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Long-term seizure, cognitive, and psychiatric outcome following trans–middle temporal gyrus amygdalohippocampectomy and standard temporal lobectomy

Clinical article

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Object. Previous comparisons of standard temporal lobectomy (STL) and selective amygdalohippocampectomy (SelAH) have been limited by inadequate long-term follow-up, variable definitions of favorable outcome, and inadequate consideration of psychiatric comorbidities.

Methods. The authors performed a retrospective analysis of seizure, cognitive, and psychiatric outcomes in a noncontemporaneous cohort of 69 patients with unilateral refractory temporal lobe epilepsy and MRI evidence of mesial temporal sclerosis after either an STL or an SelAH and examined seizure, cognitive, and psychiatric outcomes.

Results. The mean duration of follow-up for STL was 9.7 years (range 1–18 years), and for trans–middle temporal gyrus SelAH (mtg-SelAH) it was 6.85 years (range 1–15 years). There was no significant difference in seizure outcome when "favorable" was defined as time to loss of Engel Class I or II status; better seizure outcome was seen in the STL group when "favorable" was defined as time to loss of Engel Class IA status ($p = 0.034$). Further analysis revealed a higher occurrence of seizures solely during attempted medication withdrawal in the mtg-SelAH group than in the STL group ($p = 0.016$). The authors found no significant difference in the effect of surgery type on any cognitive and most psychiatric variables. Standard temporal lobectomy was associated with significantly higher scores on assessment of postsurgical paranoia ($p = 0.048$).

Conclusions. Overall, few differences in seizure, cognitive, and psychiatric outcome were found between STL and mtg-SelAH on long-term follow-up. Longer exposure to medication side effects after mtg-SelAH may adversely affect quality of life but is unlikely to cause additional functional impairment. In patients with high levels of presurgical psychiatric disease, mtg-SelAH may be the preferred surgery type.
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Key Words • **middle temporal gyrus amygdalohippocampectomy** • **standard temporal lobectomy** • **seizure outcome** • **cognitive outcome** • **psychiatric outcome** • **epilepsy**

Standard temporal lobe resection is the most commonly performed surgical procedure for treatment of medically refractory TLE associated with MTS.[15,26,46] The technique involves the removal of the head and body of the hippocampus, most of the amygdala, and variable portions of the anterior and lateral temporal neocortex depending on the practice of the epilepsy center and the side of resection. With the aim of preserving functionally intact tissue of the ATN, more restricted resections of the hippocampus and the amygdala have been developed (that is, SelAH).[22,24,30,47] Selective amygdalohippocampectomy can be performed using a variety of approaches, including transsylvian,[47] trans–middle temporal

Abbreviations used in this paper: AED = antiepileptic drug; ATN = anterior temporal neocortex; EEG = electroencephalography; MMPI-2 = Minnesota Multiphasic Personality Inventory-2; mtg-SelAH = trans–middle temporal gyrus SelAH; MTS = mesial temporal sclerosis; SelAH = selective amygdalohippocampectomy; STL = standard temporal lobectomy; TLE = temporal lobe epilepsy.

gyrus,[32,45] and subtemporal.[18] Considerations of the pros and cons of each surgical procedure lead to one central question: what is the role of the ATN in the generation of seizures, cognition, and psychiatric function in patients with TLE and MTS? Examining the differences in outcome between patients who have undergone STL versus SelAH helps to better understand the role of the ATN in this epilepsy syndrome.

Most comparisons of STL and SelAH report no significant difference with respect to seizure outcome,[10,16,29,34,42] although some investigators have found a benefit of STL[1,41] (Table 1). These findings imply that the resection of mesial structures is sufficient to control seizures in patients with MTS and that the ATN only plays a minimal role in seizure generation. Most studies comparing STL and SelAH with respect to cognitive outcome demonstrate a comparable decline in delayed verbal memory after resections performed on the language-dominant side.[10,16,24,34,41] Several investigators have reported additional deficits of verbal immediate recall in patients who have undergone an STL on the language-dominant side.[10,17] These findings suggest that the ATN may participate in some aspects of memory formation and retrieval.

