The Amygdala and Sexual Drive: Insights from Temporal Lobe Epilepsy Surgery

Amee D. Baird, BA (Hons),[1] Sarah J. Wilson, PhD,[1,2] Peter F. Bladin, MD, FRACP,[2]
Michael M. Saling, PhD,[1,2] and David C. Reutens, MD, FRACP[2,3]

The aim of this study was to explore the relationship between the amygdala and human sex drive. We compared amygdalar volume in groups of patients with or without sexual changes after temporal lobe resection and in age-matched neurologically normal subjects. Forty-five patients with intractable temporal lobe epilepsy who underwent surgical resection in the Comprehensive Epilepsy Program at the Austin and Repatriation Medical Centre completed a semistructured interview and questionnaire relating to sexual outcome after surgery. Volumetric analyses of both amygdalae were conducted on the patients' preoperative T_1-weighted magnetic resonance imaging scans and those of 46 neurologically normal controls. Patients who reported a postoperative sexual increase had a significantly larger amygdalar volume contralateral to the site of their resective surgery than patients with a sexual decrease or no change than control subjects. There was a significant positive relationship between contralateral amygdalar volume and the maximum degree of sexual change. We have demonstrated a relationship between contralateral amygdalar volume and sexual outcome in patients undergoing temporal lobe resection. This finding provides evidence for an important role of the amygdala in regulating human sexual behavior. A larger contralateral amygdala may contribute to the expression of increased or improved sexuality after temporal lobe resection.

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Previous animal studies have demonstrated a role for the temporal lobe, in particular, the amygdala, in the mediation of sexual behavior.[1] Human studies also have documented an association between temporal lobe dysfunction and altered sexual behavior, ranging from indiscriminate sexual advances[2,3] to impotence[4] and paraphilias such as fetishism.[5,6] In patients, it often has been assumed that alterations in sexual behavior reflect involvement of the amygdala, but there has been no research to our knowledge directly examining the relationship between the amygdala and human sexual behavior.

Resection of the temporal lobe is a common treatment for intractable epilepsy and may be followed by postoperative sexual changes.[7–9] The study of sexual drive in patients with temporal lobe epilepsy (TLE) before and after resection has the potential to yield insights into the structure–function relationships underlying human sex drive. Because surgery affects one amygdala either by resection or deafferentation, a role in sexual function must be mediated by the remaining contralateral amygdala. Thus, the population of patients undergoing temporal resection provides an important model for exploring the association between human sexual behavior and the amygdala.

Quantitative magnetic resonance imaging (MRI) techniques have been used to study morphological changes of the temporal lobe in patients with TLE.[10,11] Most of the research has focused on hippocampal abnormalities, but volume changes in the amygdala also have been described.[11] Volumetric assessment of mesial temporal structures, including the amygdala, has been used to examine structure–function relationships in patients with TLE.[12–14] We describe a study using MRI and amygdalar volumetry to examine the contribution of the amygdala to postoperative sexual changes. In a group of patients with intractable TLE undergoing surgical resection, we tested the hypothesis that there are differences in preoperative amygdalar volume between groups of patients who report a postoperative sexual increase, decrease, or no change.

Subjects and Methods

Subjects

All participants had undergone temporal lobe resection (TLR) in the Comprehensive Epilepsy Program at the Austin

[1]School of Behavioural Science, Department of Psychology, University of Melbourne; [2]Comprehensive Epilepsy Program, Epilepsy Research Institute, Austin and Repatriation Medical Centre; and [3]Department of Medicine, University of Melbourne, Melbourne, Australia

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Address correspondence to Dr Reutens, Department of Neurology, Austin and Repatriation Medical Centre, Heidelberg 3084, Victoria, Australia. E-mail: reutens@austin.unimelb.edu.au

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and Repatriation Medical Centre (A&RMC) between August 1995 and May 2001. The preoperative protocol and surgical approach has been described previously.[15]

A total of 107 TLRs were performed during this time period. Patients were excluded for the following reasons: (1) age younger than 17 years at the time of operation (n = 6); (2) preoperative full-scale IQ less than 70 (n = 4); (3) previous neurosurgery of any type (n = 10); (4) presence of any major surgical complications, such as perioperative stroke (n = 2); (5) clinical contraindications (eg, in which it was considered inappropriate to discuss sexual matters for cultural reasons) (n = 8); (6) patients lost to follow-up or unreachable at the time of recruitment (n = 8); (8) presence of brain lesions other than those considered to be the surgical target (n = 2); and (9) presence of a comorbid long-standing psychiatric or medical illness (n = 1). This resulted in a target sample of 66 patients, of which 58 agreed to participate in the study. Thirteen patients did not have high-resolution T1 preoperative MRI scans, leaving a sample of 45 patients available for volumetric analyses. This sample comprised 30 anterior temporal lobectomies, 1 amygdalohippocampectomy, 1 posterior hippocampal lesionectomy, 2 parahippocampal resections, and 11 limited temporal neocortical resections. Volumetric analyses also were performed on the MRI scans of 46 neurologically normal volunteers, as assessed by a brief clinical screening interview and a neurological examination.

