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BRIEF REPORT

Amygdala lesions are associated with improved mood after epilepsy surgery

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Abstract

Neuroimaging studies in healthy and clinical populations strongly associate the amygdala with emotion, especially negative emotions. The consequences of surgical resection of the amygdala on mood are not well characterized. We tested the hypothesis that amygdala resection would result in mood improvement. In this study, we evaluated a cohort of 52 individuals with medial temporal lobectomy for intractable epilepsy who had resections variably involving the amygdala. All individuals achieved good post-surgical seizure control and had pre- and post-surgery mood assessment with the Beck Depression Inventory (BDI) ratings. We manually segmented the surgical resection cavities and performed multivariate lesion-symptom mapping of change in BDI. Our results showed a significant improvement in average mood ratings from pre- to post-surgery across all patients. In partial support of our hypothesis, resection of the right amygdala was significantly associated with mood improvement ($r = 0.5$, $p = 0.008$). The lesion-symptom map also showed that resection of the right hippocampus and para-hippocampal gyrus was associated with worsened post-surgical mood. Future studies could evaluate this finding prospectively in larger samples while including other neuropsychological outcome measures.

Keywords Temporal lobe epilepsy · Lesion symptom mapping · Mood changes · Amygdala

Introduction

The amygdala is a small almond-shaped structure located in the medial temporal lobe, anterior to the hippocampus. It has been strongly implicated in mood and psychopathology, particularly in negative emotions like fear and anxiety (Phelps and LeDoux 2005; Price and Drevets 2010). The amygdala is also implicated in major depression, with prior studies demonstrating that the severity of depressive episodes is associated with larger amygdala volume, increased and prolonged amygdala activity, or an increase in amygdala blood flow (Drevets 2000, 2001; Siegle et al. 2002; Zetzsche et al. 2006). In contrast, reduced activity of the amygdala has been associated with improvements in depression or increases in positive mood in healthy individuals (Fu et al. 2004; Kraehenmann et al. 2015).

Most of these findings linking the amygdala to depression are correlative in nature. Methods that allow stronger causal inferences on the role of the amygdala in mood include electrical brain stimulation and changes that occur in the setting of acquired brain lesions. Scangos and colleagues recently demonstrated that gamma power within the amygdala correlated with depression severity, and the reduction of gamma

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power by electrical stimulation corresponded with a robust mood improvement (Scangos et al. 2021). While there are historical data on the effects of amygdala removal in psychosurgery, much of this work was focused on aggression (Mpakopoulou et al. 2008; Zhang et al. 2017; Gouveia et al. 2021), and the effects on mood are not well characterized.

In the current study, we hypothesized that surgical resection of the amygdala would be associated with an improvement in mood. To test this hypothesis, we evaluated mood outcomes in a clinical sample of patients with epilepsy who underwent medial temporal lobectomy as a treatment for medically refractory epilepsy. The Beck Depression Inventory (BDI) is a self-reported scale that assesses symptoms of depression according to the DSM-IV, and is used as our assessment of mood pre- and post-surgery (change in BDI, ΔBDI). Improvement in mood following surgery was evaluated in relation to the brain regions that were resected using multivariate lesion-symptom mapping (Pustina et al. 2018).

Materials and methods

Participants

Participants were obtained from the Patient Registry of the Division of Behavioral Neurology and Cognitive Neuroscience at the University of Iowa. The cohort was selected from a pool of 61 patients with medically refractory epilepsy who underwent unilateral medial temporal lobectomy between 1983 and 2019, completed pre- and post-surgical BDI assessment in the chronic epoch (≥ 3 months), and completed a post-surgery research-quality structural MRI scan ≥ 2 months after the surgery. We included participants who had a successful surgery with regard to seizure outcome by achieving complete or near complete seizure freedom in the first post-surgical year, with near complete seizure freedom defined as only having rare breakthrough seizures secondary to missed medications or in the presence of other provocations. The cohort included 52 participants after excluding patients who continued to have seizures following surgery ($n = 7$) or with unknown seizure outcome information ($n = 2$). 23 participants had a right temporal lobectomy (44%). The demographics of all participants are presented in Table 1.