Several limitations of these comparisons of STL and SelAH are evident. First, most investigators define favorable outcome as Engel Class II or better, placing only patients with Engel Class III and IV outcomes in the unfavorable category. Such an approach may miss subtle differences between the 2 surgical types by placing patients with slightly different surgical outcomes into the same categories. Conversely, other authors strictly define only patients in Engel Class IA as having a favorable outcome. Second, many investigators report comparisons of seizure outcomes following a 12-month follow-up period.[1,24,29] This period may be too short to fully understand the differences between the surgical types, as evidence suggests that new seizures may continue to occur for much longer after a standard temporal resection.[11,14,43] Third, although previous comparisons of STL and SelAH have adequately focused on differences in cognitive outcomes, investigators have not reported on psychiatric outcomes after surgery.

Here, we present a retrospective analysis of long-term seizure, cognitive, and psychiatric outcomes in a homogeneous cohort of patients with unilateral TLE and MRI evidence of MTS. All patients underwent either an STL or an mtg-SelAH. The 2 surgeries were done noncontemporaneously; that is, STL was the preferred procedure prior to 1996 and SelAH after 1995. To better understand if differences exist between the surgeries, we analyzed our data using progressively more stringent criteria of favorable outcome. Such an approach compares 3 distinct definitions of favorable outcome as used by previous investigators. In addition to seizure outcome, we analyzed differences in cognitive and psychiatric measures after surgery.

Methods

Patient Selection

After obtaining institutional review board approval, our surgical database was queried to identify patients with medically refractory epilepsy who underwent either an STL or an mtg-SelAH between 1992 and 2008. Pa-

TABLE 1: Previously reported comparisons of standard and selective temporal lobe surgeries for medically refractory TLE*

Authors & Year	No. of Patients	Type of Op	Type of Lesion	Duration of Follow-Up (mos)	Classification of Favorable Outcome	Seizure Outcome	Cognitive Outcome	Psychiatric Outcome
Helmstaedter et al., 1996	59	STL vs SelAH vs lesionectomy	mixed	3	completely seizure free	no difference	STL: better immediate recall	not reported
Mackenzie et al., 1997	100	STL & SelAH	nonlesional	12	Engel Class III or better	STL better	no difference	not reported
Clusmann et al., 2002	321	STL vs SelAH vs lesionectomy	mixed	38	Engel Class II or better	no difference	SelAH: better verbal memory & attention	not reported
Paglioli et al., 2006	161	STL vs SelAH	MTS only	70	Engel Class IA and Class I or better	no difference	SelAH: better verbal memory	not reported
Morino et al., 2006	49	STL vs TS-SelAH	mixed	12	completely seizure free	no difference	SelAH: better memory	not reported
Bate et al., 2007	114	STL vs SelAH	MTS	12	Engel Class II or better	STL better	not reported	not reported
Helmstaedter et al., 2008	97	M-STL vs TS-SelAH	mixed	12	only seizure-free patients included	only seizure-free patients included	M-STL: better verbal learning; TS-SelAH: better figural learning	not reported
Tanriverdi et al., 2008 & 2010	256	STL vs SelAH	MTS	60	Engel Class II or better	no difference	no difference	not reported

* M-STL = modified STL (anterior tip); TS-SelAH = transsylvian SelAH.

tients were included if they were found to have unilateral ictal onset on video EEG monitoring and had unilateral MTS on MRI. Patients were excluded if they had multifocal seizures, > 90% contralateral sharp waves, posterior temporal sharp waves, multifocal findings on MRI including bilateral MTS, or inadequate follow-up.