Procedure

This study was approved by the Human Research Ethics Committee of the A&RMC, and all participants provided informed consent. As part of their routine clinical management, all patients undergoing surgery were assessed preoperatively and were followed up at regular intervals for a minimum of 2 years postoperatively by the Seizure Surgery Follow-up and Rehabilitation Program.[16] Participants completed a semistructured interview either in person or, when this was not possible, by telephone with the same interviewer. Participants also completed a questionnaire relating to sexual outcome after surgery. A retrospective review of medical files was conducted to obtain information for the clinical characterization of the sample. All patients had undergone routine detailed preoperative and postoperative clinical psychiatric evaluation in person according to Diagnostic and Statistical Manual–IV criteria. Psychiatric evaluation was independent of the interview and questionnaire used in this study. Plasma levels of carbamazepine and phenytoin for the first 12 months after surgery were available in a subsample of 21 and 4 patients, respectively.

Measures

We designed a semistructured interview and questionnaire that provide qualitative and quantitative information, respectively, about sexual change after epilepsy surgery.[9] The areas of sexual functioning discussed in the interview included sexual interest and drive, thoughts/fantasies, and sexual activity. The questionnaire comprises two sections, the first examining the individual's perception of what constitutes "normal" sexual functioning and the second quantifying the nature and degree of postoperative change. Both sections of the questionnaire examined five areas of sexual functioning: sexual activity, thoughts, fantasies, masturbation, and drive. Participants were asked to rate the frequency of their functioning in each of these areas using a five-point Likert-type scale (1 = not at all, 5 = many times a day, see Table 1).

Both sections of the questionnaire have high internal consistency, test-retest reliability, and convergent validity with the interview.[9] From the questionnaire data, a "change score" was calculated for each area of sexual functioning considered by the patient to have changed. The purpose of this score was to determine the quantitative level of change above or below each individual's perception of "normality," and to obtain a numerical value of change for correlation with amygdalar volume. The score was generated by subtracting the frequency rating perceived to be normal by each individual from the corresponding postoperative frequency rating. Change scores for each area of sexual functioning ranged from −4 to 4. A *maximum change score* was determined using the largest change score signed in the direction reported by the patient in the interview (ie, overall postoperative sexual decrease = negative, overall postoperative increase = positive). A *mean change score* also was determined by adding each change score and dividing this figure by the number of change scores for each individual.

Image Acquisition

All patients had undergone high-resolution three-dimensional T_1-weighted MRI scans as part of routine presurgical clinical investigations. MRIs were acquired on two 1.5T clinical scanners. Patient MRI scans performed before November 1998 (n = 36) were acquired on a Siemens Magnetom 63 (Siemens Medical Systems, Erlangen, Germany). The magnetization prepared rapid gradient echo (MPRAGE) pulse sequence comprised TR 12 milliseconds, TE 4 milliseconds, TI 350 milliseconds, flip angle 10 degrees, FOV 23cm, matrix 224 × 256, NEX 1. All controls (n = 46) and patient MRI scans performed after November 1998 (n = 9) were acquired on a Signa Echospeed Superconducting Imaging System (General Electric Medical Systems, Milwaukee, WI). The three-dimensional spoiled gradient recalled echo acquisition comprised TR 10.5 milliseconds, TE 2.2 milliseconds, TI 350 milliseconds, flip angle 20 degrees, FOV 25cm, matrix 256 × 256, NEX 1.

Image Registration

Before image registration, all MRIs underwent automated scalp removal implemented using purpose-written software for MATLAB (The Mathworks, Natick, MA). The final scalped image was registered into stereotaxic coordinate space based on the 152-subject T1-weighted average template from the Montreal Neurological Institute, using a nine-parameter linear transformation (rotation, translation, and rescaling along the principal axes) and the software package AIR 3.0,[17] (http://bishopw.loni.ucla.edu/AIR3/index.html). Identifying information was removed from image filenames and the order of patient and control images was randomized.

Volumetric Analysis

Manual segmentation of both amygdalae was performed using interactive mouse-driven software which enabled simul-

Table 1. Questionnaire Items

Section 1					
1. A normal sex life in the everyday wo/man means having sex	1[a]	2	3	4	5
2. In the everyday wo/man, sexual thoughts would normally occur.	1	2	3	4	5
3. Normal sexual functioning in the everyday wo/man means masturbating	1	2	3	4	5
4. In the everyday wo/man, a healthy sex life means fantasizing about sex	1	2	3	4	5
5. A normal sex drive in the everyday wo/man means wanting sex	1	2	3	4	5
Section 2					
I experienced a change in my sex drive or sexual behavior (either brief or ongoing) after my operation.		YES		NO	
1. During the time of the change I had sex more often		YES		NO	
If YES, how often?	1	2	3	4	5
2. During the time of the change, I had sex less often.		YES		NO	
If YES, how often?	1	2	3	4	5
3. During the time of the change, I had more sexual fantasies		YES		NO	
If YES, how often?	1	2	3	4	5
4. During the time of the change, I had less sexual fantasies		YES		NO	
If YES, how often?	1	2	3	4	5
5. During the time of the change, my sex drive decreased		YES		NO	
If YES, how often have you wanted to have sex?	1	2	3	4	5
6. During the time of the change, my sex drive increased		YES		NO	
If YES, how often have you wanted to have sex?	1	2	3	4	5
7. During the time of the change, I masturbated more		YES		NO	.
If YES, how often?	1	2	3	4	5
8. During the time of the change, I masturbated less.		YES		NO	
If YES, how often?	1	2	3	4	5
9. During the time of the change, I had more sexual thoughts		YES		NO	
If YES, how often?	1	2	3	4	5
10. During the time of the change, I had less sexual thoughts		YES		NO	
If YES, how often?	1	2	3	4	5

[a]1 = not at all; 2 = once a month or less; 3 = once to a few times a week; 4 = once a day; 5 = many times a day.

taneous analysis of coronal, sagittal, and axial images. The total volume of each amygdala was calculated using a voxel-counting algorithm. The last available high-resolution preoperative MRI scan was used for volumetric analyses. The boundaries of the amygdala were defined using previously described and validated anatomical landmarks established by Watson and colleagues.[18]

Intrarater reliability of volumetric measurements was determined using 10 randomly selected MRIs segmented on two occasions separated by a 9-month interval. The difference in volume was expressed as a percentage of the average of the two volume measurements for each subject. The mean difference between volume measurements performed 9 months apart was 0.06%. An intraclass correlation coefficient of 0.8 was obtained, demonstrating high intrarater reliability.

