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Frontal lobe dysfunction as a predictor of depression and anxiety following temporal lobe epilepsy surgery

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ABSTRACT

Objective: Predictors of psychiatric outcome following TLE surgery have proved elusive and represent a current challenge in the practice of TLE surgery. This prospective study investigated whether frontal lobe dysfunction is *predictive* of poorer psychiatric outcomes.

Methods: Forty-nine unilateral TLE surgical patients were assessed using the Beck Depression Inventory–Fast Screen (BDI-FS) and Beck Anxiety Inventory (BAI) preoperatively and 6 and 12 months postoperatively. Measures of intellectual function, semantic knowledge, memory and executive function were completed preoperatively, at 6 and 12 months following surgery.

Results: Preoperatively, 33 (67%) patients had minimal depressive symptoms, 8 (16%) were mildly depressed, 2 (4%) were moderately depressed, and 6 (12%) reported severe depressive morbidity. Twenty-three (47%) patients reported minimal anxiety, 18 (37%) were mildly anxious, 6 (12%) were moderately anxious and 2 (4%) patients reported severe anxiety symptoms. A mixed-model repeated-measures analysis was performed on the BDI-FS and BAI scores, adjusting for pertinent covariates identified in univariable analyses. At a year following TLE surgery, anxiety symptoms significantly improved but depressive morbidity did not. Indicators of frontal lobe dysfunction moderated the *magnitude* and *direction* of mood change. Specifically, pre-surgical cognitive measures of frontal lobe dysfunction predicted increased depression and anxiety symptoms following surgery. There was no relationship between preoperative BDI-FS or BAI scores and seizure outcome at 12 months or change in affective morbidity and seizure outcome.

Significance: This is the first longitudinal study to provide evidence that specific pre-surgical *cognitive* and *behavioural* indices of frontal dysfunction are predictive of poorer psychiatric outcome following TLE surgery. In addition, our findings highlight the potential utility of a dysexecutive behavioural rating scale (DEX) as an assessment tool in epilepsy. Examination of executive functioning in pre-surgical evaluations may lead to an increase in the power of prognostic models used to predict the psychiatric outcome of TLE surgery.

1. Introduction

Neurosurgery for refractory temporal lobe epilepsy (TLE) is an effective treatment with a 60–70% chance of seizure freedom (Engel, 1996). For many surgical patients, relief from intractable seizures affords long-term psychosocial gains (Mikati et al., 2006) and an enhanced quality of life, compared to patients who are medically treated (Wiebe, 2010). Following TLE surgery, however, anxiety and depression can worsen or develop for the first time (de novo), even in patients rendered seizure free (Cleary et al., 2012). The reported prevalence of de novo affective morbidity is highly variable owing to divergent methodologies and diagnostic classifications, with estimates ranging between 3% and 26% (Cleary et al., 2013).

The pathogenic mechanisms and identification of surgical candidates at risk of affective morbidity represent a current challenge in the practice of TLE surgery. Neurobiological factors (Halley et al., 2010; Iranzo-Tatay et al., 2017; Mathon et al., 2017; Pope et al., 2014; Salzberg et al., 2006; Wrench et al., 2009), psychosocial factors (Wilson et al., 2004) and preoperative psychiatric status (Cleary et al., 2013; Devinsky et al., 2005; Filho et al., 2012; Iranzo-Tatay et al., 2017;

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Malmgren et al., 2002; Mathon et al., 2017; Quigg et al., 2003; Wrench et al., 2011) have been proposed to account for affective morbidity following TLE surgery. Investigation of heterogeneous samples, limited information regarding preoperative psychiatric status, short-term follow-up, and the application of diverse diagnostic criteria and/or inappropriate application of statistical methods impedes firm conclusions being drawn.

Although it is well documented that temporal and extra-temporal cognitive function may be compromised in TLE (Bell et al., 2011; Stretton et al., 2012) and associated with interictal psychopathology (Corcoran and Upton, 1993; Dulay et al., 2004; Helmstaedter et al., 2004; Hermann et al., 1991; Paradiso et al., 2001; Wishart et al., 2017), few studies have directly investigated whether frontal dysfunction is *predictive* of poorer psychiatric outcomes following surgery. This is of interest given evidence that structural (Halley et al., 2010; Pope et al., 2014; Wrench et al., 2009) and functional (Salzberg et al., 2006) imaging abnormalities extending beyond the epileptogenic temporal lobe may have a role in the development postoperative psychopathology.

We previously reported that executive skills weakness did not predict those at increased risk of developing a de novo psychiatric diagnosis (Cleary et al., 2012). This earlier study was retrospective in nature and the executive skills data available was limited. Furthermore, as we employed a clinical diagnosis of pre- and postoperative psychiatric symptoms derived from patient medical notes, we were not able to investigate whether psychiatric *change* following TLE surgery, which may have been sub-diagnostic, was related to preoperative executive dysfunction.

The aim of this longitudinal study was to use multilevel modelling (MLM) to explore predictor(s) of psychiatric (depression and anxiety) outcome following TLE surgery. Specifically:

1 To examine whether TLE patients with evidence of frontal lobe dysfunction are at increased risk of depression or anxiety postoperatively.
2 To determine whether preoperative depressed mood is predictive of poor psychiatric, and/or seizure outcome.

2. Methods

2.1. Study sample

We studied 49 patients with medically intractable TLE. There were 25 with right TLE (20 females); median age 42 years, range 17–68 years and 24 with left TLE (10 females); median age 38 years, range 18–62 years. Apart from two patients, all were on poly-therapy and had tried an average of three AEDs prior to surgery. All patients underwent surgery from September 2009 to December 2012 at the National Hospital for Neurology and Neurosurgery, London. Forty-six (n = 46/49; 94%) underwent a standard anterior temporal lobe resection (ATLR), while 3 (n = 3/49; 6%) underwent lesionectomies (1 = right; 2 = left). Clinical characteristics are summarised in Table 1.

Table 1
Clinical Characteristics of the TLE surgical cohort.

Number	49
Epilepsy:	
Age of onset :mean (SD)	15 years (11 years)
Duration: mean(SD)	23 years (14 years)
Predisposing factors N:(%):	
Febrile convulsions	16 (33%)
Head trauma	7 (8%)
CNS infections	3 (6%)
Family history of epilepsy	11 (22%)
Seizures:	
Secondarily generalised N:(%)	18 (37%)
CPSs/month (median; range)	8 (1-40)
SGTCs/month (median; range)	1 (0-3)
History of status (N:%)	4 (8%)
Anti-epileptic medication: N(%)	
monotherapy	2 (4%)
poly-therapy	47 (96%)
MRI findings N(%)	
normal	6 (12%)
hippocampal sclerosis	29 (59%)
focal cortical dysplasia	2 (4%)
cavernomas	3 (6%)
DNETs	9 (18%)
other	7 (14%)
dual pathology	7 (14%)
hippocampal volumes: mean(SD)	
ipsilateral	2.2 (0.6)
contralateral	2.7 (0.44)
Video-telemetry findings N(%)	
concordant ictal EEG	29 (59%)
concordant interictal EEG	36 (74%)

All patients had a detailed pre-surgical evaluation including 3 T structural MRI with qualitative assessment and quantification of hippocampal volumes and T_2 relaxation times and prolonged interictal and ictal video-EEG monitoring.