Data Collection

Study information was obtained from medical records of outpatient visits; hospital discharge summaries; and neuropsychology, pathology, and radiology reports. Information on age at seizure onset, history of febrile seizures, CNS infections, head trauma with loss of consciousness, duration of epilepsy, side of resection, frequency of seizures after surgery at yearly intervals, and results of preoperative and postoperative neuropsychological testing was obtained.

Type of Surgery

The decision to perform an STL or an SelAH was based on timing. Patients who underwent surgery for TLE with MTS chronologically earlier in our series received an STL as this was the practice at our center. In 1996, the SelAH was adopted as the standard operation for TLE with MTS. All surgeries were performed by a single surgeon (D.W.R.).

Standard temporal lobectomy involved the removal of the anterior temporal lobe, the amygdala, the hippocampus, and surrounding structures. Resection of the temporal neocortex was performed extending back 4.5 cm on the language-dominant side and 5.5 cm on the nondominant side, including the superior temporal gyrus on the latter. Venous structures dictated the posterior border of the temporal lobe resection. The temporal horn was entered, and a subpial dissection was carried out anterior to the hippocampus to include the region of the uncus and then posteriorly, a length of 3.5–4 cm along the fusiform and parahippocampal gyri. The choroidal fissure was identified, and the hippocampal tail was divided and retracted, exposing the entry to the hippocampal sulcus and sequential vascular pedicles, which were divided. The hippocampal head was transected using microsurgical technique, and the hippocampus was delivered en bloc.

Selective amygdalohippocampectomy involved the resection of the amygdala and hippocampus. A 15-mm cortical line of incision was made along the anterior portion of the middle temporal gyrus, and the dissection was carried down through the white matter to the anterior temporal horn of the lateral ventricle. The parahippocampal gyrus and region of the uncus were resected in a subpial fashion. The choroidal fissure was identified, the hippocampal tail was divided and retracted, and the vascular pedicles to the hippocampal sulcus were divided. At the anterior aspect of the choroidal fissure, the hippocampus was transected up to the region of the initial uncal resection and then delivered en bloc.

Medication Weaning Protocol

After surgery, patients remained on presurgical medications. In general, a decision to wean medications was made on an individual basis based on the severity of epilepsy, patient preference, and appearance of epileptiform activity on postsurgical EEG. Clinical charts were assessed, and medication weaning in each patient was characterized.

Seizure Outcome Assessment

Patients were seen in the outpatient center 2 months, 6 months, and subsequently at yearly intervals after surgery. The Engel classification system was used for seizure outcome assessment. Engle Class IA outcome comprises patients who are completely seizure free following surgery; Class IB outcome, those who only have auras; Class IC outcome, those who have been seizure free for 2 years; Class ID outcome, those who only have seizures with loss of consciousness upon withdrawal of medications; Class II outcome, those who have some seizures with loss of consciousness; Class III outcome, those who have experienced significant improvement in seizures; and Class IV outcome, those who have experienced no improvement in epilepsy.

Neuropsychological and Psychiatric Symptom Assessment

All patients completed an extensive battery of neuropsychological tests and self-report measures. For the present analyses, we examined scores from the Wechsler Adult Intelligence,[44] California Verbal Learning Test,[13] Wechsler Memory Scale,[44] Boston Naming Test,[19] Beck Depression Inventory,[2] State Trait Anxiety Inventory,[40] and MMPI-2 Paranoia Scale.[4]

Pathological Examination

All surgical specimens were analyzed by members of the Dartmouth-Hitchcock pathology department.

Statistical Analysis

Kaplan-Meier time-to-event analyses were then carried out to investigate whether there were differences in seizure outcomes dependent on type of surgery (STL or SelAH). We defined the event as the seizure that changed a patient's Engel classification. The neuropsychological and psychiatric outcomes were analyzed using repeated-measures ANOVAs.