Statistical Analyses

Four analyses were conducted. A two-way between-groups multivariate analysis of variance (MANOVA) investigated differences in amygdalar volume as a function of sexual outcome and side of resection. The two dependent variables were contralateral and ipsilateral amygdalar volume, and the two independent variables were sexual outcome (increase, decrease, or no change) and side of resection. Preliminary assumption testing showed no violations, and a Bonferroni adjusted α level of 0.025 was used. Sexual outcome groups were compared with planned simple contrasts (increase vs decrease; increase vs no change).

Spearman correlational analyses examined the relationship between the quantitative degree of postoperative sexual change (using the maximum or mean change score) and preoperative contralateral or ipsilateral amygdalar volume.

Two separate two-way ANOVAs investigated the impact of other variables, specifically pathology and type of temporal resection, on the relationship between sexual outcome and amygdalar volume. The first ANOVA examined differences in contralateral amygdalar volume as a function of pathology of resection (mesial temporal sclerosis [MTS] vs non-MTS such as cortical dysplasia) and sexual outcome. The dependent variable was contralateral amygdalar volume and the independent variables were pathology of resection and sexual outcome. The second two-way ANOVA examined differences in contralateral amygdalar volume as a function of type of temporal resection (cortical vs mesial [including anterior temporal lobectomy]) and sexual outcome. The dependent variable was contralateral amygdalar volume, and the independent variables were type of resection and sexual outcome.

Finally, two separate independent t tests were used to compare the amygdalar volumes of patients reporting a sexual increase to control amygdalar volumes. Given that controls have no "contralateral" amygdala, the analyses were conducted separately for each side of resection. The first t

test examined differences in right amygdalar volume as a function of group (controls vs left-sided TLR patients). The second t test examined differences in left amygdalar volume as a function of group (controls vs right-sided TLR patients).

Results

Demographics

The demographic features of the sample are shown in Table 2. There were no significant effects of group (patient vs control) as a function of age at the time of MRI scan [$t(89) = 0.3$, $p = 0.80$], gender distribution (Fisher's exact test, $p = 1$), or handedness (Fisher's exact test, $p = 0.46$).

Amygdalar volume ipsilateral or contralateral to the side of resection in patients did not vary as a function of preoperative or postoperative psychiatric morbidity ($p > 0.05$ for all comparisons; Table 3).

Sexual Outcome

Twenty-one patients reported a postoperative sexual increase, 14 described no sexual change, and 10 reported a sexual decrease. These changes are described in detail in Baird and colleagues.[9] The area of sexual function in which the maximum change typically occurred was sexual drive (21/31), followed by thoughts (15/31), activ-

Table 2. Sample Characteristics of TLR Patients and Controls

	TLR Patients (N = 45)			
Variable	Sexual Increase (n = 21)	No Change (n = 14)	Sexual Decrease (n = 10)	Controls (N = 46)
Gender n (%)				
Male	12 (57)	6 (43)	4 (40)	22 (48)
Female	9 (43)	8 (57)	6 (60)	24 (52)
Laterality of resection n (%)				
Left	11 (52)	11 (79)	5 (50)	N/A
Right	10 (48)	3 (21)	5 (50)	
Type of temporal resection, n (%)				
Mesial (including ATL)	14 (66)	12 (86)	9 (90)	N/A
Cortical	7 (34)	2 (14)	1 (10)	
Age at MRI scan (yr)				
Mean ± SD	33 ± 10	35 ± 8	39 ± 10	34 ± 13
Range	17–53	22–51	22–52	18–63
Age at operation (yr)				
Mean ± SD	34 ± 9	35 ± 8	39 ± 10	N/A
Range	17–53	23–51	22–52	
Pathology, n (%)				
MTS	12 (57)	9 (64)	6 (60)	N/A
Non-MTS[a]	9 (43)	5 (36)	4 (40)	
Handedness[b], n (%)				
Left	1 (4)	2 (14)	2 (20)	2 (4)
Right	20 (96)	12 (86)	8 (80)	43 (96)
Preoperative psychiatric morbidity[c]	n = 5	n = 7	n = 7	N/A
Anxiety	1	0	1	
Depression	2	3	3	
Postictal psychosis	0	2	0	
Eating disorder	1	1	0	
Personality disorder	0	0	2	
Hypomania	0	1	0	
Nonepileptic seizures	1	0	1	
Postoperative psychiatric morbidity[c]	n = 5	n = 5	n = 6	N/A
Anxiety	1	0	1	
Depression	4	3	4	
Adjustment disorder	0	0	1	
Eating disorder	0	1	0	
Postictal psychosis	0	1	0	

[a]This category includes pathology other than MTS such as cortical dysplasia or a foreign tissue lesion.
[b]Based on the Edinburgh Handedness Inventory. This information was not available for one control.
[c]Based on psychiatric evaluations using DSM-IV criteria for diagnosis. There were five patients who had two preoperative psychiatric diagnoses (one who reported a sexual increase, two who reported a decrease, and two who reported no change) and one who had two postoperative diagnoses (who reported no sexual change).

