Pre-Surgical Mood Predicts Memory Decline after Anterior Temporal Lobe Resection for Epilepsy

Robyn M. Busch1,2,*, Mario F. Dulay3, Kevin H. Kim4, Jessica S. Chapin1,2, Lara Jehi1, Colleen C. Kalman2, Richard I. Naugle1,2, Imad M. Najm1

1 Cleveland Clinic Epilepsy Center, Neurological Institute, Cleveland, OH, USA
2 Department of Psychiatry and Psychology, Cleveland Clinic, Cleveland, OH, USA
3 Department of Neurosurgery, The Methodist Neurological Institute, Houston, TX, USA
4 School of Education, University of Pittsburgh, Pittsburgh, PA, USA

*Corresponding author at: Cleveland Clinic Epilepsy Center, Neurological Institute, 9500 Euclid Avenue, P57, Cleveland, OH 44195, USA.
Tel.: +1-216-444-9042; fax: +1-216-444-4525.
E-mail address: buschr@ccf.org (R.M. Busch).

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Abstract

This study examined pre-surgical depressed mood as a predictor of post-surgical memory change in adults who underwent temporal lobe resections (TLRs; n = 211). Patients completed the Wechsler Memory Scale-III and Beck Depression Inventory-Second Edition (BDI-II) before and after TLR (left = 110, right = 101) and were divided into two groups (clinically elevated depressive symptoms or not depressed) based on BDI-II score. Left-TLR patients with poorer pre-surgical mood had greater verbal memory declines after surgery compared with nondepressed left- or right-TLR patients and right-TLR patients with poor mood. Further, pre-surgical BDI-II score demonstrated incremental validity in predicting post-surgical memory change in left-TLR patients beyond pre-surgical memory scores. Differences in seizure outcome and post-surgical mood change could not account for memory decline. Results suggest that elevated pre-surgical depressive symptomatology is a risk factor for post-surgical memory decline and indicate that mood should be considered when advising patients about cognitive risks associated with temporal lobectomy. Results are discussed in terms of poor pre-surgical mood as an indicator of reduced cognitive reserve.

Keywords: depression; learning and memory; epilepsy

Introduction

Depressive disorders and cognitive difficulties are frequently observed in patients with epilepsy (Gilliam, Hecimovic, & Sheline, 2003; Gilliam & Kanner, 2002; Gilliam, Mendiratta, Pack, & Bazil, 2005; Hermann, Seidenberg, & Bell, 2000; Jacoby, Baker, Steen, Potts, & Chadwick, 1996). Research suggests that cognitive difficulties may contribute to the existence of depression in epilepsy and, conversely, symptoms of depression may contribute to cognitive impairment (Biringer et al., 2007). Co-occurring cognitive impairments and poor mood state may also reflect a common underlying factor that is contributing to both problems, such as limbic system disruption related to seizure activity (Kanner, 2005) or reduced cognitive reserve (Dulay, Schefft, Fargo, Privitera, & Yeh, 2004).

In patients with medically intractable temporal lobe epilepsy (TLE), depressive symptoms on screening measures, such as the Beck Depression Inventory (BDI), are associated with poorer memory compared with patients with fewer depressive symptoms (Corcoran & Thompson, 1993; Dulay et al., 2004; Helmstaedter, 2004; Paradiso, Hermann, Blumer, Davies, & Robinson, 2001; Wishart, Strauss, Hunger, Pinch, & Wada, 1993), particularly among patients whose seizures arise from the left temporal lobe (Dulay et al., 2004; Helmstaedter, 2004; Paradiso et al., 2001). This relationship is also evident after anterior temporal lobe resection (TLR; Dulay et al., 2004). What remains unclear is whether mood state is related to change in memory functioning...
from before to after surgery and, if so, whether mood state improves the prediction of post-operative memory outcome and above pre-surgical memory performance and side of surgery, well-established predictors of memory outcome (Chelune, Naugle, Luders, & Awad, 1991; Jokeit et al., 1997; Stroup et al., 2003).