Results

Patient Characteristics

Ninety-four patients with history of TLE and MTS on MRI who underwent temporal lobe surgery at the Dartmouth-Hitchcock Medical Center were identified. Of these, 25 patients were excluded due to inadequate follow-up (14), predominance of multiple lesions on MRI (3), bilateral seizure onset on video EEG (5), and > 90% contralateral sharp waves (3). Thus, a total of 69 patients were included in the analysis: 30 patients underwent STL and 39 underwent SelAH (Table 2). The average follow-up duration was longer for the STL group ($p = 0.002$). There was no significant difference in other variables between the groups. Pathological evaluation revealed hippocampal sclerosis in a high proportion of the surgical specimens (Table 2).

TABLE 2: Patient characteristics by surgery type

Parameter	STL	mtg-SelAH	p Value
no. of patients	30	39	
mean duration of follow-up in yrs (range)	9.70 (1–18)	6.85 (1–15)	0.002*
mean age at seizure onset in yrs (range)	10.2 (2–36)	8.4 (2–28)	0.864
mean age at surgery in yrs (range)	34.7 (16–48)	35.1 (17–61)	0.561
mean duration of epilepsy in yrs	25.1	26.5	0.467
side of resection			0.8
rt	16	23	
lt	14	16	
% of patients w/ pathology-proven MTS after surgery	94%	97%	0.987

* Significant difference.

Seizure Outcome

The mean time to loss of Engel Class II status after STL was 15.2 years (95% CI 13.2–17 years), and after mtg-SelAH it was 13.8 years (95% CI 11.9–16.2 years). The difference was not significant (p = 0.536). The mean time to loss of Engel Class I status after STL was 15.2 years (95% CI 13.2–17 years), and after mtg-SelAH it was 13.1 years (95% CI 11.9–16.2 years). The difference was not significant (p = 0.536). The mean time to loss of Class IA status after STL was 14.6 years (95% CI 12.2–17 years), and after mtg-SelAH it was 7.9 (95% CI 6.1–9.7 years). The difference was significant (p = 0.034) (Fig. 1).

Medication Withdrawal

Data on withdrawal of medications were available in 28 patients in the STL group and in 29 patients in the mtg-SelAH group. In the STL group, 18 patients (62%) attempted complete medication withdrawal; 14 (77%) of those 18 patients were able to stay off of medications. In the remaining 4 patients (23%), medications had to be restarted due to recurrent seizures. In the mtg-SelAH group, only 9 complete medication withdrawals were attempted (31% of patients); only 2 (22%) of these 9 patients were able to stay off medication for the duration of follow-up. In 7 (82%) of the 9 patients, seizures recurred and medications were restarted. The average time to medication withdrawal in the STL group was 4.1 years, compared with 5.6 years in the mtg-SelAH group (p = 0.089). The rate of seizure recurrence after attempted medication withdrawal was lower for the STL group than for the mtg-SelAH group (2-tailed, p = 0.0115, Fisher exact test).

Cognitive Outcome

No significant difference was seen for the effect of surgery type on measures of IQ, verbal memory, language, or attention (Table 3). Comparison of nonverbal memory could not be completed because of the change in type of test administered to patients over the years.

Psychiatric Outcome

Data on psychiatric outcome measures were available only for a subset of patients (14 patients after SelAH and 15 patients after mtg-SelAH). This difference was related to differences in the treating neuropsychologist. No differences were seen between the groups with regard to depression and anxiety measures (Table 3). A significant effect of surgery type on change on the MMPI-2 Paranoia Scale is seen (p = 0.048) where the STL group had an overall increase and the mtg-SelAH group an overall decrease in measures of paranoia (Table 3). Individual changes between pre- and postsurgical scores on the MMPI-2 Paranoia Scale are shown in Fig. 2. In the STL group, 4 patients had significant worsening of the paranoia score (change of > 10 points, or 1 SD) and none had significant improvement (Fig. 2A). In the mtg-SelAH group, 3 patients had significant worsening of the paranoia score and 3 patients had significant improvement (Fig. 2B). From Fig. 2B and C, no effect of side of resection or presurgical level of paranoia is seen on the degree of postoperative change.