All patients were routinely assessed by a neuropsychiatrist (JF) as part of their presurgical evaluation. Psychiatric diagnoses were made following a clinical interview, and written documentation of psychiatric treatment was recorded. Details of past psychiatric history and family history of psychiatric illness were documented. The psychiatric diagnoses were categorised according to Diagnostic and Statistical Manual of Mental disorders, Fourth Edition, Text Revision (DSM IV-TR) Axis I diagnoses, namely mood and anxiety disorders. The presence of postictal psychoses (PIP), interictal psychosis and nonepileptic seizures (NES) was also recorded. Patients completed mood and behavioural rating scales pre-operatively (within 6 months prior to surgery) and at 6 and 12 months postoperatively. These were administered at the same time intervals as the cognitive tests.

The study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee. Written informed consent was obtained from all subjects.

2.2. Psychiatric rating scales

2.2.1. Beck Depression Inventory – Fast Screen (BDI-FS)

This scale measures seven items derived from the 21-item Beck Depression Inventory-II (Beck et al., 1996) pertaining to sadness, pessimism, personal failures, perceived decreases in self confidence, self-criticalness, loss of pleasure (anhedonism) and suicidal ideation. Somatic items are excluded to increase specificity for medical patients. Items are rated for the past two weeks on a four-point likert scale from 0 (not present) to 3 (severe), yielding scores ranging from 0 to 21. Recommend cut-off scores are 0–3 (minimal symptoms); 4–6 (mild symptoms); 7–9 (moderate symptoms); 10–21 (severe symptoms).

2.2.2. Beck anxiety inventory

This scale measures 21 symptoms associated with anxiety (Beck et al., 1988). Symptoms for the past week are rated on a four-point likert scale ranging from 0 (not present) to 3 (severe). Scores range from 0-63. Recommended cut-offs are 0–7 (minimal anxiety); 8–15 (mild anxiety); 16–25 (moderate anxiety); 26–63 (severe anxiety).

2.3. Cognitive and behavioural measures

2.3.1. Intellectual function

Wechsler Adult Intelligence Scale-III (WAIS-III) and the National Adult Reading Test (NART) were used as measures of current intellectual status and intellectual potential respectively (Bright et al., 2002; McGurn et al., 2004). A discrepancy between the NART predicted IQ and the current IQ provides a measure of intellectual decline, and an indicator of extra-temporal cerebral disturbance.

2.3.2. Semantic knowledge

Two measures assessing semantic knowledge were employed. A Category fluency test which required participants to name as many exemplars from the category 'animals' in 60 s and the Graded Naming Test (McKenna and Warrington, 1980) which assessed naming capacity by requiring participants to name 30 black and white drawings arranged in a hierarchy of difficulty.

2.3.3. Memory

Episodic memory was assessed using the List- and Design- Learning subtests from the BIRT Memory and Information Processing Battery (BMIPB) (Coughlan et al., 2007). These tests have been previously described and have been reported to be sensitive to temporal lobe pathology and temporal lobe surgery (Baxendale and Thompson, 2010). For this investigation raw test scores were converted into Z-scores.

2.3.4. Executive functions

i The Spatial Working Memory (SWM) subtest from the Cambridge Automated Test Battery (CANTAB) (Sahakian and Owen, 1992) was chosen as it has been shown to be sensitive to frontal lobe pathology Owen et al., 1996). This self-paced computerised test measures executive function (search strategy) and the updating and monitoring of spatial information in working memory (WM). The subject has to remember the location of previously found 'tokens' while searching for new tokens at different levels of difficulty. The 'between errors' and 'search strategy' performance indices were selected for subsequent statistical analyses as previous research has shown them to be sensitive to neurocognitive dysfunction in patients with primary depressive disorder (Porter et al., 2003). This test has previously been well described (Flugel et al., 2006).

ii Wisconsin Card Sorting Task – This is an established measure of cognitive flexibility and responsiveness to feedback. We employed a shortened version that is routinely used as a clinical tool in our service (Nelson, 1976). Participants are required to sort cards according to a given criterion (colour, shape or number). Whatever category is first chosen by the subject is scored correct and after six consecutive correct responses the sorting rule is changed. After each card is sorted, the tester provides feedback as to whether the response is correct. The test continued until six categories have been achieved or all the 48 stimulus cards have been sorted. Two scores were calculated: the number of categories completed (maximum 6) and the number of perseveration errors (i.e. the number of cards classified on the basis of a previous sorting criterion). The latter was used in statistical analyses as an indicator of executive dysfunction; with higher perseveration scores indicating poor set-shifting ability.

iii Trail Making Test also measures set-shifting capacity. In part A the subject connects a series of 25 encircled numbers in numerical order. In part B, the subject connects 25 encircled numbers and letters in numerical and alphabetical order, alternating between numbers and letters (Bowie and Harvey, 2006). The performance indicator was the time taken to complete part B, which tests higher level cognitive skills such as mental flexibility, and the ability to modify a plan of action or to maintain two trains of thought simultaneously. (Arbuthnott and Frank, 2000; Crowe, 1998).

iv The Digit Span subtest from the WAIS-III was used as a measure of verbal working memory.

v Phonemic fluency: Patients were required to name as many words beginning with "S" in a 60 s epoch. Research has demonstrated this task is highly sensitive and specific to frontal lobe damage (Robinson et al., 2012) with structural and functional imaging showing that frontal lobe pathology disproportionately impairs phonemic fluency, while temporal lobe damage has a greater effect on semantic fluency (Bird et al., 2004).

vi Dysexecutive Questionnaire is a 20-item questionnaire constructed to sample a range of 'everyday' symptoms of dysexecutive (or 'frontal lobe') syndrome (Burgess et al., 1998). The DEX assesses a number of characteristics, including abstract thinking problems, impulsivity, confabulation, planning problems, euphoria, lack of insight, apathy disinhibition, distractability, knowledge-response dissociation, lack of concern, and disregard for social rules. Each item was scored on a 5-point Likert scale, ranging from 'never' to 'very often', with a high score indicating higher frequency of dysexecutive behaviour in everyday life. One version of the questionnaire was completed by someone who knew the patient well (usually either a relative or carer; DEX-I), and the other version was completed by the patient (DEX-S). Internal consistency is reported to be high (> 0.90), and investigators have reported a significant positive relation between the DEX and measures of executive dysfunction (Bennett et al., 2005).

