for certain medications, and the likelihood of seizure freedom after epilepsy surgery, as well as neuropsychological outcomes such as cognitive decline or vulnerability to other psychiatric illnesses (see Kanner, this Special Issue [9]). Also important is whether appropriate and timely treatment of depression can be protective against cognitive decline or worsening seizures. This approach would allow complications and impairments to be anticipated and proactively treated in an early stage of the disease and in a more targeted

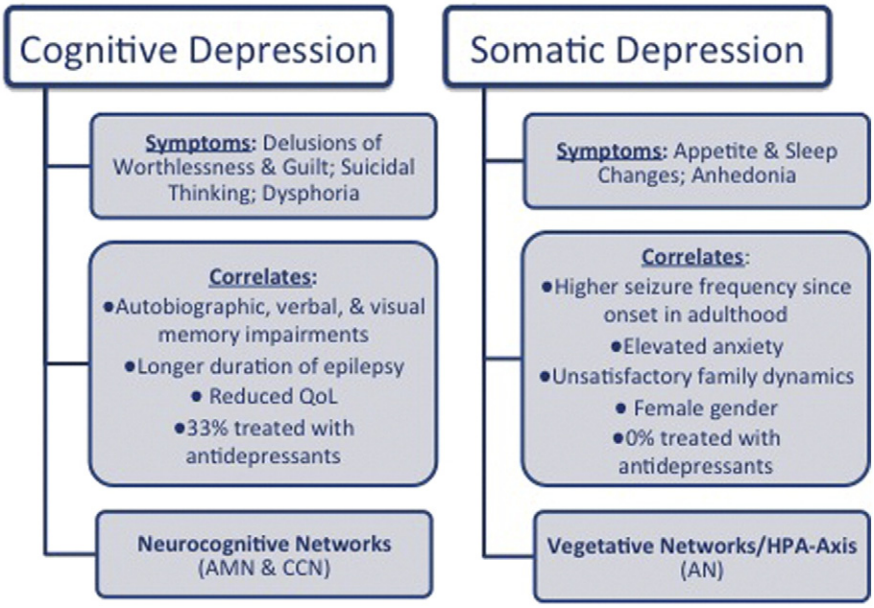


Fig. 4. Symptom profiles of the two phenotypes of depression in epilepsy, together with their psychosocial and cognitive correlates and putative underlying networks. AMN = autobiographic memory network; AN = affective network; CCN = cognitive control network.

manner. Inherent in this idea is that behavioral phenotypes and their outcomes are not immutable; rather, the clinical picture can be changed through active intervention.

4.4. Potential of phenotyping to yield fresh classification insights

The validity of the phenotypes described herein will ultimately be confirmed or disproven through the identification of specific biological markers at the network, cellular, or genetic level [49]. For instance, a recent paper by Busch et al. [50] noted that genetic anomalies underlie many epilepsy syndromes with phenotypic patterns of cognitive impairment, which will likely be polygenetic. Using neuropsychological profiling enriches our understanding of differing epilepsy syndromes by linking observable patterns of cognitive or behavioral impairment to underlying genetic or structural–metabolic abnormalities. This is consistent with the ILAE's aim to make epilepsy classification flexible and easy to update as new knowledge comes to light.

4.5. Conclusions

Critical to the treatment of patients with depression and epilepsy is the accurate and early diagnosis of the comorbidity. The significance of the current pilot study is the delineation of distinct phenotypes that are seen in other populations, including the finding unique to this cohort that the Somatic phenotype was less common. In addition to highlighting the utility of the ILAE's new descriptive approach to psychiatric comorbidity, we would hope that, in the immediate future, this typology can be replicated and will improve the recognition and management of depression in the busy neurology clinic. Looking forward, it is anticipated that meaningful phenotypes will provide clearer insights into the pathogenesis of depression in epilepsy and, ultimately, guide the development of individually tailored treatments.

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Conflict of interest

None to disclose.

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