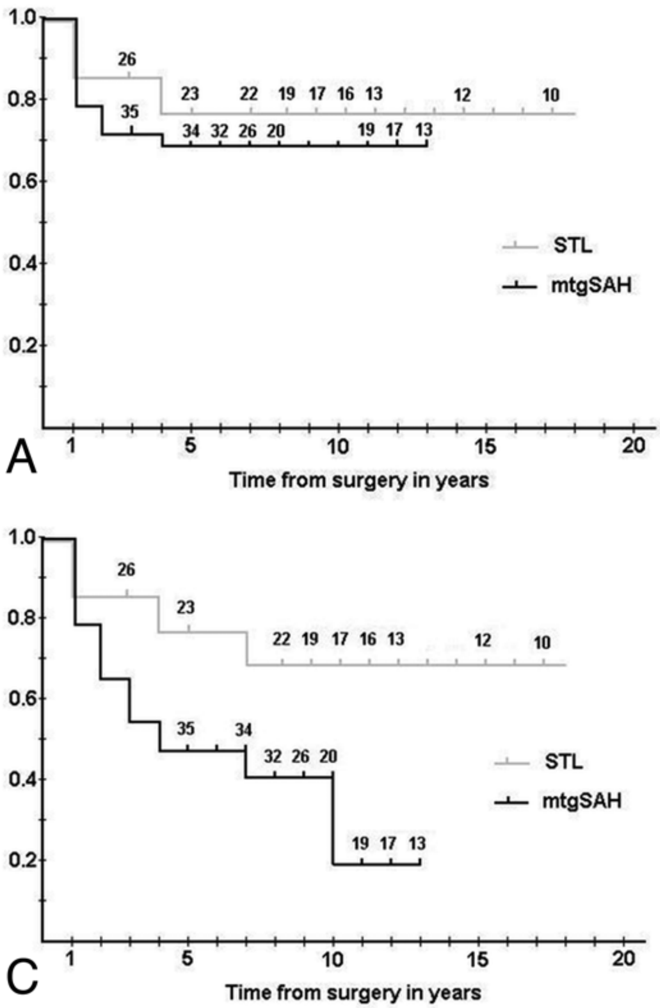
Discussion

This study compared long-term seizure, cognitive, and psychiatric outcomes between 2 different types of surgical treatment for a homogeneous yet noncontemporaneous cohort of patients with TLE and MRI evidence of MTS. Patients who did not have MRI evidence of MTS, who did not have an ictal pattern ipsilateral to the MTS, and who had dual pathology as noted on MRI or had multifocal disease by video EEG were excluded from this study. Our surgical groups were relatively well matched with respect to age of onset of epilepsy, duration of epilepsy, and side of resection.

Seizure Outcome

We found that long-term seizure outcome in this highly selected cohort of patients was excellent for both surgical groups. Even many years after surgery, a large proportion of patients after both STL and mtg-SelAH continued to enjoy freedom from debilitating seizures. This rate of seizure freedom is consistent with previously reported rates after temporal lobectomy in patients with MRI evidence of MTS[23,35] and is understandably higher than reported rates after temporal lobectomy in nonlesional or mixed patient cohorts.[12] The difference in outcome between the groups becomes significant only when favorable outcome is defined as time to loss of Engel Class IA status. Conversely, no difference is seen when defining favorable outcome as time to loss of Engel Class I status, or time to loss of Engel Class II status.