TLR = temporal lobe resection; N/A = not applicable; ATL = anterior temporal lobectomy; MRI = magnetic resonance imaging; MTS = mesial temporal sclerosis; SD = standard deviation.

Table 3. Mean Amygdalar Volume by Preoperative and Postoperative Psychiatric Morbidity in TLR Patients

Sexual Outcome	Left Amygdalar Volume, Mean (SD) cm^3	Right Amygdalar Volume Mean (SD) cm^3
Left TLR (N = 27)		
Preop psychiatric morbidity[a]		
Present (n = 7)	2.56 (0.56)	2.59 (0.34)
Absent (n = 19/20[b])	2.77 (0.47)	2.73 (0.47)
Postop psychiatric morbidity[1]		
Present (n = 9)	2.60 (0.50)	2.60 (0.40)
Absent (n = 17/18)	2.78 (0.49)	2.75 (0.45)
Right TLR (N = 18)		
Preop psychiatric morbidity		
Present (n = 6)	2.86 (0.57)	2.95 (0.58)
Absent (n = 12)	2.99 (0.60)	2.83 (0.37)
Postop psychiatric morbidity		
Present (n = 6)	2.91 (0.52)	2.89 (0.62)
Absent (n = 12)	2.97 (0.62)	2.85 (0.35)

[a]Based on psychiatric evaluations using DSM-IV criteria for diagnosis.
[b]The left amygdalar volume in one patient who underwent left TLR could not be measured because landmarks were distorted by an arachnoid cyst.

TLR = temporal lobe resection; SD = standard deviation; Preop = preoperative; postop = postoperative.

ity (15/31), masturbation (14/31), and fantasy (14/31). There were no significant differences between sexual outcome groups as a function of gender, side of resection, age at operation, age at the time of MRI scan, type of pathology (mesial temporal sclerosis [MTS] vs non-MTS), type of temporal resection (mesial vs cortical), handedness, or incidence of preoperative or postoperative psychiatric morbidity ($p > 0.05$ for all comparisons; see Table 2). Furthermore, there was no significant difference in plasma levels of carbamazepine between sexual outcome groups in a subsample of 21 patients (sexual increase $n = 10$; mean 33.7 ± 10.3 μmol/L; no sexual change, n = 7; mean 36.3 ± 12.6μmol/L; sexual decrease n = 4, mean 36.8 ± 8.3μmol/L; $F[2, 18] = 0.17$, $p = 0.84$).

Analysis 1. Amygdalar Volume as a Function of Side of Resection and Sexual Outcome

The mean preoperative amygdalar volumes of patients and controls are shown in Table 4. The two-way MANOVA showed a significant main effect of sexual outcome for the contralateral amygdalar volume ($F[2, 38] = 8.59$, $p = 0.002$, partial $\eta^2 = 0.28$). Planned simple contrasts showed that patients reporting a postoperative sexual increase had significantly larger contralateral amygdalar volumes than those reporting a decrease ($p = 0.001$) or no change ($p = 0.01$). There was no significant main effect of side of resection on contralateral amygdalar volume ($F[1, 38] = 2.2$, $p = 0.15$), and no interaction effect between side of resection and sexual outcome ($F[2, 38] = 0.13$, $p = 0.88$). For ipsilateral amygdalar volume, there was no significant main effect of sexual outcome ($F[2, 41] = 0.65$, $p = 0.53$), or side of resection ($F[1, 38] = 0.48$, $p = 0.49$), and no significant interaction effect ($F[2, 38] = 0.01$, $p = 0.99$).

Analysis 2. Amygdalar Volume and the Degree of Quantitative Sexual Change

There was a positive relationship between the amygdalar volume contralateral to the side of resection and the degree of sexual change. Specifically, a one-tailed Spearman's correlation showed a significant positive relationship between contralateral amygdalar volume and the maximum change score ($r = 0.35$, $p = 0.01$; Fig 1). Contralateral amygdalar volume and mean change score were positively correlated, but this did not reach statistical significance ($r = 0.21$, $p = 0.09$; Fig 2). There was no significant relationship between ipsilateral amygdalar volume and the maximum or mean change score ($r = -0.14$, $p = 0.19$ and $r = -0.18$, $p = 0.13$, respectively).

Analysis 3. Effect of Pathology and Type of Temporal Resection

The first two-way ANOVA explored differences in contralateral amygdalar volume as a function of pathology (MTS or non-MTS) and sexual outcome. Consistent with Analysis 1, there was a significant main effect of sexual outcome on contralateral amygdalar volume ($F[2, 39] = 0.81$, $p = 0.0005$). Planned simple contrasts showed that this effect lay in the sexual increase group. There was no significant main effect of pathology ($F[1, 39] = 1.83$, $p = 0.18$) and no interaction effect between sexual outcome and pathology ($F[2, 39] = 0.81$, $p = 0.45$; Table 5).