Lesion segmentation

All participants had a medial temporal lobe resection with visible lesion boundaries evident from a research-quality structural MRI (T1 and T2 sequences). The surgical resection cavity was traced manually for each participant using the MAP-3 method of lesion tracing for individuals who enrolled in the Patient Registry prior to 2006, which involves manual tracing of lesion borders on a template brain (Damasio and Frank 1992; Fiez et al. 2000). After 2006, lesions were manually traced on native T1-weighted scans (Smith et al. 2004) and then transformed to the 1-mm Montreal Neurological Institute (MNI-152) template brain (fsl.fmrib.ox.ac.uk/fsl/) using nonlinear registration and lesion masking techniques available in ANTs (Avants et al. 2008). The anatomical accuracy of the lesion boundaries was reviewed and edited as needed in native and MNI space by a neurologist (A.D.B.) blinded to mood rating outcomes.

Lesion analyses

A data-driven multivariate lesion-symptom mapping of mood change, measured as the difference in BDI scores from pre- to post-surgery, was used to identify brain structures that, when lesioned, are significantly associated with changes in BDI. We used the LESYMAP package in R (https://github.com/dorianps/LESYMAP), which uses a sparse canonical correlation analysis for neuroimaging (SCCAN) (Pustina et al. 2018). The SCCAN method involves an optimization procedure to assign a continuous weight to each voxel (range 0 – 1) to maximize the multivariate correlation with the true behavioral scores. The validity of the map is evaluated using a fourfold cross-validation (with 25% of the sample held out at each fold). The optimal sparseness and statistical significance of the lesion–behavior association is tested by comparing the actual change in mood to that predicted by the model. Significance is tested on the entire map, which avoids problems associated with multiple comparison correction. The multivariate analysis was conducted with all participants combined and for each hemisphere run independently to account for potential differences related to lesion laterality. We also generated a proportional subtraction map to show regional changes in the lesion locations associated with changes in BDI ratings for descriptive purposes. The lesion overlap map of individuals with improved mood was subtracted from the lesion overlap of individuals with worsened mood. The voxels remaining from the subtraction were damaged at a proportionally higher rate in participants with mood improvement (e.g., if a voxel was affected in 70% of improved individuals and 5% of worsened individuals, then this voxel would have a difference value of 70% − 5% = 65%). This qualitative analysis can display regional trends that may not reach statistical significance in the multivariate lesion-symptom mapping analysis.

Results

Overall, participants showed a significant post-surgical improvement in mood with lower post-surgical BDI ratings (mean ± SD: 8.37 ± 7.38 points, median 6 points) compared