The primary goal of the present study was to assess the value of a commonly used depressive symptomatology screening tool (i.e., BDI-II), administered pre-surgically, as a predictor of change in memory abilities from before to after TLRs and to examine the incremental validity of pre-operative BDI-II score in predicting post-operative memory change above and beyond pre-surgical memory scores.

Methods

Participants

This study involved an IRB approved, retrospective review of previously collected and archived data from 211 adult patients (51.7% women; 96.2% Caucasian, 3.8% African American) with medically intractable TLE (left hemisphere = 110; right hemisphere = 101). Patients were included in the study if they: (a) had undergone an anterior TLR that included mesial temporal structures, (b) were right-handed or left-hemisphere dominant for language as determined with Wada testing, (c) completed pre- and post-operative neuropsychological testing that included the Wechsler Memory Scale-III (WMS-III) and BDI-II, and (d) had a Full-Scale IQ score ≥70 as measured by the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997a). Participants ranged in age from 16 to 65 years ($M = 35.38$, $SD = 11.45$) and in education from 6 to 20 years ($M = 13.02$, $SD = 2.23$). The mean age at seizure onset for the group was 15.77 years ($SD = 11.97$), and the mean duration of seizures was 19.55 years ($SD = 12.88$). Demographic and seizure data for the study patients are provided in Table 1.

Measures

As part of standard pre- and post-surgical evaluations, participants completed a comprehensive neuropsychological battery. The BDI-II (Beck, Steer, & Brown, 1996) was used to assess mood state. The BDI-II is a valid indicator of mood in individuals with epilepsy (Jones et al., 2005). Memory abilities were assessed with the following indices of the WMS-III (Wechsler, 1997b): Auditory Immediate Memory Index, Auditory Delayed Memory Index, Visual Immediate Memory Index, and Visual Delayed Memory Index. The mean interval between pre- and post-surgical neuropsychological evaluations was 11.21 months ($SD = 4.79$), and the mean interval between surgery and post-operative testing was 7.39 months ($SD = 3.72$). Seventy-five percent of the sample completed testing between 5 and 7 months following surgery.

Table 1. Demographic and seizure data for study patients by depression subgroup and surgical side

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nondepressed ($n = 152$)</th>
<th>Poor mood state ($n = 59$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left ($n = 77$)</td>
<td>Right ($n = 75$)</td>
</tr>
<tr>
<td>Age (years) ($M [SD]$)</td>
<td>36.08 (11.93)</td>
<td>34.19 (11.82)</td>
</tr>
<tr>
<td>Education (years) ($M [SD]$)</td>
<td>13.38 (2.43)</td>
<td>12.76 (2.16)</td>
</tr>
<tr>
<td>Age at seizure onset ($M [SD]$)</td>
<td>16.19 (13.75)</td>
<td>13.81 (10.31)</td>
</tr>
<tr>
<td>Duration of Seizures ($M [SD]$)</td>
<td>19.75 (13.19)</td>
<td>20.43 (13.27)</td>
</tr>
<tr>
<td>Number of AEDs ($M [SD]$)</td>
<td>1.94 (0.61)</td>
<td>1.88 (0.64)</td>
</tr>
<tr>
<td>HS on Pathology ($n [%]$)</td>
<td>58 (76.3)</td>
<td>49 (65.3)</td>
</tr>
<tr>
<td>Antidepressants ($n [%]$)</td>
<td>5 (6.5)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Anxiolytics ($n [%]$)</td>
<td>0 (0.0)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Sex ($n [%]$)</td>
<td>Men = 40 (51.9)</td>
<td>Men = 41 (54.7)</td>
</tr>
<tr>
<td></td>
<td>Women = 37 (48.1)</td>
<td>Women = 34 (45.3)</td>
</tr>
<tr>
<td>Race ($n [%]$)</td>
<td>White = 76 (98.7)</td>
<td>White = 73 (97.3)</td>
</tr>
<tr>
<td></td>
<td>Black = 1 (1.3)</td>
<td>Black = 2 (2.7)</td>
</tr>
<tr>
<td>Good Seizure Outcome ($n [%]$)</td>
<td>73 (94.8)</td>
<td>70 (93.3)</td>
</tr>
</tbody>
</table>

Notes: AED = antiepileptic drug; HS = hippocampal sclerosis.