2.4. Statistical analyses

2.4.1. Multilevel modelling (MLM)

A mixed-model repeated measures analysis was implemented using Stata 10 to identify preoperative predictors of change in mood rating scales (BDI-FS/BAI) at 6 and 12 months compared to baseline (i.e. preoperative scores). This model allowed the same set of commands to be applied to different outcomes of interest (i.e. BDI-FS and BAI) in a single step. We first performed univariable analyses using logarithmic (log) random intercept only models for BDI-FS and BAI, adjusting for the main effect of time. Variables that had a p-value < 0.2 on univariable analysis were selected for the multivariable model. This less conservative p-value was adopted as predictors that may have borderline significance in a univariable model may potentially be significant when controlling for covariates in a multivariable model. The selected variables were entered as a single block into the multivariable log random intercept model.

2.4.2. Logistic regression

Logistic regression analyses were used to examine whether postoperative mood rating scores (BDI-FS and BAI) or change (i.e. postoperative minus preoperative) in mood (BDI-FS/BAI) rating scales at 12 months, were related to seizure outcome (ILAE = 1).

Univariable logistic regression analyses were also used to investigate whether de novo psychiatric symptoms that developed within the 12 months following surgery was related to preoperative factors; specifically, seizure laterality, TLE duration, presence of SGTCs during the pre-surgical evaluation or a family history of psychopathology.

3. Results

3.1. Preoperative psychiatric disorder: lifetime and current

18 patients (n = 18/49; 37%) had a lifetime psychiatric history (depression, n = 13/18; panic disorder without agoraphobia, n = 2; generalised anxiety disorder, n = 3; PIP, n = 3; non-epileptic seizures (NES), n = 1). Four patients (n = 4/18; 22%) had more than one lifetime psychiatric diagnosis (depression and panic disorder without agoraphobia, n = 1; depression and NES, n = 1; depression and generalised anxiety disorder, n = 2).

Half of the patients with a lifetime psychiatric history (n = 9/18) had a psychiatric diagnosis at the time of TLE surgery (depression, n = 6/9; 67%; anxiety disorders, n = 3/9; 33%: panic disorder without agoraphobia, n = 1; not otherwise specified, n = 2). Eight patients (n = 8/9; 89%) were receiving psychotropic medication.

Of the nine patients with a clinically significant mental health problem at the time of surgery, seven (n = 7/9; 78%) were seen six months postoperatively and five (n = 5/9; 56%) at the twelve month follow-up. During this time period, no patient had remission of their pre-surgical psychiatric disorder and all patients continued on psychotropic medication.

3.2. De novo psychiatric disorder

Of the 31 patients with no history of psychopathology, five (16%) developed de novo psychiatric disorders within 12 postoperative months (depression, n = 2; generalised anxiety disorder, n = 3; adjustment disorder, n = 1; NES, n = 1); of which, two patients (n = 2/5) had de novo comorbid psychiatric disorders (depression and generalised disorder, n = 1; depression and adjustment disorder, n = 1), within 6 months follow-up. All patients (n = 5; 100%) required psychotropic medication (SSRI: citalopram; anxiolytic; diazepam) and one de novo case (depression and generalised disorder) reported prominent suicidal ideation in the early (< 3 months) postoperative period in the context of seizure freedom.

Logistic regression analysis indicated that de novo psychiatric disorder (n = 5 cases) was unrelated to seizure laterality (or: 0.67, 95%CI: 0.10–4.39, p = 0.67), TLE duration (OR: 0.98, 0.91–1.05, p = 0.50) or a family history of psychiatric disorder (OR: 3.67, 95%CI: 0.53–23.98, p = 0.19). Patients with a pre-surgical history of SGTCs were more likely to develop a de novo psychiatric disorder within 12 months postoperatively compared to those without (80% vs 32%) although it was only of borderline statistical significance (OR: 8.5, 95%CI: 0.87–83.9, p = 0.06).

3.3. Mood rating scores

Of the pre-surgical TLE cohort (n = 49), 33 patients reported minimal depressive symptoms whilst 16 (33%) patients reported depressive symptoms: 8 (16%) mildly depressed; 2 (4%) moderately depressed; and 6 (12%) severely depressed. 23 patients reported minimal anxiety, whilst 26 (53%) patients reported significant anxiety symptoms ranging from mild (n = 18; 37%), moderate (n = 6;12%) and severe (n = 2;4%: see Fig. 1). There was wide intersubject variation in the BDI-FS and BAI scores at all timepoints. Mean BDI-FS scores were 3.6 (range 0–17) presurgical, 3.2 (range 0–15) at 6 months and 3.0 (range 0–16) at 12 months. Mean BAI scores were 8.9 (range 0–38) presurgical, 7.5 (range 0–30) at 6 months and 6.2 (range 0–36) at 12 months.

3.4. Preoperative cognitive performance

Intellectual ability levels and IQ potential levels based on NART reading performance fell toward the lower end of the average range (WAIS IQ = 92 +/−14: NART pre-morbid IQ = 95+/−14). Performance levels in other cognitive domains are given in Table 2. The raw scores were converted to z scores to allow comparison across the number of different tests.

Table 2
Cognitive test results of the TLE surgical cohort.

Cognitive test	Scores (means;SDs)	Z score (means;SDs)
Memory; BMIPB		
List learning:	42.3 (10.1)	−0.9 (1.2)
List delay	9.3 (3.3)	−0.8 (1.2)
Design learning	33.2 (7.9)	−0.6 (1.1)
Design delay	6.4 (2.7)	−1.1 (1.7)
Semantic knowledge:		
Graded Naming Test	16.0 (5.0)	−0.8 (1.2)
Category fluency	18.0 (5.0)	−0.9 (1.1)
Executive skills		
WCST: perseverative errors	2.0 (range 0-11)	0.6 (0.9)
phonemic fluency	14.0 (6.0)	−0.18 (1.2)
CANTAB		
Spatial WM: total between errors	30.9 (23.1)	0.5 (1.2)
Spatial WM: strategy	31.1 (7.3)	0.1 (1.7)
DEX informant	20.0 (0-59)	
DEX subject	20.0 (2-47)	

3.5. Multivariable model: predicting change in depressive symptoms following TLE surgery

There was a non-significant decrease in mean BDI-FS rating scores following TLE surgery compared to preoperative (baseline) levels, controlling for preoperative cognitive and psychiatric variables (random intercept only BDI-FS model at 6 months: −0.81, 95%CI: −1.67–1.3, p = 0.81; random intercept only BDI-FS model at 12 months: −0.47, 95%CI: −2.47, 1.18, p = 0.57).