Table 1 Description of participants

	Right temporal lobectomy ($n=23$)	Left temporal lobectomy ($n=29$)
Sex	10 females (43%)	16 females (55%)
Handedness	20 Right-handed (87%)	24 Right-handed (83%)
Seizure onset age (range; mean ± SD; median)	1 mo.—38 years; 15.16 ± 11.94 years; 14 years	1 mo.—42 years; 15.22 ± 11.72 years; 16 years
Education (range; mean ± SD; median)	10–18 years; 13.65 ± 2.10 years; 13 years	10–18 years; 13.62 ± 1.93 years; 14 years
Age at surgery (range; mean ± SD; median)	18–58 years; 35.11 ± 10.34 years; 33 years	22–63 years; 38.85 ± 11.67 years; 33 years
Pre-surgical psychiatric diagnosis		
None	9 (39%)	13 (45%)
Anxiety or mood disorder	10 (43%)	13 (45%)
Adjustment disorder or subclinical/transient mood symptoms (no formal diagnosis)	2 (9%)	2 (7%)
Psychotic disorder or post-ictal psychosis	2 (9%)	1 (3%)
BDI post-surgical assessment time (range; mean ± SD; median)	3 mo.—8 years; 1.73 ± 1.73 years.; 1.11 years	3 mo.—11 years; 1.60 ± 2.10 years.; 1.03 years
Pre-surgical BDI score (range; mean ± SD; median)	0–24 points; 10 ± 8.45 points; 9 points	0–39 points; 13 ± 10.23 points; 9 points
Post-surgical BDI score (range; mean ± SD; median)	0–29 points; 8 ± 7.66 points; 4 points	0–30 points; 9 ± 7.29 points; 6 points
ΔBDI (improved; worsened; no change)	11 (48%); 11 (48%); 1 (4%)	18 (62%); 9 (31%); 2 (7%)
Etiology of epilepsy/pathology		
Unclear	4 (17%)	4 (14%)
Sclerosis	11 (48%)	12 (41%)
Gliosis	0	5 (17%)
Cortical dysplasia	1 (4%)	5 (17%)
Mixed pathology	2 (9%)	1 (3%)
Mass	2 (9%)	2 (7%)
Trauma or other risk factors	3 (13%)	0

Δ*BDI* change in Beck depression inventory ratings from pre- to post-surgery

to pre-surgical ratings (mean ± SD: 11.75 ± 9.53 points, median 9 points); paired sample *t* test ($p=0.045$). Post-surgical mood improvement was observed in 56% of participants ($n=29$; mean ± SD: 11.28 ± 8.99 points, median 9 points), mood worsening in 38% ($n=20$; mean ± SD of 7.55 ± 6 points, median 5.5 points), and no change in mood assessment in 6% ($n=3$). An independent sample *t* test and a chi-square test showed no significant relationship between the ΔBDI with lesion laterality, handedness, or gender ($p>0.05$).

Lesion analyses

The location of the brain lesions from the 52 individuals included in the analysis is shown in Fig. 1a. The lesion-symptom mapping analysis of right medial temporal lobectomy lesions was the only analysis that reached a statistical significance ($r=0.5$, $p=0.008$). The map highlighted the right amygdala as the region most strongly associated with mood improvement, including the ventral basolateral nucleus and peri-amygdaloid cortical transition area (Tyszka and Pauli 2016), with a peak voxel at MNI coordinate (15, − 5, − 21), Fig. 1b. The proportional subtraction analysis was similar in highlighting the same region of the right amygdala with peak coordinates at (14, − 5, − 23), Fig. 1c. The same pattern of association was also seen on the left hemisphere with a left amygdala peak at (− 22, − 5, − 19), but this did not reach a statistical significance in the LESYMAP analysis. Additional findings that were observed within the same multivariate lesion-symptom map as the amygdala finding (but were not a part of our a priori hypothesis) included a significant association of lesions of the right hippocampus and surrounding cortex with higher post-surgical BDI ratings, including perirhinal, ectorhinal cortex (22, 0, − 35), and the para-hippocampal area 1 (21, − 38, − 10) (Glasser et al. 2016).

Discussion

This study investigated the effects of surgical resection of the amygdala on mood using multivariate lesion-symptom mapping, which provides a data-driven approach for relating changes in mood symptoms to the anatomy of the surgical