The second two-way ANOVA examined differences in contralateral amygdalar volume as a function

Table 4. Mean Amygdalar Volume by Sexual Outcome and Side of Resection in TLR Patients

Sexual Outcome	Left Amygdalar Volume, Mean (SD) cm^3	Right Amygdalar Volume, Mean (SD) cm^3
Left TLR (N = 27)		
Sexual increase (n = 11)	2.77 (0.48)	3.02 (0.37)
No sexual change (n = 10/11[a])	2.62 (0.49)	2.53 (0.31)
Sexual decrease (n = 5)	2.80 (0.58)	2.35 (0.35)
Right TLR (N = 18)		
Sexual increase (n = 10)	3.16 (0.63)	2.89 (0.52)
No sexual change (n = 3)	2.73 (0.50)	2.75 (0.28)
Sexual decrease (n = 5)	2.66 (0.36)	2.88 (0.40)
Controls (N = 46)		
N/A	2.47 (0.35)	2.55 (0.37)

[a]The left amygdalar volume in one patient who underwent left TLR could not be measured because landmarks were distorted by an arachnoid cyst.

TLR = temporal lobe resection; SD = standard deviation;
N/A = not applicable.

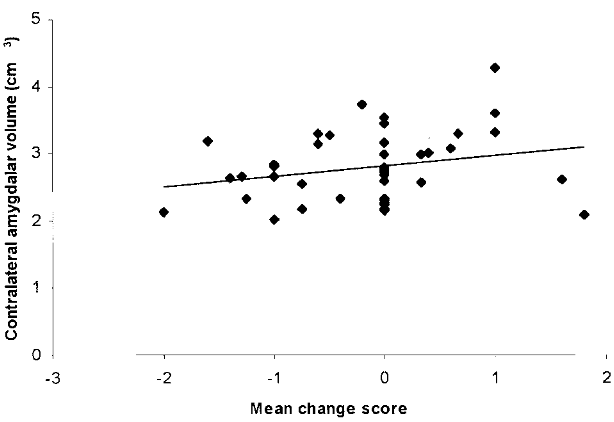

Fig 1. Relationship between contralateral amygdalar volume and maximum change score (r = 0.35, p = 0.01).

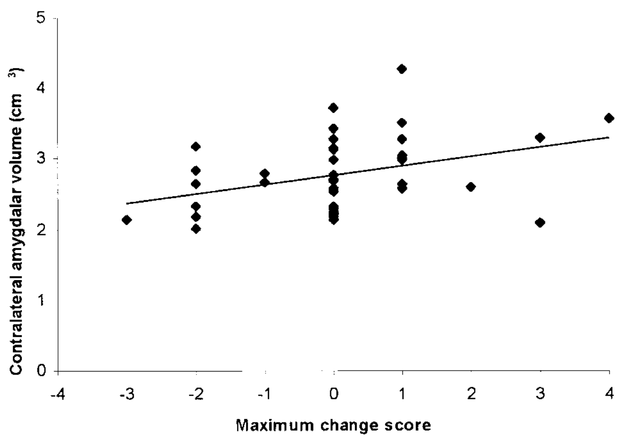

Fig 2. Relationship between contralateral amygdalar volume and mean change score (r = 0.21, p = 0.09).

of type of temporal resection and sexual outcome. Again, a significant main effect of sexual outcome was observed ($F[2, 39] = 6.97$, $p = 0.0005$), but there was no significant main effect of type of temporal resection ($F[1, 39] = 0.62$, $p = 0.44$) and no interaction effect ($F[2, 39] = 1.04$, $p = 0.36$; Table 6).

Analysis 4. Comparison with Control Amygdalar Volumes

The first t test examined differences in right amygdalar volume between controls and left TLR patients who reported a postoperative sexual increase. It showed that right (contralateral) amygdalar volume in left-sided TLR patients was significantly larger than the corresponding amygdalar volume in controls ($t[55] = 3.8$, $p = 0.0005$; see Table 4). The second t test examined differences in left amygdalar volume between controls and right-sided TLR patients who reported a postoperative sexual increase. It showed that left (contralateral) amygdalar volume was significantly larger in right-sided TLR patients than controls ($t[54] = 4.7$, $p = 0.0005$; see Table 4].

Discussion

We have demonstrated an association between preoperative amygdalar volume contralateral to the side of resection and postoperative sexual change in patients undergoing TLR. This is the first study to our knowledge to specifically examine the relationship between amygdalar volume and sexual functioning in humans. The principal findings of this study are that patients who reported a postoperative sexual increase have a larger contralateral amygdalar volume than those who reported a sexual decrease or no sexual change. In addition, the mean contralateral amygdalar volume in the sexual increase group was significantly greater than that of the corresponding amygdala in controls. This finding occurred irrespective of side or type of temporal resection and pathology. Furthermore, there was a significant positive relationship between contralateral

Table 5. Mean Amygdalar Volume by Side of Resection, Pathology, and Sexual Outcome in TLR Patients

Sexual Outcome	Left Amygdalar Volume, Mean (SD) cm^3	Right Amygdalar Volume, Mean (SD) cm^3
Left TLR MTS pathology (N = 18)		
Sexual increase (n = 7)	2.54 (0.29)	3.07 (0.35)
No sexual change (n = 7)	2.50 (0.48)	2.56 (0.32)
Sexual decrease (n = 4)	2.59 (0.42)	2.44 (0.33)
Right TLR MTS pathology (N = 9)		
Sexual increase (n = 5)	2.70 (0.43)	2.56 (0.54)
No sexual change (n = 2)	2.45 (0.18)	2.63 (0.26)
Sexual decrease (n = 2)	2.58 (0.36)	2.73 (0.11)
Left TLR non-MTS[a] pathology (N = 9)		
Sexual increase (n = 4)	3.16 (0.54)	2.94 (0.45)
No sexual change (n = 3/4)[b]	2.90 (0.49)	2.47 (0.32)
Sexual decrease (n = 1)	3.61	2.01
Right TLR non-MTS[a] pathology (N = 9)		
Sexual increase (n = 5)	3.62 (0.43)	3.22 (0.23)
No sexual change (n = 1)	3.29	3.00
Sexual decrease (n = 3)	2.71 (0.43)	2.98 (0.53)

[a]This category includes pathology other than MTS such as cortical dysplasia or a foreign tissue lesion.
[b]The left amygdalar volume in one patient who underwent left TLR could not be measured because landmarks were distorted by an arachnoid cyst.