The multivariable analysis indicated that two cognitive variables, WCST perseveration errors and DEX-subjective ratings, were independent predictors of postoperative BDI-FS score, adjusting for time, category fluency and a current or lifetime affective (mood/anxiety) disorder (WCST: B = 0.41, SE B = 0.13, 95%CI: 0.15–0.67, p = 0.002) and DEX-subjective rating: B = 0.11, SE B = 0.03, 95%CI: 0.04–0.17, p = 0.001). The significant beta coefficient of 0.41 specifies that for every preoperative WCST perseveration error, postoperative BDI-FS increases by a factor of 0.41, adjusting for time and other included covariates. Similarly, after the effects of all the other predictors are held constant, postoperative depressive morbidity increases by a factor of 0.11 (beta value, B) per unit increase in pre-surgical patient-reported dysexecutive behaviours.

The presence of a *current* affective (depression/anxiety) diagnosis within 6 months of surgery remained a strong predictor of postoperative BDI-FS, after adjusting for time and other pre-surgical factors: compared to patients without a current affective diagnosis, patients with a diagnosis had a substantial increase in post-surgical depressive symptoms (B = 3.70, SE B = 1.56, 95%CI: 0.60–6.73, p = 0.02). There was a similar trend for a lifetime diagnosis, but this failed to reach significance (B = 1.61, SE B = 0.95, 95%CI: −0.24–3.48, p = 0.09).

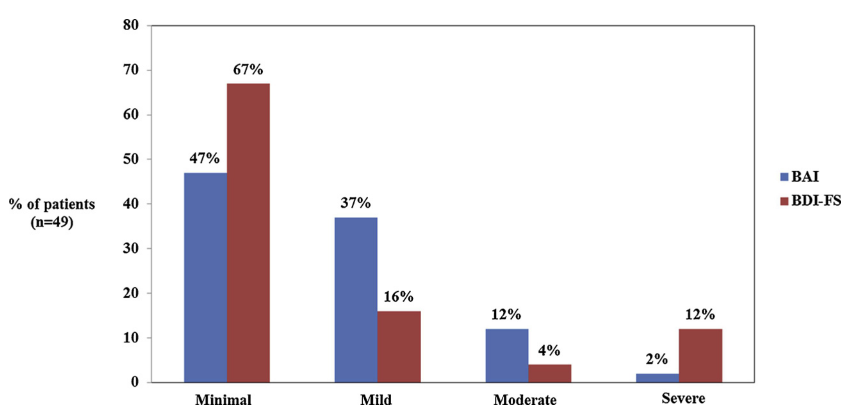

Fig. 1. Preoperative mood rating scores (BDI-FS and BAI) for the TLE surgical cohort (n = 49).

3.6. Seizure outcome: relation to depressive symptoms

23 patients (79%; n = 23/29) were seizure free (ILAE 1) at 12 month follow-up. There was no relationship between preoperative depressive symptoms (BDI-FS) and seizure outcome (ILAE 1 vs 2–6) at 12 months (OR: 1.15, 95%CI: 0.84–1.56, p = 0.38), or change in depressive symptoms at 12 months compared to preoperative levels (OR: 0.92, 95%CI: 0.76-1.10, p = 0.34). In addition, a lifetime history of depression was not related to seizure outcome (OR: 1.41, 95%CI: 0.20–9.81, p = 0.72).

3.7. Multivariable model: predicting change in anxiety symptoms following TLE surgery

In contrast to the BDI-FS multivariable model, there was a significant decrease in mean BAI rating scores following TLE surgery compared to preoperative (baseline) levels, controlling for preoperative cognitive and psychiatric variables (random intercept only BAI model at 6 months: B = -3.73, SE B = 1.19, 95%CI: −6.06–−1.39, $p < 0.001$; random intercept only BAI model at 12 months: B = −3.91, SE B = 1.4, 95%CI: −6.64–−1.18, $p < 0.001$). The small degree of change (−0.18) in the beta coefficients between six (B: −3.73) and twelve (B: −3.91) months suggests that there is a significant reduction in mean BAI rating at 6 months, but no *additional* reduction from 6 to 12 month follow-up. To investigate this further, the reference (baseline) category in the multivariable BAI model was changed from the preoperative mean BAI score to the mean BAI score at 6 months, and the model was re-run. As suspected, the mean preoperative BAI level was significantly higher (+3.73 points) relative to the 6 months BAI score (B: 3.73, 95%CI: 1.39–6.06, p = 0.002); but this was not the case for the mean BAI score at 12 months (B: −0.18, 95%CI: −3.00–2.62, p = 0.90).

The multivariable analysis also indicated that the rate of change (decrease) in mean BAI score over time is significantly reduced in the context of preoperative dysexecutive behaviours (DEX-S), after adjusting for other cognitive (digit span, trail making B) and psychiatric variables (B: 0.23, SE B = 0.06, 95%CI: 0.10–0.36, p = 0.01). None of the other variables included significantly predicted self-reported anxiety symptoms following TLE surgery.

3.8. Seizure outcome: relation to anxiety symptoms

There was no relationship between preoperative anxiety symptoms (BAI) and seizure outcome (ILAE 1 vs 2–6) at 12 months (OR: 1.04, 95%CI: 0.91–1.20, p = 0.57, or change in BAI at 12 months compared to preoperative levels (OR: 0.84, 95%CI: 0.66–1.60, p = 0.14). In addition, a past history of anxiety disorder was not related to seizure outcome (OR:2.1, 95%CI:0.16–28.02, p = 0.58).

4. Discussion

In keeping with previous reports, a significant number of TLE patients in our study reported psychiatric symptoms pre- and postoperatively, particularly affective disturbance (Desai et al., 2014; Gaitatzis et al., 2004; Prayson et al., 2017; Swinkels et al., 2005; Wrench et al., 2009, 2011). A novel finding was that the *magnitude* and the *direction* of mood change following TLE surgery was significantly moderated by preoperative cognitive indicators of frontal lobe dysfunction. Patients with greater impairment on selected executive skills measures had a worsening in depressive and anxiety symptoms following surgery, as predicted. Anxiety symptoms in our patients significantly improved in the year following surgery, while depressive morbidity did not. Furthermore, an affective disorder at the time of surgery was predictive of postoperative depressive morbidity, replicating previous reports (Devinsky et al., 2005; Malmgren et al., 2002; Pintor et al., 2007; Quigg et al., 2003; Wrench et al., 2011).