1. Information regarding medication is based on patients’ medication regimen at the time of pre-operative neuropsychological testing.

2. Hippocampal pathology data were not available for two patients (one left nondepressed and one left depressed).

3. There was a larger proportion of individuals in the depressed groups taking antidepressant medications when compared with the nondepressed groups—$\chi^2(6) = 9.979$, $p = .019$, $\phi = 0.217$.

4. There were more African American patients in the left temporal lobe epilepsy, poor mood state group—$\chi^2(3) = 7.849$, $p = .049$, $\phi = 0.193$.

5. Good seizure outcome = Engel Class 1A or 1B at time of post-operative neuropsychological evaluation (Engel, 1987).
**Classification**

Patients were classified into one of two groups based on pre-surgical BDI-II total score. Patients with scores from 0 to 15 were classified as nondepressed \((n = 152; 72\% \text{ of the sample})\) and patients with scores of \(\geq 16\) were classified as having poor mood \((n = 59, 28\% \text{ of the sample})\). We used these scores to dichotomize level of symptoms suggestive of depressed mood based on research that demonstrated that a BDI-II cutoff score of \(> 15\) had a sensitivity of 0.84 and a specificity of 0.88 in identifying epilepsy patients classified as having current major depression (Jones et al., 2005) using the Structured Clinical Interview for DSM-IV (First, Spitzer, & Gibbon, 2001).

**Statistical Analyses**

First, possible between-group differences in demographic and disease-related variables were assessed using \(2 \times 2\) ANOVAs, with side of surgery and depression group as fixed factors, and \(\chi^2\) analyses. Similar analyses were conducted to examine group differences in pre- and post-operative memory performance. Second, several three-way mixed ANOVAs were performed with each memory index as the dependent variable (Auditory Immediate Memory, Auditory Delayed Memory, Visual Immediate Memory, and Visual Delayed Memory), side of surgery (left, right) and mood status (poor mood, not depressed) as between-group factors, and time (pre-surgery, post-surgery) as a repeated factor. Finally, a series of hierarchical linear regression analyses were used to determine whether pre-surgical mood state significantly adds to the prediction of post-surgical memory performance after TLR over and above pre-surgical memory ability. Analyses were conducted separately for each of the WMS-III Index scores. For Block 1 of each regression, a pre-surgical WMS-III Index score was entered (e.g., Auditory Immediate Memory Index). Total score on BDI-II prior to surgery was entered for Block 2. Change in memory score (i.e., post-surgical minus pre-surgical memory performance) was entered as the dependent variable. Standard scores were used for the memory data, and raw scores were used for the mood state data in all regression analyses. Regressions were conducted separately for left-sided and right-sided surgeries given the finding that the relationship between depression and recall is moderated by side of seizure focus (see Dulay et al., 2004). The significance of the addition of the mood state score (Block 2) was defined by a statistically significant change in \(R^2\). All statistics were tested against an \(\alpha\) of \(p < .05\).

**Results**

**Demographic and Disease Related Variables**

There were no significant differences between the groups in age, education, sex, age at seizure onset, duration of epilepsy, number of antiepileptic drugs, surgery type, or hippocampal pathology. There was a larger proportion of individuals in the depressed groups taking antidepressant medications when compared with the nondepressed groups, \(\chi^2(3) = 9.979, p = .019, \phi = 0.217\) (Table 1), but there were no differences between groups in the number of patients taking anxiolytic medications. Race distributions were different such that there were more African American patients in the left TLE, poor mood state group (i.e., 4 vs. 1 or 2), \(\chi^2(3) = 7.849, p = .049\). While this finding was statistically significant, the effect size was very small (\(\phi = 0.193\)); therefore, we did not statistically control for this demographic factor. There were no significant differences between groups (poor mood and not depressed), collapsed across seizure side, in WMS-III memory performance (Table 2).