TLR = temporal lobe resection; SD = standard deviation; MTS = mesial temporal sclerosis.

Table 6. Mean Amygdalar Volume by Side and Type of Temporal Resection and Sexual Outcome in TLR Patients

Sexual Outcome	Left Amygdalar Volume, Mean (SD) cm^3	Right Amygdalar Volume, Mean (SD)cm^3
Left TLR cortical temporal resection (N = 5)		
Sexual increase (n = 3)	3.34 (0.51)	2.92 (0.55)
No sexual change (n = 2)	3.18 (0.17)	2.46 (0.45)
Sexual decrease (n = 0)	—	—
Right TLR cortical temporal resection (N = 5)		
Sexual increase (n = 4)	3.69 (0.46)	3.30 (0.17)
No sexual change (n = 0)	—	—
Sexual decrease (n = 1)	2.66	3.18
Left TLR mesial temporal resection (N = 22)		
Sexual increase (n = 8)	2.55 (0.27)	3.06 (0.33)
No sexual change (n = 8/9)[a]	2.48 (0.45)	2.54 (0.30)
Sexual decrease (n = 5)	2.80 (0.58)	2.35 (0.35)
Right TLR mesial temporal resection (N = 13)		
Sexual increase (n = 6)	2.80 (0.46)	2.62 (0.50)
No sexual change (n = 3)	2.73 (0.50)	2.75 (0.28)
Sexual decrease (n = 4)	2.66 (0.42)	2.81 (0.42)

[a]The left amygdalar volume in one patient who underwent left TLR could not be measured because landmarks were distorted by an arachnoid cyst.

TLR = temporal lobe resection; SD = standard deviation.

amygdalar volume and the maximum degree of sexual change.

These findings are consistent with the evidence from previous research demonstrating a role for the amygdala in sexual behavior. There is substantial evidence for an association between amygdalar damage and altered sexual behavior in experimental animals.[1,19] Furthermore, amygdalar activation has been observed in rodents[20,21] and cats[22] during mating behavior. Recent research in humans has found amygdalar activation in response to erotic film excerpts using functional MRI,[23] supporting a role for the amygdala in the processing of the emotional significance of stimuli and specifically in the appraisal of sexual incentives.

There has been no previous research on the relationship between amygdalar volume and human sexual behavior, but there is some evidence to suggest that a bigger amygdala is associated with increased sexual functioning in animals, as found in our study. Previous studies in rats,[24] hamsters,[25] sheep,[26] and primates[27] have demonstrated a positive association between amygdalar size and sexual functioning. Proposed mechanisms accounting for the role of the amygdala in sexual behavior include (1) amygdalohypothalamic connections controlling endocrine substrates of sexual behavior, and (2) the amygdala's role in processing of potentially significant sexual stimuli.

Endocrine Mechanisms

Previous articles have argued that the amygdala plays an inhibitory role in the regulation of endocrine mechanisms associated with sexual behavior through its extensive connections with the hypothalamus. Schreiner and Kling[28,29] proposed that hypersexuality after amygdalectomy in cats reflected the disinhibition of neuroendocrine mechanisms including the hypothalamus. Some researchers have adopted this notion as an explanation for sexual changes in TLE patients.[30,31] It has been proposed that temporal lobe seizure discharges act to suppress the underlying endocrine mechanism associated with normal sexual behavior, causing hyposexuality.[30–32] Excision of the temporal lobe seizure focus eliminates the amygdala's inhibitory action on the hypothalamus, prompting a postoperative increase in sexual behavior.[30] Walker[30] has argued that multiple inputs to hypothalamic centers from other regions including the intact temporal lobe may account for variation in sexual outcome after temporal lobectomy.

Emotional Processing

An alternative hypothesized mechanism emphasizes the amygdala's role in the processing of emotional stimuli. It has been proposed that the amygdala regulates the attachment of appropriate emotional significance to sensory stimuli and determines reinforcing or discriminative properties of stimuli.[19] According to this notion, amygdaloid lesions do not disrupt a specific sexual/endocrinological mechanism; rather, they disturb emotional processing of stimuli, which, in turn, causes inappropriate and indiscriminate responses.[19,33,34] Thus, rather than playing an inhibitory role, the amygdala has a positive effect on sexual behavior by allowing the appropriate attachment of emotional significance to external sexual cues or stimuli. This hypothesis has been adopted by some as an alternative explanation for the variation in sexual outcome after temporal lobe resection. For example, Ellison[35] suggested that, in a patient with TLE, amygdalar dysfunction may cause an impaired ability to be aroused by an appropriate mate, whereas removal of the amygdala will improve matters, if a *properly functioning* contralateral amygdala remains.

In our study, a larger contralateral amygdala to the side of resection was associated with a better sexual outcome in the form of a sexual increase. Given that the volumetric analyses were performed on the patient's preoperative MRI scans and the sexual changes occurred postoperatively, it is proposed that a preexisting large amygdala contralateral to the side of the temporal lobe seizure focus predisposed individuals to a postoperative sexual increase. Indeed, a larger contralateral amygdala may be a prerequisite for the expression of increased or improved sexuality after temporal lobe resection. The mechanism underlying this relationship is unclear. One possibility is that a larger amygdala functions better in its role as a processor of emotional stimuli, specifically social/sexual cues, and in the attachment of significance to such stimuli. This would increase the likelihood of sexual response, resulting in a sexual increase.