This is the first prospective study to demonstrate that pre-surgical cognitive and behavioural measures of frontal lobe dysfunction are significant predictors of poor psychiatric outcome following TLE surgery. Increased WCST perseveration errors and self-reported dysexecutive behaviours prior to surgery were independently predictive of increased depressive morbidity postoperatively. Multivariable analyses indicated that these factors remained significant after controlling for the effects of other confounding variables (time, category fluency and lifetime affective history). Correlational studies have demonstrated that depressed TLE patients exhibit frontal lobe dysfunction (Helmstaedter et al., 2004; Hermann et al., 1991) consistent with the unipolar depression literature (Rogers et al., 2004). The current finding extends correlational approaches, as executive dysfunction was predictive of the *development* of depressive morbidity. This suggests that executive impairment may be causally related to mood disturbance in TLE, rather than a reactive functional change. The mechanism responsible for frontal lobe dysfunction in TLE remains unclear (Devinsky et al., 2005). Suggestions include more widespread brain pathology, the spread of epileptic activity from the epileptogenic zone impacting on frontal brain circuitry and the propagation of temporal lobe hypo-metabolism to the thalamus, secondarily affecting the frontal lobes (Bell et al., 2011; Hermann et al., 1991).

Postoperative anxiety symptoms also worsened in the context of pre-surgical executive dysfunction. Multivariable analysis confirmed that preoperative patient-reported dysexecutive behaviours significantly predicted increased post-surgical anxiety, after the effects of other predictors were held constant. Animal and human studies have pointed to an association between anxiety and the amygdala (Damsa et al., 2009; Phelps and LeDoux, 2005). Resection of an amygdala of normal volume has been associated with postoperative anxiety in mesial TLE patients, regardless of seizure outcome (Halley et al., 2010; Phelps and LeDoux, 2005). Bonelli et al. (2009) reported a positive relationship in right TLE patients between preoperative ipsilateral amygdala activation on viewing fearful faces and postoperative change in anxiety levels; with greater preoperative activation being related with worsening severity of anxiety following ATLR. However, converging structural and functional neuroimaging also indicate that the prefrontal cortex particularly the OFC is implicated in the pathophysiology of anxiety disorders (Jackowski et al., 2012; Milad and Rauch, 2007). These findings are supported by neuropsychological evidence of executive dysfunction in anxiety disorders (Ferreri et al., 2011). The OFC is involved in a variety of higher-order executive tasks, including: control and inhibition of inappropriate behavioural/emotional responses, decision making and maintaining behavioural flexibility. Therefore, preoperative dysexecutive behaviour may indicate prefrontal lobe dysfunction which predisposes TLE patients to post-surgical anxiety.

In keeping with previous reports, a significant number of our TLE patients had psychiatric comorbidity (Cleary et al., 2013; Wrench et al., 2011). More than a third of patients had a psychiatric diagnosis before surgery, mainly depression.(Desai et al., 2014; Devinsky et al., 2005; Filho et al., 2012; Glosser et al., 2000; Mathon et al., 2017). This finding coupled with the detrimental impact of depression on quality of life (Boylan et al., 2004), and the deleterious interaction with seizure freedom following TLE surgery (Anhoury et al., 2000; Cleary et al., 2012; Guarnieri et al., 2009; Kanner et al., 2009), underscores the need for a thorough pre-surgical psychiatric assessment. The 16% rate of de novo psychiatric disorder is similar to previous reports using psychiatric diagnostic interviews pre- and postoperatively (Desai et al., 2014; Hellwig et al., 2012). Anxiety and depression were the most common de novo diagnoses, with all cases emerging within 6 months postoperatively, and necessitating psychotropic medication (Altshuler et al., 1999; Blumer et al., 1998; Cleary et al., 2012; Koch-Stoecker et al., 2017; Wrench et al., 2011). Seizure laterality, epilepsy duration and a family history of psychiatric illness did not predict de novo psychiatric disturbance, replicating previous research (Desai et al., 2014).

An interesting finding in our study was the improvement in anxiety symptoms but not depressive symptoms in the year following surgery. Mean preoperative anxiety reduced from 'mild' to 'minimal' levels after TLE surgery, with a steeper reduction in the immediate postoperative period ($\leq$ 6 months). Although unrelated to seizure control, this suggests that neurobiological and/or psychological factors that improve emotional well-being are active within in the early postoperative epoch (Desai et al., 2014; Devinsky et al., 2005). Candidate neurobiological anxiety-protective factors include an enlarged ipsilateral amygdala volume (Halley et al., 2010) and/or the absence of pre-surgical fear auras (Kohler et al., 2001) whereas a reduced fear of experiencing seizures, improved sense of self-control and/or a positive change in family dynamics may be important psychosocial factors. Alternatively, this initial reduction may be due to a placebo response (transient effect of surgery) and/or social desirability effects. These latter explanations seem unlikely however, as depressive symptoms recorded on the same day did not follow the same postoperative trajectory.

The lack of a *significant* improvement in depressive symptoms in our patients following TLE surgery contrasts with previous reports (Devinsky et al., 2005; Hamid et al., 2011; Pintor et al., 2007). This may be due to methodological differences between studies. Firstly, this study measured change in depressive symptomatology using the BDI-FS; specifically developed for screening medical patients. The standard BDI scores in the previous studies may reflect alterations in seizure or medication status following TLE surgery, rather than changes in depressive symptoms *per se*. This may explain the improvement in mood following surgery in seizure-free cohorts previously reported (Devinsky et al., 2005; Hamid et al., 2011). Thus, using validated specific psychiatric screening tools for epilepsy cohorts may be more appropriate. Second, the application of multilevel modelling, rather than repeated-measures statistical designs e.g., paired-sample t-tests/ANOVAs (Prayson et al., 2017), afforded investigation of postoperative BDI-FS change, adjusting for patient variability in baseline (preoperative) depression levels (BDI-FS range: 0–17). Furthermore, this statistical technique reduced the chance of a Type I error (i.e. erroneously concluding BDI-FS score reduces postoperatively), by accounting for the auto-correlation in residual scores produced from measuring the same subject on several occasions.

This study also highlights the importance of the timing of pre-surgical psychiatric assessments. It has been unclear whether TLE patients with varying degrees of pre-surgical affective morbidity have the same risk of postoperative mood disturbance following surgery. In our previous retrospective study, a lifetime diagnosis of a psychiatric disorder was found to be a risk factor of postsurgical psychiatric morbidity (Cleary et al., 2012). In this current study, psychiatric assessment, in addition to patients' rating scale scores, allowed investigation into whether affective disorder refractoriness influenced psychiatric outcome. We found that patients with an affective disorder at the point of surgery had a greater risk of post-surgical depression than those who had recovered. Our findings suggest that pre-surgical psychiatric assessments would be more appropriate closer to the time of surgery to ensure that psychiatric disorders, if present, are treated prior to surgery as this could reduce the risk of postoperative psychiatric disturbance.