This difference in the time to loss of Class IA status is related to the different rates of seizure recurrence after attempted medication withdrawal. This difference is important as it suggests that fewer patients are able to discontinue AEDs and are more likely to require longer treatment with AEDs after mtg-SelAH than after STL. It is important to understand that our data are limited in that they do not inform us on the long-term success of medica-



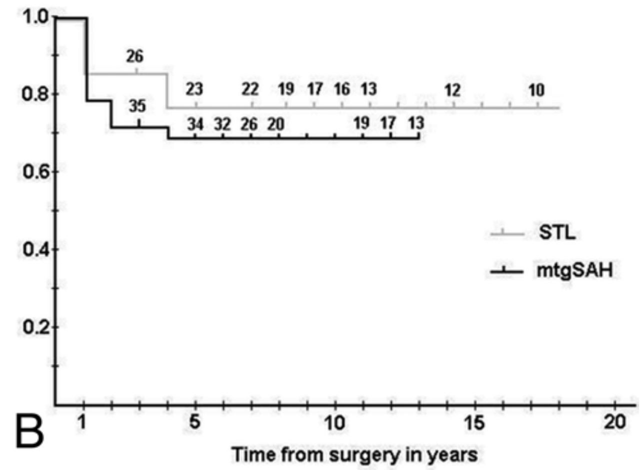


Fig. 1. Seizure outcome following STL and mtg-SelAH (mtg-SAH). **A:** Time to loss of Engel Class I or II status in years. **B:** Time to loss of Engel Class I status in years. **C:** Time to loss of Engel Class IA status in years. Numbers above the lines indicate the number of patients used for analysis at each time point.

TABLE 3: Comparison of average presurgical and postsurgical neuropsychological scores between STL and mtg-SelAH*

Test	Pre-STL	Post-STL	Mean Change	Pre–mtg-SelAH	Post–mtg-SelAH	Mean Change	p Value
FSIQ	85.74	89.32	+3.58	92.70	92.29	−0.41	0.78
VIQ	85.35	88.95	+3.60	92.00	90.63	−1.37	1.4
PIQ	89.17	96.16	+6.99	91.00	95.75	+4.75	0.23
CVLT 1–5	45.40	43.50	−1.90	46.07	45.79	−0.28	0.64
CVLT SD	8.10	7.78	−0.32	8.88	9.25	+0.37	0.95
CVLT LD	8.16	7.39	−0.77	9.35	8.92	−0.43	0.79
CVLT R	12.84	13.78	+0.94	14.12	14.58	+0.46	0.75
BNT	47.65	45.65	−2.00	50.22	49.38	−0.84	0.23
CFL	27.26	29.15	+1.89	32.52	33.50	+0.98	0.089
Beck Depression	11.89	8.87	−3.02	8.07	5.00	−3.93	0.54
MMPI-2 Paranoia Scale	57.84	62.86	+5.02	56.35	54.06	−2.29	0.048†
Beck State Anxiety	43.19	39.27	−3.92	39.96	35.25	−4.71	0.23
Beck Trait Anxiety	38.76	39.27	+0.51	40.81	38.00	−2.81	0.45

* BNT = Boston Naming Test; CFL = categorical fluency; CVLT = California Verbal Learning Test; FSIQ = full scale IQ; LD = long delay; PIQ = performance IQ; R = recognition; SD = short delay; VIQ = verbal IQ.
† Significant difference.