Klüver–Bucy Syndrome: Increased versus Indiscriminate Sexual Behavior?

Klüver and Bucy[1] observed altered sexual behavior in rhesus monkeys after bilateral temporal lobectomy in the form of increased, indiscriminate sexual activity including mounting of animals of the same sex, other species, and inanimate objects. This behavior was termed *hypersexuality* and is considered a central feature of Klüver–Bucy syndrome. Subsequent studies in primates,[29] cats,[29,30] and rodents[29] found that these sexual changes could be produced after bilateral ablation of the amygdala.

The sexual increase described by the patients in our study was qualitatively different from the sexual changes observed in Klüver–Bucy syndrome. Hypersexual behavior in animals after bilateral amygdalar damage consists of indiscriminate sexual responses to inappropriate objects.[34] Similarly, sexual changes in human Klüver–Bucy syndrome comprise "inappropriate" or "indiscriminate" sexual behaviors ranging from sexual advances (verbal or physical) toward strangers[36] to homosexual advances that were previously uncharacteristic in the patient.[2,3] Coital movements and exhibitionistic behavior such as disrobing and public masturbation have also been described.[37] These behaviors are best interpreted as a "decrease in selectivity" of the target of sexual advances and the time and place of sexual expression. In contrast, the postoperative sexual increase described by our patients primarily consists of an increase in sex drive without indiscriminate sexual behavior. The use of the term *hypersexuality* in Klüver–Bucy syndrome has the potential to confound indiscriminate and increased sexual behavior.

Finally, our quantitative findings demonstrated a *positive* relationship between the amygdalar volume contralateral to the side of temporal resection and the maximum degree of sexual increase, which was most commonly in the area of sex drive. If a Klüver–Bucy mechanism was responsible, an inverse relationship would be expected. Hence, our findings suggest that increased sex drive after temporal resection does not reflect a Klüver–Bucy mechanism and supports the distinction between indiscriminate and increased sexual behavior.[33] Furthermore, it suggests that these two sexual behavioral features potentially arise from different neurobiological mechanisms.

Methodological Issues

In this study, the volumetric measurements were performed utilizing the three planes of view and the criteria established by Watson and colleagues.[18] A high intrarater reliability was observed. The use of Watson and colleagues[18] criteria to determine the anatomical boundaries of the amygdala during volumetric measurements has been found to provide highly reliable results, although it does produce larger volumes than other methods.[38] Viewing the amygdala in all three planes further improves the accuracy of anatomical delineation.[38]

The observation that a pre-existing large contralateral amygdala causes predisposition to postoperative sexual increase suggests that this is a trait rather than state association. Previous studies have found enlarged amygdalar volumes in patients with a range of affective disorders compared with healthy controls, including dysthymia and "psychosis of epilepsy" in patients with TLE,[39,40] depression,[41] bipolar disorder,[42] autism,[43] and generalized anxiety disorder in children.[44] In our study, we found no difference in amygdalar volumes between patients with or without preoperative or postoperative psychiatric morbidity. This suggests that that our finding of larger contralateral amygdalar volumes in patients with a postoperative sexual increase cannot be accounted for by the presence of affective disorders in these patients.

In conclusion, we have demonstrated a relationship between contralateral amygdalar volume and sexual outcome in patients undergoing temporal lobe resection. This finding provides evidence for an important role for the amygdala in regulating human sexual behavior. A larger contralateral amygdala may contribute to the expression of increased or improved sexuality after temporal lobe resection.