We did not find an association between pre-surgical depression and seizure outcome in this study. Although many previous studies (Anhoury et al., 2000; Cleary et al., 2012; Kanner et al.,2009; Koch-Stoecker et al., 2017; Metternich et al., 2009) suggest that presurgical depression predicts surgical outcome, others have not found this (Adams et al., 2012; Altalib et al., 2018; Guarnieri et al., 2009; Lackmayer et al., 2013). Methodological differences may account for the conflicting findings. Most of the previous studies were retrospective and reported longer term seizure outcome whilst our current study was prospective and confined to a year postoperatively. Prevalence rates of presurgical depression, sample sizes and methodologies of psychiatric evaluation differed across the various studies, with the use of dimensional or categorical measures. Furthermore, the limitations of using self-reported measures of depression should be considered. An elevated BDI-FS score indicates an increased probability of having an actual depressive disorder, but is not a diagnostic measure. It is therefore possible that the severity of depressive morbidity (trait versus state) may play a modulatory role in the relation between depression and seizure outcome, accounting for divergent findings.

Several aspects of the study limit interpretation and generalisability of our findings. Despite using a linear mixed-effects model that is unaffected by missing data, statistical power limited the number of predictors used in the multivariable models, the ability to predict de novo psychiatric presentations, and the investigation of cognitive change. In addition, due to the small sample size, statistical analyses examining cognitive performance as a function of laterality were not performed. Given the prospective nature and limited time frame of the study, we were only able to collect follow up data for 12 months. Although a few cases of severe late-onset psychiatric morbidity in post-operative (seizure-free) TLE patients have been reported (Shukla et al., 2016), for the vast majority, postoperative mood disturbance is usually apparent within the first year of surgery (Cleary et al., 2012; Desai et al., 2014; Macrodimitris et al., 2011).

Only two of the measures of executive function i.e. the WCST (perseverative errors) and DEX scores in our study were found to be significant predictors in the multivariable model which may be attributed to the mild degree of frontal dysfunction in our TLE patients. We found that the higher the number of perseverative errors on the WCST prior to surgery, the worse the postoperative BDI depression scores in our patients. Many neuroimaging studies, including those in epilepsy, suggest that WCST performance is associated with activation of a widely distributed neural network but primarily involving prefrontal regions (Nyhus and Barceló, 2009; Riley et al., 2011; Zhang et al., 2017). Interestingly, it has also been proposed that there are differential neural correlates involved for the different aspects of the WCST (Lie et al., 2006; Terada et al., 2011). Findings from a SPECT study in patients with mild Alzheimer's disease suggested that perseverative errors on the WCST may be a sensitive index of orbitofrontal dysfunction (Terada et al., 2011).

Neuroimaging studies have linked key components of the limbic system to postoperative mood disturbance, including the OFC (Pope et al., 2014; Salzberg et al., 2006), the hippocampus (Wrench et al., 2009) and the amygdala (Halley et al., 2010). More recently, molecular abnormalities in hippocampal formation subfields of mesial TLE specimens from patients with and out without major depression, compared to those from controls without epilepsy, have been documented (Kandratavicius et al., 2014, 2015). It would therefore be interesting to examine longitudinally whether preoperative executive dysfunction is associated with pre-surgical volumetric abnormalities in the prefrontal lobe. In addition, future research to determine whether TLE patients with widespread pre-surgical *functional* brain abnormalities have a greater psychiatric risk following surgery would enhance our understanding of the underlying pathogenic mechanisms.

5. Conclusion

In conclusion, this longitudinal study provides evidence that pre-surgical cognitive and behavioural indices of frontal lobe dysfunction are predictive of poor psychiatric outcome following TLE surgery. The high rate of psychopathology pre- and postoperatively suggest that patients undergoing resective surgery, particularly those with a current affective diagnosis and/or evidence of executive dysfunction, should be counselled about this potential risk.

Conflicts of interest

None of the authors has any conflict of interest of disclose.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