**Mixed ANOVAs**

Results revealed a significant three-way interaction of depression \(\times\) time \(\times\) surgical side for Auditory Delayed Memory, \(F(1,207) = 4.407, p = .037, \eta_p^2 = 0.021\). There were no significant three-way interactions for Auditory Immediate Memory, \(F(1,207) = 1.135, p = .288, \eta_p^2 = 0.005\); Visual Immediate Memory, \(F(1,207) = 2.035, p = .155, \eta_p^2 = 0.010\); or Visual Delayed Memory, \(F(1,207) = 2.338, p = .128, \eta_p^2 = 0.011\).

Fig. 1A and B graphically depict the relationship between pre-surgical mood state, side of surgery, and Auditory Delayed Memory performance. This significant three-way interaction revealed that individuals with poor pre-surgical mood state who underwent left TLR demonstrated greater declines in memory test performance compared with nondepressed patients after left TLR (Fig. 1A). In contrast, depressed and nondepressed patients who underwent right-sided surgeries demonstrated slight improvements or no change in memory test scores (Fig. 1B).
Among left anterior temporal lobectomy (ATL) patients, BDI-II score demonstrated incremental validity, over and above pre-surgical memory scores, in predicting post-surgical memory change on all WMS-III Memory Indices. Specifically, pre-surgical immediate verbal recall (Block 1) accounted for 16.2% of the variance in post-surgical immediate verbal recall change \(\rho = .001\) such that higher pre-surgical scores were associated with greater memory loss from before to after surgery. Pre-surgical mood state (Block 2) accounted for an additional 7.0% of the variance in verbal recall change \(\rho = .01\) over and above pre-surgical immediate verbal memory score. For delayed verbal recall in left ATL patients, Block 1 accounted for 22.6% of the variance in change of delayed verbal recall \(\rho = .001\) and pre-surgical mood state (Block 2) accounted for an additional 3.6% of the variance in verbal recall change \(\rho = .05\). Pre-surgical mood state also demonstrated incremental validity in predicting post-surgical change in visual immediate and visual delayed memory with added variance of 3.7% (above 9.3% accounted for by visual immediate memory) and 6.2% (above 10.2% accounted for by visual delayed memory), respectively.

In contrast, although pre-surgical memory score significantly predicted post-surgical memory change on all of the WMS-III memory indices except the Auditory Immediate Memory Index among patients who underwent right ATLs, pre-surgical poor mood did not add significantly to any of the prediction models.

### Post hoc Analyses

In order to rule out the possibility that extraneous factors may have accounted for the decline on the Auditory Delayed Memory Index observed in depressed patients following left temporal lobectomy, several post hoc analyses were conducted. First, to determine whether an increase in depressive symptoms following surgery might account for the decline in memory scores following surgery, repeated-measures ANOVA examined BDI-II scores as a function of mood state group. This revealed a significant two-way interaction between mood state group and time—\(F(1,209) = 57.35, \rho < .001, \eta_p^2 = 0.215\)—such that depressed patients endorsed fewer depressive symptoms following surgery indicating a post-surgical improvement in their mood (Fig. 2A and B). Therefore, the observed decline in memory scores in the depressed left-TLR patients cannot be attributed to an increase in depressive symptoms following surgery.