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References

1. Klüver H, Bucy PC. Preliminary analysis of functions of the temporal lobes in monkeys. Arch Neurol Psychiatry 1939;42: 979–1000.
2. Terzian H, Dalle Ore G. Syndrome of Klüver and Bucy reproduced in man by bilateral removal of the temporal lobes. Neurology 1955;5:373–380.
3. Marlowe WB, Mancall EL, Thomas JL. Complete Klüver Bucy Syndrome in man. Cortex 1975;11:53–59.
4. Johnson J. Sexual impotence and the limbic system. Br J Psychiatry 1965;111:300–303.
5. Kolarsky A, Freund K, Machek J, Polak O. Male sexual deviation: association with early temporal lobe damage. Arch Gen Psychiatry 1967;17:735–743.
6. Epstein AW. Relationship of fetishism and transvestism to brain and particularly temporal lobe dysfunction. J Nerv Men Dis 1961;133:247–253.
7. Blumer D, Walker AE. Sexual behaviour in temporal lobe epilepsy: a study of the effects of temporal lobectomy on sexual behaviour. Arch Neurol 1967;16:37–43.
8. Baird AD, Wilson SJ, Bladin PF, et al. Hypersexuality after temporal lobe resection. Epilepsy Behav 2002;3:173–181.
9. Baird AD, Wilson SJ, Bladin PF, et al. Sexual outcome after epilepsy surgery. Epilepsy Behav 2003;4:268–278.
10. Lee JW, Andermann F, Dubeau A, et al. Morphometric analysis of the temporal lobe in temporal lobe epilepsy. Epilepsia 1998;39:727–736.
11. Cendes F, Leproux F, Melanson D, et al. MRI of amygdala and hippocampus in temporal lobe epilepsy. J Comput Assist Tomog 1993;17:206–210.
12. Wood AG, Saling MM, O'Shea MF, et al. Components of verbal learning and hippocampal damage assessed by T2 relaxometry. J Int Neuro Soc 2000;6:529–538.
13. Cendes F, Andermann F, Gloor P, et al. Relationship between atrophy of the amygdala and ictal fear in temporal lobe epilepsy. Brain 1994;117:739–746.
14. Tebartz van Elst L, Woermann FG, Lemieux L, et al. Affective aggression in patients with temporal lobe epilepsy. A quantitative MRI study of the amygdala. Brain 2000;123:234–243.
15. Berkovic SF, McIntosh AM, Kalnins RM, et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. Neurology 1995;45:1358–1363.
16. Wilson SJ, Saling MM, Lawrence J, Bladin PF. Outcome of temporal lobectomy: expectations and the prediction of perceived success. Epilepsy Res 1999;36:1–14.
17. Woods RP, Grafton ST, Watson JDG, et al. Automated image registration. II. Intersubject validation of linear and nonlinear models. J Comput Assist Tomogr 1998;22:153–165.
18. Watson C, Andermann F, Gloor P, et al. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 1992;42:1743–1750.
19. Weiskrantz L. Behavioural changes associated with ablation of the amygdaloid complex in monkeys. J Comp Physiol Psychol 1956;49:381–391.
20. Pfaus JG, Heeb MM. Implications of immediate-early gene induction in the brain following sexual stimulation of female and male rodents. Brain Res Bull 1997;44:397–407.
21. Minerbo G, Albeck D, Goldberg E, et al. Activity of peptidergic neurons in the amygdala during sexual behavior in the male rat. Exp Brain Res 1994;97:444–450.
22. Holmes E, Egan K. Electrical activity of the cat amygdala during sexual behavior. Physiol Behav 1972;10:863–867.
23. Karama S, Lecours AR, Leroux JM, et al. Areas of brain activation in males and females during viewing of erotic film excerpts. Hum Brain Mapp 2002;16:1–13.
24. Cooke BM, Chowanadisai W, Breedlove SM. Post-weaning social isolation of male rats reduces the volume of the medial amygdala and leads to deficits in adult sexual behavior. Behav Brain Res 2000;117:107–113.
25. Alexander BM, Rose JD, Stellfung JN, et al. Low sexually performing rams but not male oriented rams can be discriminated by cell size in the amygdala and preoptic area: a morphometric study. Behav Brain Res 2001;119:15–21.
26. Romeo RD, Sisk CL. Pubertal and seasonal plasticity in the amygdala. Brain Res 2001;889:71–77.
27. Pellis SM, Iwaniuk, AN. Brain system size and adult-adult play in primates: a comparative analysis of the roles of the non-visual neocortex and the amygdala. Behav Brain Res 2002;134:31–39.

28. Schreiner L, Kling A. Rhinencephalon and behaviour. Am J Neurophysiol 1956;184:486–490.
29. Schreiner L, Kling A. Behavioural changes following rhinencephalic injury in cat. Neurophysiol 1953;16:643–659.
30. Walker AE. Man and his temporal lobes. John Hughlings Jackson Lecture. Surg Neurol 1973;1:69–79.
31. Herzog AG, Seibel MM, Schomer DL, et al. Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. Arch Neurol 1986;43:341–346.
32. Herzog AG, Seibel MM, Schomer DL, et al. Reproductive endocrine disorders in men with partial seizures of temporal lobe origin. Arch Neurol 1986;43:347–350.
33. Aronson LR, Cooper ML. Amygdaloid hypersexuality in male cats reexamined. Physiol Behav 1979;22:257–265.
34. Kling AS, Brothers LA. The amygdala and social behaviour. In: Aggleton JP, (ed). The amygdala: neurobiological aspects of emotion, memory and mental dysfunction. New York: Wiley, 1992. 353–377.
35. Ellison JM. Alterations of sexual behaviour in temporal lobe epilepsy. Psychosomatics 1982;23:499–509.
36. Friedman HM, Allen N. Chronic effects of complete limbic lobe destruction in man. Neurology 1969;19:679–690.
37. Shraberg D, Weisberg L. The Klüver-Bucy syndrome in man. J Nerv Ment Dis 1978;166:130–134.
38. Brierly B, Shaw P, David AS. The human amygdala: a systematic review and meta-analysis of volumetric magnetic resonance imaging. Brain Res Rev 2002;39:84–105.
39. Tebartz van Elst L, Woermann F, Lemieux L, Trimble MR. Amygdala enlargement in dysthymia—a volumetric study of patients with temporal lobe epilepsy. Biol Psychiatry 1999;46: 1614–1623.
40. Tebartz van Elst L, Baeumer D, Lemieux L, et al. Amygdala pathology in psychosis of epilepsy. A magnetic resonance imaging study in patients with temporal lobe epilepsy. Brain 2001; 125:140–149.
41. Tebartz van Elst L, Woermann F, Lemieux L, Trimble MR. Increased amygdala volumes in female and depressed humans. A quantitative magnetic resonance imaging study. Neurosci Lett 2000;281:2–3.
42. Strakowski SM, Delbello MP, Kenji SW, et al. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry 1999;56:254–260.
43. Howard MA, Cowell J, Boucher P, et al. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. Neuroreport 2000;11:2931–2935.
44. De Bellis MD, Casey BJ, Dahl RE, et al. A pilot study of amygdala volumes in pediatric generalised anxiety disorder. Biol Psychiatry 2000;48:51–57.