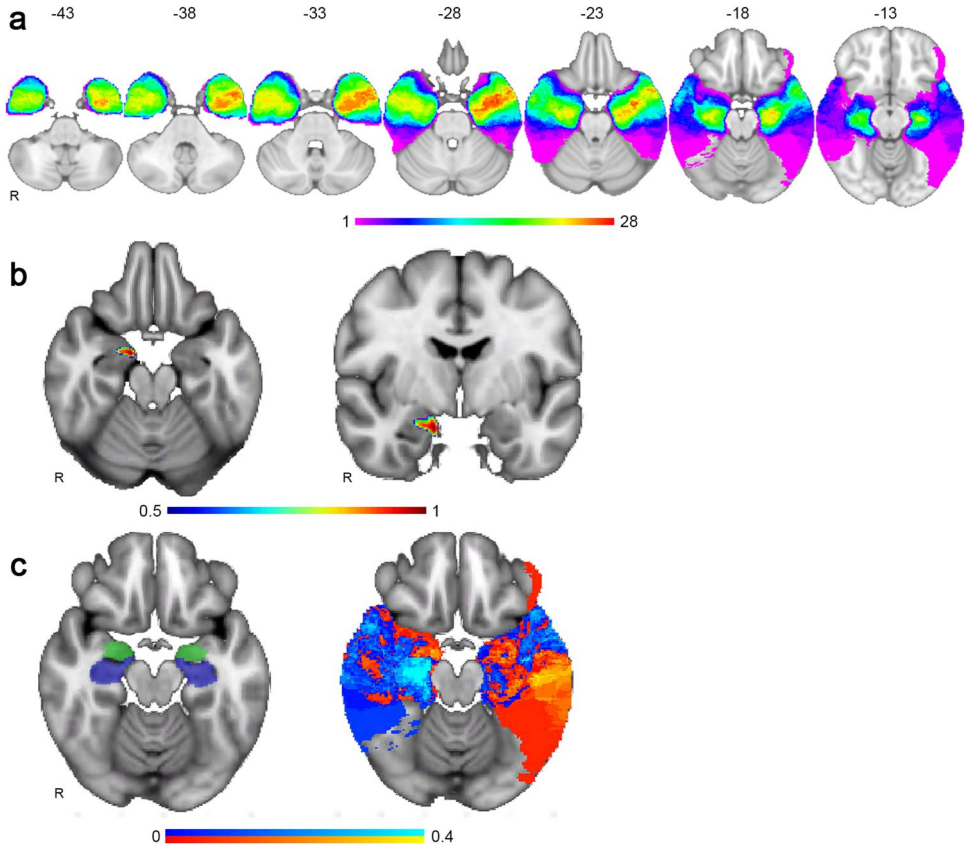

Fig. 1 **a** Lesion overlap. Lesion overlap map of the surgical resection cavities used in this analysis ($N=52$), with a peak overlap in the left medial temporal lobe $n=28$ of 52 at (− 40, − 4, − 25). **b** Multivariate lesion-symptom mapping. The lesion-symptom map of participants with right hemisphere lesions, showing an association of right amygdala lesions with improvement in post-surgical mood, with voxel weights displayed using a unit-less scale with values closer to 1 reflecting a stronger lesion–mood association. ($r=0.5$, $p=0.008$). **c** Lesion proportional subtraction map. The image on the left shows the location of the amygdala and hippocampus in green and blue, respectively, as a reference. The image on the right shows proportional subtraction results, where the red color scale displays regions preferentially associated with improved mood and the blue color scale displaying regions associated with mood worsening. Note the sharp contrast that respects that anatomical boundary between the hippocampus and amygdala, with hippocampus lesions more commonly associated with mood worsening and amygdala lesions associated with a higher likelihood of post-surgical improvement in mood

resection cavity. We hypothesized that amygdala resection would be associated with improvement in self-reported mood, as assessed with BDI ratings. Our hypothesis was partially supported, as resection of the right amygdala was significantly associated with improvement in mood based on multivariate lesion-symptom mapping. A similar trend was observed for the left amygdala, but this did not reach statistical significance. These findings are consistent with the role of the amygdala in processing negative emotions and psychopathology, including symptoms of depression (Donegan et al. 2003; Tranel et al. 2007; Victor et al. 2010). The association of a right-lateralized anterior temporal lobe lesions with improved mood was also a prominent finding in a recent large lesion study of depressed mood ($N=526$, Trapp et al. 2022). That study excluded individuals with epilepsy and thus there was no overlap with participants in the current study.