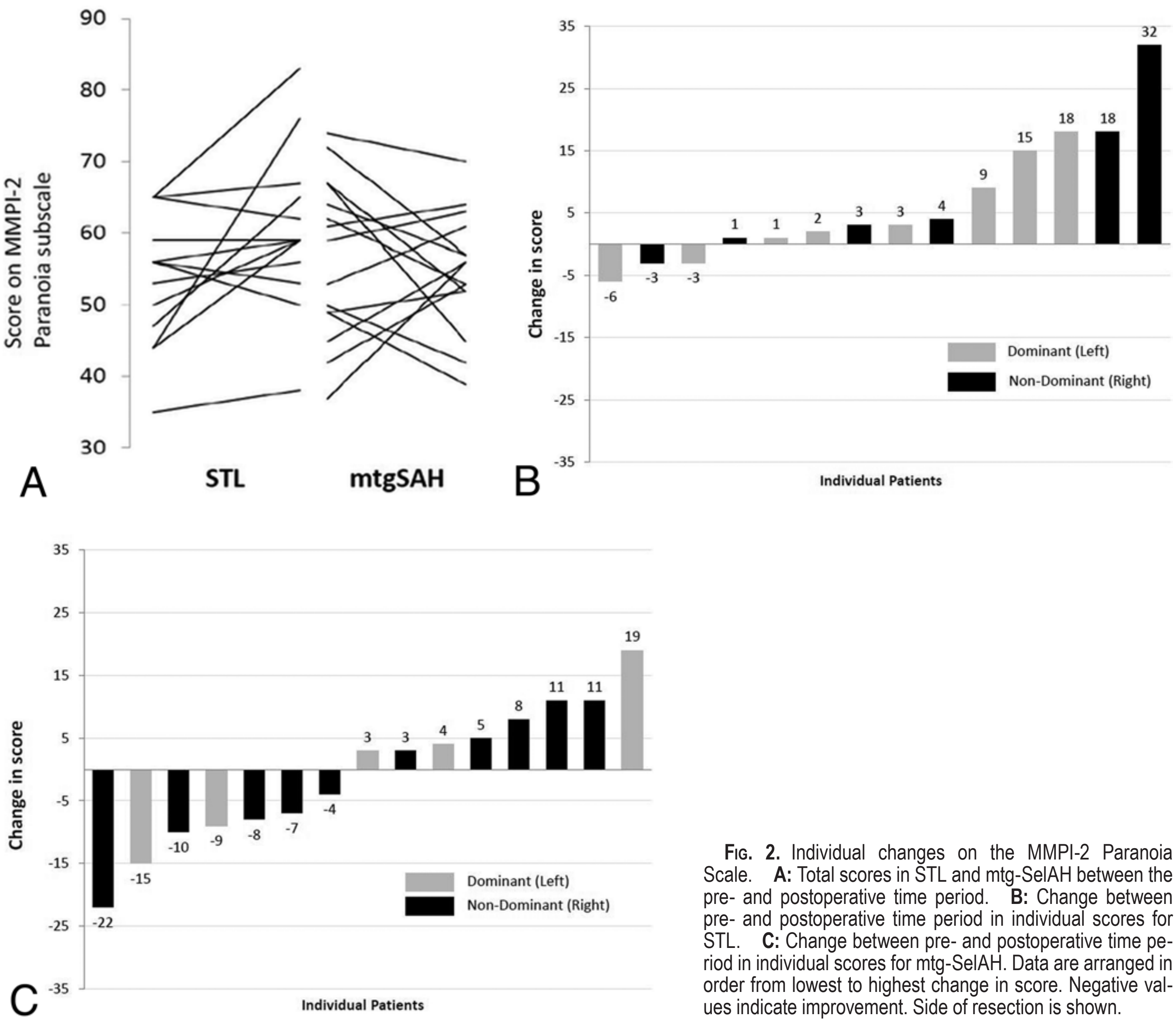


Fig. 2. Individual changes on the MMPI-2 Paranoia Scale. **A:** Total scores in STL and mtg-SelAH between the pre- and postoperative time period. **B:** Change between pre- and postoperative time period in individual scores for STL. **C:** Change between pre- and postoperative time period in individual scores for mtg-SelAH. Data are arranged in order from lowest to highest change in score. Negative values indicate improvement. Side of resection is shown.

tion weaning. For instance, it is possible that subsequent trials to discontinue medications were successful.