Adams, S.J., Velakoulis, D., Kaye, A.H., Corcoran, N.M., O'Brien, T.J., 2012. Psychiatric history does not predict seizure outcome following temporal lobectomy for mesial temporal sclerosis. Epilepsia 53 (10), 1700–1704.
Altalib, H.H., Berg, A.T., Cong, X., Vickrey, B.G., Sperling, M.R., Shinnar, S., Langfitt, J.T., Walczak, T.S., Bazil, C.W., Sukumar, N., Devinsky, O., 2018. Presurgical depression and anxiety are not associated with worse epilepsy surgery outcome five years postoperatively. Epilepsy Behav. 83 (June), 7–12.
Altshuler, L., Rausch, R., Delrahim, S., Kay, J., Crandall, P., 1999. Temporal lobe epilepsy, temporal lobectomy, and major depression. J. Neuropsychiatry Clin. Neurosci. 11, 436–443.
Anhoury, S., Brown, R.J., Krishnamoorthy, E.S., Trimble, M.R., 2000. Psychiatric outcome after temporal lobectomy: a predictive study. Epilepsia 41, 1608–1615.
Arbuthnott, K., Frank, J., 2000. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. J. Clin. Exp. Neuropsychol. 22, 518–528.
Baxendale, S., Thompson, P., 2010. Beyond localization: the role of traditional neuropsychological tests in an age of imaging. Epilepsia 51, 2225–2230.
Beck, A., Epstein, N., Brown, G., Steer, R., 1988. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56, 893–897.
Beck, A., Steer, R., Brown, G., 1996. Manual for the Beck Depression Inventory II. Psychological Corporation, San Antonio, Texas.
Bell, B., Lin, J.J., Seidenberg, M., Hermann, B., 2011. The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat. Rev. Neurol. 7, 154–164.
Bennett, P.C., Ong, B., Ponsford, J., 2005. Assessment of executive dysfunction following traumatic brain injury: comparison of the BADS with other clinical neuropsychological measures. J. Int. Neuropsychol. Soc. 11, 606–613.
Bird, C.M., Papadopoulou, K., Ricciardelli, P., Rossor, M.N., Cipolotti, L., 2004. Monitoring cognitive changes: psychometric properties of six cognitive tests. Br. J. Clin. Psychol. 43, 197–210.
Blumer, D., Wakhlu, S., Davies, K., Hermann, B., 1998. Psychiatric outcome of temporal lobectomy for epilepsy: incidence and treatment of psychiatric complications. Epilepsia 39, 478–486.
Bonelli, S.B., Powell, R., Yogarajah, M., et al., 2009. Preoperative amygdala fMRI in temporal lobe epilepsy. Epilepsia 50, 217–227.
Bowie, C., Harvey, P., 2006. Administration and interpretation of the Wisconsin Card Sorting Test. Natl. Proc. 1, 2277–2281.
Boylan, L.S., Flint, L.A., Labovitz, D.L., Jackson, S.C., Starner, K., Devinsky, O., 2004. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology 62, 258–261.
Bright, P., Jaldow, E., Kopelman, M.D., 2002. The National Adult Reading Test as a measure of premorbid intelligence: a comparison with estimates derived from demographic variables. J. Int. Neuropsychol. Soc. 8, 847–854.
Burgess, P., Alderman, N., Evans, J., Emslie, H., Wilson, B., 1998. The ecological validity of tests of executive function. J. Int. Neuropsychol. Soc. 4, 547–558.
Cleary, R.A., Thompson, P.J., Fox, Z., Foong, J., 2012. Predictors of psychiatric and seizure outcome following temporal lobe epilepsy surgery. Epilepsia 53, 1705–1712.
Cleary, R.A., Baxendale, S.A., Thompson, P.J., Foong, J., 2013. Predicting and preventing psychopathology following temporal lobe epilepsy surgery. Epilepsy Behav. 26, 322–334.
Corcoran, R., Upton, D., 1993. A role for the hippocampus in card sorting? Cortex 29, 293–304.
Coughlan, A., Oddy, M., Crawford, J., 2007. BIRT Memory and Information Processing Battery. Brain Rehabilitation Trust, London.
Crowe, S.F., 1998. The differential contribution of mental tracking, cognitive flexibility, visual search, and motor speed to performance on parts A and B of the trail making test. J. Clin. Psychol. 54, 585–591.
Damsa, C., Kosel, M., Moussally, J., 2009. Current status of brain imaging in anxiety disorders. Curr. Opin. Psychiatry 22, 96–110.
Desai, S., Shukla, G., Goyal, V., et al., 2014. Changes in psychiatric comorbidity during early postsurgical period in patients operated for medically refractory epilepsy–a MINI-based follow-up study. Epilepsy Behav. 32, 29–33.
Devinsky, O., Barr, W.B., Vickrey, B.G., et al., 2005. Changes in depression and anxiety after resective surgery for epilepsy. Neurology 65, 1744–1749.
Dulay, M.F., Schefft, B.K., Fargo, J.D., Privitera, M.D., Yeh, H.S., 2004. Severity of depressive symptoms, hippocampal sclerosis, auditory memory, and side of seizure focus in temporal lobe epilepsy. Epilepsy Behav. 5, 522–531.
Engel, J., 1996. Jr. Surgery for seizures. N. Engl. J. Med. 334, 647–652.
Ferreri, F., Lapp, L.K., Peretti, C.S., 2011. Current research on cognitive aspects of anxiety disorders. Curr. Opin. Psychiatry 24, 49–54.
Filho, G.M., Mazetto, L., Gomes, F.L., et al., 2012. Pre-surgical predictors for psychiatric disorders following epilepsy surgery in patients with refractory temporal lobe epilepsy and mesial temporal sclerosis. Epilepsy Res. 102, 86–93.
Flugel, D., Cercignani, M., Symms, M.R., et al., 2006. Diffusion tensor imaging findings and their correlation with neuropsychological deficits in patients with temporal lobe epilepsy and interictal psychosis. Epilepsia 47, 941–944.
Gaitatzis, A., Trimble, M.R., Sander, J.W., 2004. The psychiatric comorbidity of epilepsy. Acta Neurol. Scand. 110, 207–220.
Glosser, G., Zwil, A.S., Glosser, D.S., O'Connor, M.J., Sperling, M.R., 2000. Psychiatric aspects of temporal lobe epilepsy before and after anterior temporal lobectomy. J. Neurol. Neurosurg. Psychiatry 68, 53–58.
Guarnieri, R., Walz, R., Hallak, J.E., et al., 2009. Do psychiatric comorbidities predict postoperative seizure outcome in temporal lobe epilepsy surgery? Epilepsy Behav. 14, 529–534.
Halley, S.A., Wrench, J.M., Reutens, D.C., Wilson, S.J., 2010. The amygdala and anxiety after epilepsy surgery. Epilepsy Behav. 18, 431–436.
Hamid, H., Liu, H., Cong, X., et al., 2011. Long-term association between seizure outcome and depression after resective epilepsy surgery. Neurology 77, 1972–1976.
Hellwig, S., Mamalis, P., Feige, B., Schulze-Bonhage, A., van Elst, L.T., 2012. Psychiatric comorbidity in patients with pharmacoresistant focal epilepsy and psychiatric outcome after epilepsy surgery. Epilepsy Behav. 23, 272–279.
Helmstaedter, C., Sonntag-Dillender, M., Hoppe, C., Elger, C.E., 2004. Depressed mood and memory impairment in temporal lobe epilepsy as a function of focus lateralization and localization. Epilepsy Behav. 5, 696–701.
Hermann, B.P., Seidenberg, M., Haltiner, A., Wyler, A.R., 1991. Mood state in unilateral temporal lobe epilepsy. Biol. Psychiatry 30, 1205–1218.
Iranzo-Tatay, C., Rubio-Granero, T., Gutierrez, A., et al., 2017. Psychiatric symptoms after temporal epilepsy surgery. a one-year follow-up study. Epilepsy Behav. 70, 154–160.
Jackowski, A.P., Araujo Filho, G.M., Almeida, A.G., et al., 2012. The involvement of the orbitofrontal cortex in psychiatric disorders: an update of neuroimaging findings. Rev. Bras. Psiquiatr. 34, 207–212.
Kandratavicius, L., Hallak, J.E., Carlotti, C.G., Assirati Jr., J.A., Leite, J.P., 2014. Neurotrophin receptors expression in mesial temporal lobe epilepsy with and without psychiatric comorbidities and their relation with seizure type and surgical outcome. Acta Neuropathol. Commun. 2, 81.
Kandratavicius, L., Peixoto-Santos, J.E., Monteiro, M.R., et al., 2015. Mesial temporal lobe epilepsy with psychiatric comorbidities: a place for differential neuroinflammatory interplay. J. Neuroinflamm. 12, 38.
Kanner, A.M., Byrne, R., Chicharro, A., Wuu, J., Frey, M., 2009. A lifetime psychiatric history predicts a worse seizure outcome following temporal lobectomy. Neurology 72, 793–799.
Koch-Stoecker, S.C., Bien, C.G., Schulz, R., May, T.W., 2017. Psychiatric lifetime diagnoses are associated with a reduced chance of seizure freedom after temporal lobe surgery. Epilepsia 58, 983–993.
Kohler, C.G., Carran, M.A., Bilker, W., O'Connor, M.J., Sperling, M.R., 2001. Association of fear auras with mood and anxiety disorders after temporal lobectomy. Epilepsia 42, 674–681.
Lackmayer, K., Lehner-Baumgartner, E., Pirker, S., Czech, T., Baumgartner, C., 2013. Preoperative depressive symptoms are not predictors of postoperative seizure control in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. Epilepsy Behav. 26 (January (1)), 81–86.
Lie, C.H., Specht, K., Marshall, J.C., Fink, G.R., 2006. Using fMRI to decompose the neural processes underlying the Wisconsin Card sorting Test. Neuroimage 30 (3), 1038–1049.
Macrodimitris, S., Sherman, E.M., Forde, S., et al., 2011. Psychiatric outcomes of epilepsy surgery: a systematic review. Epilepsia 52, 880–890.
Malmgren, K., Starmark, J.E., Ekstedt, G., Rosen, H., Sjoberg-Larsson, C., 2002. Nonorganic and organic psychiatric disorders in patients after epilepsy surgery. Epilepsy Behav. 3, 67–75.
Mathon, B., Bielle, F., Samson, S., et al., 2017. Predictive factors of long-term outcomes of surgery for mesial temporal lobe epilepsy associated with hippocampal sclerosis. Epilepsia 58, 1473–1485.
McGurn, B., Starr, J.M., Topfer, J.A., et al., 2004. Pronunciation of irregular words is preserved in dementia, validating premorbid IQ estimation. Neurology 62, 1184–1186.
McKenna, P., Warrington, E., 1980. Testing for nominal dysphasia. J. Neurol. Neurosurg. Psychiatry 43, 781–788.
Metternich, B., Wagner, K., Brandt, A., et al., 2009. Preoperative depressive symptoms predict postoperative seizure outcome in temporal and frontal lobe epilepsy. Epilepsy Behav. 16, 622–628.
Mikati, M.A., Comair, Y.G., Rahi, A., 2006. Normalization of quality of life three years after temporal lobectomy: a controlled study. Epilepsia 47, 928–933.
Milad, M.R., Rauch, S.L., 2007. The role of the orbitofrontal cortex in anxiety disorders. Ann. N. Y. Acad. Sci. 1121, 546–561.
Nelson, H.E., 1976. A modified card sorting test sensitive to frontal lobe defects. Cortex 12, 313–324.
Nyhus, E., Barceló, F., 2009. The Wisconsin Card sorting Test and the cognitive assessment of prefrontal executive functions: a critical update. Brain Cogn. 71 (3), 437–451.
Owen, A.M., Morris, R.G., Sahakian, B.J., Polkey, C.E., Robbins, T.W., 1996. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Brain 119 (Pt 5), 1597–1615.
Paradiso, S., Hermann, B.P., Blumer, D., Davies, K., Robinson, R.G., 2001. Impact of depressed mood on neuropsychological status in temporal lobe epilepsy. J. Neurol. Neurosurg. Psychiatry 70, 180–185.

Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48, 175–187.
Pintor, L., Bailles, E., Fernandez-Egea, E., et al., 2007. Psychiatric disorders in temporal lobe epilepsy patients over the first year after surgical treatment. Seizure 16, 218–225.
Pope, R.A., Centeno, M., Flugel, D., et al., 2014. Neural correlates of de novo depression following left temporal lobe epilepsy surgery: a voxel based morphometry study of pre-surgical structural MRI. Epilepsy Res. 108, 517–525.
Porter, R.J., Gallagher, P., Thompson, J.M., Young, A.H., 2003. Neurocognitive impairment in drug-free patients with major depressive disorder. Br. J. Psychiatry 182, 214–220.
Prayson, B.E., Floden, D.P., Ferguson, L., Kim, K.H., Jehi, L., Busch, R.M., 2017. Effects of surgical side and site on psychological symptoms following epilepsy surgery in adults. Epilepsy Behav. 68, 108–114.
Quigg, M., Broshek, D.K., Heidal-Schiltz, S., Maedgen, J.W., Bertram III, E.H., 2003. Depression in intractable partial epilepsy varies by laterality of focus and surgery. Epilepsia 44, 419–424.
Riley, J.D., Moore, S., Cramer, S.C., Lin, J.J., 2011. Caudate atrophy and impaired frontostriatal connections are linked to executive dysfunction in temporal lobe epilepsy. Epilepsy Behav. 21 (1), 80–87.
Robinson, G., Shallice, T., Bozzali, M., Cipolotti, L., 2012. The differing roles of the frontal cortex in fluency tests. Brain 135, 2202–2214.
Rogers, M.A., Kasai, K., Koji, M., et al., 2004. Executive and prefrontal dysfunction in unipolar depression: a re iew of neuropsychological and imaging evidence. Neurosci. Res. 50, 1–11.
Sahakian, B.J., Owen, A.M., 1992. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J. R. Soc. Med. 85, 399–402.
Salzberg, M., Taher, T., Davie, M., et al., 2006. Depression in temporal lobe epilepsy surgery patients: an FDG-PET study. Epilepsia 47, 2125–2130.
Shukla, G., Agarwal, P., Sagar, R., et al., 2016. Does antiepileptic drug withdrawal predispose patients undergoing temporal lobe epilepsy surgery to late onset of psychiatric morbidity? a report of three cases. Ann. Indian Acad. Neurol. 19, 377–380.
Stretton, J., Winston, G., Sidhu, M., et al., 2012. Neural correlates of working memory in temporal lobe epilepsy–an fMRI study. Neuroimage 60, 1696–1703.
Swinkels, W.A., Kuyk, J., van, D.R., Spinhoven, P., 2005. Psychiatric comorbidity in epilepsy. Epilepsy Behav. 7, 37–50.
Terada, S., Sato, S., Honda, H., Kishimoto, Y., Takeda, N., Oshima, E., Yokota, O., Uchitomi, Y., 2011. Perseverative errors on the Wisconsin Card Sorting Test and brain perfusion imaging in mild Alzheimer's disease. Int. Psychogeriatr. 23 (10), 1552–1559.
Wiebe, S.A., 2010. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N. Eng. J. Med. 345, 311–318.
Wilson, S.J., Bladin, P.F., Saling, M.M., 2004. Paradoxical results in the cure of chronic illness: the "burden of normality" as exemplified following seizure surgery. Epilepsy Behav. 5, 13–21.
Wishart, H., Strauss, E., Hunter, M., Pinch, D., Wada, J., 2017. Cognitive correlates of interictal affective and behavioural disturbances in people with epilepsy. J. Epilepsy 6, 98–104.
Wrench, J.M., Wilson, S.J., Bladin, P.F., Reutens, D.C., 2009. Hippocampal volume and depression: insights from epilepsy surgery. J. Neurol. Neurosurg. Psychiatry 80, 539–544.
Wrench, J.M., Matsumoto, R., Inoue, Y., Wilson, S.J., 2011. Current challenges in the practice of epilepsy surgery. Epilepsy Behav. 22, 23–31.
Zhang, C., Yang, H., Qin, W., Liu, C., Qi, Z., Chen, N., Li, K., 2017. Functional connectivity in intractable unilateral temporal lobe epilepsy patients with impaired executive control function. Front. Hum. Neurosci. 11, 609.