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**Table 2.** WMS-III and BDI-II scores before and after temporal lobectomy by depression group and surgical side

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nondepressed ((n = 152))</th>
<th>Poor mood state ((n = 59))</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Left ((n = 77)) ((M [SD]))</td>
<td>Right ((n = 75)) ((M [SD]))</td>
</tr>
<tr>
<td>Pre-surgical Scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI-IIa</td>
<td>7.79 (4.35), range = 0–15</td>
<td>5.64 (4.07), range = 0–15</td>
</tr>
<tr>
<td>Auditory Delayed Memory Indexb</td>
<td>87.13 (15.16)</td>
<td>94.52 (17.29)</td>
</tr>
<tr>
<td>Visual Delayed Memory Index</td>
<td>89.18 (15.77)</td>
<td>85.19 (15.99)</td>
</tr>
<tr>
<td>Post-surgical Scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI-IIa</td>
<td>6.95 (7.94)</td>
<td>5.61 (6.71)</td>
</tr>
<tr>
<td>Auditory Delayed Memory Indexb</td>
<td>84.69 (14.33)</td>
<td>95.96 (18.08)</td>
</tr>
<tr>
<td>Visual Delayed Memory Indexb</td>
<td>91.88 (16.07)</td>
<td>83.64 (14.58)</td>
</tr>
</tbody>
</table>

**Notes:** WMS-III = Wechsler Memory Scale-III; BDI-II = Beck Depression Inventory-Second Edition.

aDepressed groups endorsed significantly more symptoms of depression on the BDI-II than nondepressed groups both prior to and following temporal lobectomy

bThere were no significance differences in memory performance between depressed and nondepressed groups collapsed across seizure side.

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**Fig. 1.** (A) Change in Auditory Delayed Memory Score following left TLR; (B) change in Auditory Delayed Memory Score following right TLR.

**Hierarchical Regression Analyses**

Among left anterior temporal lobectomy (ATL) patients, BDI-II score demonstrated incremental validity, over and above pre-surgical memory scores, in predicting post-surgical memory change on all WMS-III Memory Indices. Specifically, pre-surgical immediate verbal recall (Block 1) accounted for 16.2% of the variance in post-surgical immediate verbal recall change \(\rho < .001\) such that higher pre-surgical scores were associated with greater memory loss from before to after surgery. Pre-surgical mood state (Block 2) accounted for an additional 7.0% of the variance in verbal recall change \(\rho < .01\) over and above pre-surgical immediate verbal memory score. For delayed verbal recall in left ATL patients, Block 1 accounted for 22.6% of the variance in change of delayed verbal recall \(\rho < .01\) and pre-surgical mood state (Block 2) accounted for an additional 3.6% of the variance in verbal recall change \(\rho < .05\). Pre-surgical mood state also demonstrated incremental validity in predicting post-surgical change in visual immediate and visual delayed memory with added variance of 3.7% (above 9.3% accounted for by visual immediate memory) and 6.2% (above 10.2% accounted for by visual delayed memory), respectively.

In contrast, although pre-surgical memory score significantly predicted post-surgical memory change on all of the WMS-III memory indices except the Auditory Immediate Memory Index among patients who underwent right ATLs, pre-surgical poor mood did not add significantly to any of the prediction models.
Next, to determine whether differences in seizure outcome may have accounted for the decline in memory scores following surgery, \( \chi^2 \) analyses were conducted separately for patients with right and left TLRs. Patients were classified into one of two seizure groups based on their seizure status at the time of their post-operative neuropsychological evaluation (seizure-free, not seizure-free). Patients were considered “seizure-free” if they met criteria for Engel Class 1A or 1B outcome at the time of their post-operative neuropsychological evaluation (Engel, 1987). No significant differences in seizure outcome were found between depressed and nondepressed groups in patients who underwent right—\( \chi^2(1) = 0.013, p = .909 \)—or left—\( \chi^2(1) = 0.687, p = .407 \)—temporal resections (Table 1). Thus, the decline in memory scores observed in depressed left-TLR patients cannot be attributed to poorer seizure outcome.