Many studies have shown that seizure freedom is the single most significant contributor to functional outcome and quality of life after epilepsy surgery, accounting for as much as 80% of the variance.[38,39] For this reason, we do not think that differences solely in relapse at time of medication withdrawal would lead to any appreciable differences in functional outcome between the surgery types (for example, the ability to drive a car). However, greater exposure to medication side effects may have significant effects on daily functioning and impact overall cost of health care delivery, and patients may be impacted by the psychological burden of knowing that seizures may recur if medications are stopped. Previous studies on medication withdrawal after surgery suggest that seizures that occur at time of medication withdrawal generally are easily controlled when medications are reinitiated.[20,36,37] This was likewise true in our cohort.

Cognitive Outcome

Comparison of cognitive scores in our 2 surgical groups reveals little difference between STL and mtg-SelAH, including measures of IQ, attention, language, and verbal memory. The lack of difference adds evidence to the notion that sparing the ATN in these patients does not lead to major cognitive benefits. This is supported by cerebral PET and MRI studies that show that the ATN is frequently hypometabolic and atrophic in patients with TLE and MTS.[3,8] Furthermore, it is important to consider that the ATN in healthy humans plays only a minor role in episodic memory and language function[6,7,21,31,48] while having a more robust role in emotional and social cognitive domains.[5,28,33] Therefore, the lack of significant difference in cognitive function between the surgical groups may be because the standard neuropsychological evaluation does not assess the full range of the complex cognitive functions of the ATN.

Psychiatric Outcome

Overall, we did not find any significant effect of surgery type on measures of anxiety and depression. Conversely, we found significant increases in levels of paranoia in the STL group. Association of increased paranoia with resection of the ATN is not surprising. The ATN is considered paralimbic cortex and is anatomically situated between limbic regions of the amygdala (important in the processing of negatively valenced emotional states), and the temporal neocortex (important in the processing of auditory, visual, and olfactory sensory information from the environment).[28,48] Dysfunction of the ATN may therefore lead to inappropriate activation of the limbic system during normal everyday experiences and to the experience of paranoia.

Our data do not address the issue of whether the significantly higher levels of paranoia in the STL group translate into any clinical relevance. Our initial concern was that STL may cause higher rates of de novo postsurgical psychosis as both STL and mtg-SelAH have been associated with it.[9,25,27] However, not a single patient in either surgical group was diagnosed clinically with de novo postsurgical psychosis by the treating neurologist based on review by the medical record.

Study Limitations

This study has multiple major limitations due to its retrospective and noncontemporaneous design and limited number of patients. Confounding variables such as increasing experience of the surgeon, changes in the experience of the treating neurologists, changes in postoperative medication weaning philosophy or weaning duration, and other unconsidered factors may have impacted our results. Our cohort of patients was a highly selected subgroup of all patients who received selective and standard temporal lobectomies. Therefore, our conclusions should not be extended to other epilepsy populations, such as those with nonlesional TLE. Since the mtg-SelAH cohort was chronologically later in time, advances in AEDs, antidepressants, and antipsychotics over the 2 time periods may have affected the results. For instance, the rate of use of first-generation AEDs may have been different between the groups. In addition, more aggressive treatment of comorbid depression and anxiety in the chronologically later group (mtg-SelAH group) may have influenced psychiatric outcomes.

Conclusions

The results of this study provide more precise understanding of the subtle differences in long-term seizure, cognitive, and psychiatric outcomes between STL and mtg-SelAH in patients who have TLE associated with MTS. The observed differences are generally small and do not clearly establish if one surgery is favorable over the other.

Longer reliance on AEDs for seizure control after mtg-SelAH may adversely impact quality of life, although likely not functional outcome. Trans–middle temporal gyrus SelAH may be a better procedure for patients with high levels of concurrent psychiatric disease, especially paranoia.

Disclosure

Dr. Dinnerstein is a primary investigator for an unrelated clinical trial sponsored by Pfizer, Inc.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bujarski, Thadani. Acquisition of data: Preston. Analysis and interpretation of data: Hirashima, Roberts, Jobst, Gilbert, Roth, Flashman, McDonald, Saykin, Scott, Dinnerstein. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Bujarski. Decisions for surgery: Williamson.

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