This study builds on prior studies of mood outcomes following a medial temporal lobe resection (Spencer et al. 2003; MacRodimitris et al. 2011; Smith et al. 2018; Bijanki et al. 2020; Hebel et al. 2021). Our findings also suggest that surgical resection of the right hippocampus and adjacent medial temporal lobe cortex was associated with increased depression symptoms, which also has precedent in the literature (Videbech and Ravnkilde 2004; Yang et al. 2007; Cheng et al. 2018; Rolls et al. 2020). There is ample evidence of amygdala–hippocampal subnetworks that are relevant for mood (Kirkby et al. 2018). The effect of lesions on these structures in humans is not well understood, but we think it is plausible that lesions to these structures are associated with opposing effects on mood, as suggested by the current results. Hippocampal damage has previously been shown in association with more intense or prolonged experiences of emotion (Feinstein et al. 2010; McCormick et al.

2016), greater moodiness (Warren et al. 2012), and feelings of being overwhelmed (McCormick et al. 2016). In contrast, amygdala lesions have been associated with anxiolysis and an approach-oriented fearless behavior in human and experimental animal research (Feinstein et al. 2011; Harrison et al. 2015; Korn et al. 2017). Taken together, these findings support the notion that medial temporal lobe structures have a causal role in mood. It is an intriguing possibility that lesions of the amygdala and hippocampus/para-hippocampal gyrus may have opposing effects on mood. This is supported by the sharp contrast at the amygdalo-hippocampal border that shows an association with mood improvement and worsening, respectively (Fig. 1c). Further research will be needed to support or refute the notion of opposing amygdala–hippocampal influences on mood following focal brain lesions.

The lack of any significant structure–function relationship on the left hemisphere was unexpected. We observed that left amygdala resection was also associated with a higher likelihood of improved mood (Fig. 1c), but this was less robust relative to the right hemisphere findings. The observed laterality is consistent with evidence of a right-sided hemispheric lateralization of emotion processing and mood (Gainotti 2019). However, this lateralization has not translated into consistent findings of lesion studies investigating post-lesion mood outcomes with regard to laterality (Nickel and Thomalla 2017). At this stage, we believe it is premature to ascribe much significance to the laterality differences noted here given the same general direction of non-significant results observed in Fig. 1c, but this will be an important topic of further investigation.

Limitations of the analysis include a lack of cognitive outcome data, so the influence of cognitive changes on mood is unclear, and a lack of standardization in the timing of post-surgical mood assessments that ideally would have been accompanied uniformly by psychiatric evaluations pre- and post-surgery among all participants. Moreover, mood changes observed in epileptic patients post-surgery could have been influenced by several biological and non-biological factors. These could include changes in cognition, changes in seizure medications, or changes in lifestyle, with the independence afforded by improved seizure control that may be associated with reduced anxiety and greater confidence in social settings. It is likely that the anatomical location of the surgery resection cavity and the disruption of functional brain networks that results from it would explain only part of the overall variance in mood. Further prospective studies of large cohorts that extensively characterize multiple variables that may influence mood will be useful in further characterizing the role of medial temporal lesion location and mood outcomes.

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Author contributions FMA: conducted the data analysis and drafted the manuscript and figures. NTT: conducted a chart review of the participants' records to evaluate for psychiatric diagnosis and the revision of the manuscript. DT and MAH: contributed to the data acquisition and the revision of the manuscript. ADB: contributed to the conceptualization, design, and supervision of the study. All authors revised and approved the final version of the manuscript.

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Data availability The datasets generated and/or analyzed during the current study are available upon request from the corresponding author.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethics approval All procedures performed in the study were in accordance with the University of Iowa Institutional Review Board.

Consent to participate Informed consents were obtained from all participants in accordance with the University of Iowa Institutional Review Board.

Consent to publish Not applicable.

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