**Discussion**

The present study examined pre-surgical depressed mood state as a predictor of post-surgical memory change after TLR for treatment of medically intractable seizures and sought to determine if pre-surgical poor mood state was useful in predicting memory change following TLR over and above pre-surgical memory performance. Results indicated that patients with depressed mood before surgery who underwent left TLR had significantly larger declines on a measure of verbal delayed memory after surgery compared with left- or right-TLR patients without depressed mood and right-TLR patients with depressed mood. Further, depressed mood state demonstrated incremental validity in predicting post-operative memory outcome on all WMS-III memory indices in patients who underwent left TLR. Given that depression may have a transient effect on memory functioning (e.g., Biringer et al., 2007) and may result in an underestimate of pre-surgical memory abilities, the magnitude of true memory decline following surgery may be even greater than these results suggest.

Similar to our results, others have reported an interaction between depressive symptoms and cognitive impairment after left but not right hemisphere stroke (Spalletta, Guida, De Angelis, & Caltagirone, 2002) as well as in nonsurgical candidates with left, but not right-sided, seizure foci (Dulay et al., 2004; Helmstaedter, 2004; Paradiso et al., 2001). Our post hoc analyses suggest that the observed declines in memory among depressed left-TLR patients cannot be attributed to an increase in depressive symptoms or to poorer seizure outcome after surgery. Results suggest that clinically elevated depressive symptoms before surgery are a risk factor for decline in memory after surgery. Further, results show that consideration of clinically elevated depressive symptoms improves the prediction of post-operative memory change over and above pre-surgical memory performance in patients who undergo left TLR. Our findings suggest that mood state should be taken into account when evaluating and providing feedback to patients about the cognitive risks associated with temporal lobectomy.

The greater decline in auditory memory observed in depressed patients following surgery may partly be related to limited functional reserve capacity. Functional reserve refers to the idea that individuals with neurological impairment may be able to compensate for focal damage by using other intact parts of their brain. In the case of individuals with temporal lobe seizures, the functional reserve hypothesis has been used to suggest that post-operative memory decline is largely a function of the capacity of the contralateral mesial temporal structures to support memory following resection of the ipsilateral structures (Chelune, 1995). In recent years, a number of studies have demonstrated that patients with epilepsy and comorbid depression show greater neuroimaging abnormalities than nondepressed epilepsy patients and/or normal controls. Specifically, elevated depressive symptomatology in patients with epilepsy is associated with mesial temporal sclerosis (Quiske, Helmstaedter, Lux, & Elger, 2000), bilateral reduction in inferior frontal glucose metabolism (Bromfield et al., 1992), and focal ipsilateral orbitofrontal hypometabolism (Salzberg et al., 2006) using F-fluorodeoxyglucose-positron emission tomography, lower contralateral temporal and bilateral frontal perfusion and higher occipital perfusion using single photon emission computed tomography (Schmitz et al., 1997), and metabolic abnormalities in the temporal lobes using \(^{1}H\) magnetic resonance spectroscopy.
More studies will be required to replicate these findings and to identify the reasons for the significant decline in memory observed in left-TLR patients with depressive symptoms. Future studies should also investigate whether these findings are specific to depressive symptoms as measured by the BDI-II or if they generalize to other measures of depression. Research will also need to determine whether these findings hold true for other memory measures and at longer post-operative intervals. Finally, it will be important to determine if pharmacologic intervention, remediation, or compensatory strategies could be used to help improve a person’s functional reserve capacity pre-surgically thereby reducing the likelihood of post-surgical declines. If findings from the current study are cross-validated, our results would suggest that pre-surgical depressed mood state is an important indicator of cognitive risk associated with TLR, particularly in patients undergoing left-sided temporal resections. Further study of the relationship between depression and neuropsychological performance will improve the accuracy of our assessment of the strengths, weaknesses, and needs of depressed individuals with epilepsy.

**Conflict of Interest**

None declared.

**References**


