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Cognitive outcome after stereotactic amygdalohippocampectomy

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ABSTRACT

Purpose: We sought to determine the neuropsychological outcome after stereotactic radiofrequency amygdalohippocampectomy performed for intractable mesial temporal lobe epilepsy.
Methods: The article describes the cases of 31 patients who were evaluated using the Wechsler Adult Intelligence Scale-Revised and the Wechsler Memory Scale-Revised prior to, and one year after, surgery.
Key findings: Patients showed increases in their mean Full Scale, Verbal and Performance IQ scores of 4, 3 and 4 IQ points respectively ($p < .05$). 5 (17.2%), 4 (13.8%) and 4 (13.3%) patients improved in their Full-scale, Verbal and Performance IQ respectively. No significant changes were found in memory performance – with a mean increase of 1, 3 and 0 MQ points in Global, Verbal and Visual memory respectively ($p < .05$). Global memory improved in 3 (10.3%) patients, verbal memory in 1 (3.4%) and 1 patient (3.3%) showed deterioration in visual memory.
Significance: Our results provide evidence for unchanged memory in patients with MTLE after the procedure. No verbal memory deterioration was detected in any of our patients, while improvements were found in intellectual performance. The results suggest that stereotactic radiofrequency amygdalahippocampectomy could be superior to open surgery in terms of its neurocognitive outcomes. A larger randomised trial of these approaches is justified.

1. Introduction

Surgery has become a treatment option for some patients with intractable epilepsy. Mesial temporal lobe epilepsy (MTLE) with mesial temporal sclerosis (MTS) is the most surgically amenable epilepsy diagnosis. The results of epilepsy surgery are clearly superior to prolonged medical therapy.[1,2] However, patients who could benefit from the procedure might be deterred from undergoing surgical evaluation due to concerns regarding surgery-induced memory deficits.[3,4]

The most frequently performed surgery for MTLE is anterior temporal lobectomy. During this procedure white matter tracts may be transected or functional tissue that is not necessarily epileptogenic may be removed. Sparing these structures may be important in terms of memory preservation. Results of some studies suggest that selective ablation of mesial temporal lobe structures (amygdalohippocampectomy) is an alternative to anterior temporal lobectomy with respect to seizure control.[5] Neuropsychological outcomes are reported to be somewhat better in more restricted procedures.[6–8] However, the minimal extent of mesial temporal resection necessary to obviate adverse neuropsychological outcomes with an equal chance of postoperative seizure freedom remains unclear.[9]

Stereotactic radiofrequency amygdalohippocampectomy (SAHE) is an alternative therapy for MTLE.[10] It was reintroduced in a modern setup by the London-Ontario group.[11] Stereotactic thermo-lesion of amygdalo-hippocampal complex (AHC) using a modified technical approach has been used at our institution since 2004 and studies describing the favorable epileptological outcome of this procedure have been published.[12,13]

We hypothesized that the less complete destruction of mesial temporal structures compared to microsurgical resection could preserve postoperative memory functions. The aim of this study is to summarize the neuropsychological results after SAHE.

Abbreviations: AHC, amygdalo-hippocampal complex; MTLE, mesial temporal lobe epilepsy; MTS, mesial temporal sclerosis; SAHE, stereotactic radiofrequency amygdalohippocampectomy.

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2. Methods

2.1. Patient selection

We prospectively studied neuropsychological changes in 31 patients who underwent SAHE (25 left-sided) at the Department of Stereotactic and Radiation Surgery at our institution during the period from 2004 to 2009. Only those who had been neuropsychologically evaluated by one neuropsychologist (LK) and followed up at our center were included. We excluded 8 patients who had been diagnosed and followed up elsewhere and 3 otherwise eligible patients who had failed to complete a neuropsychological evaluation one year after surgery (one seizure-free patient committed suicide, one Class II patient died due to an accident and one seizure-free subject refused to participate). 3 patients who have not had a two-year follow-up and 6 patients who have both not had sufficient follow-up and were followed-up elsewhere were also excluded.

Demographic data and the results of the diagnostic evaluation are summarized in supplementary material (Table A1). These patients are a subset of 51 patients on whom SAHE has been performed in our institution to date. There were 15 men and 16 women with a mean age at the time of operation of 37.7 (SD 11.2, 18–65) years and an illness duration of 22.1 (SD 11.1, 6–37) years. The mean duration of formal education was 11.8 (SD 2.1, 7–17) years. Mean seizure frequency 6 months prior to the operation was 5 per month (SD 4.5, 1–20). 24 patients were right-handed, 3 left-handed and 4 were ambidexterous. The larger proportion of left-sided patients is certainly a referral bias as referring physicians tend to send patients at risk for postoperative memory decline to our center for a procedure which, in the event of failure, could be followed by standard surgery.

Preoperatively (supplementary material, Table A2), patients underwent a standard non-invasive evaluation protocol (magnetic resonance imaging – MRI, interictal and ictal scalp video-electroencephalography – video-EEG, ^{18}F-fluorodeoxyglucose positron emission tomography – PET, Wada test, visual field and complex neuropsychological assessment). In one patient, the MRI showed right-sided MTS but PET hypometabolism and the ictal EEG pattern were bilateral. This patient was evaluated using a combination of depth and subdural electrodes. In two patients, the MRI was normal but temporal hypometabolism and the ictal pattern collocalized to the same temporal lobe. In one patient, the ictal pattern was bilateral but the MRI showed MTS and the PET confirmed this. In two patients, PET was not performed. In one patient, a more widespread mesiotemporal dysplastic lesion on the same side as the mesial temporal sclerosis was evident. All patients were subsequently diagnosed with intractable MTLE.

After completion of the preoperative evaluation, the patients were informed of their treatment options and SAHE was mentioned as one of these. If they chose SAHE, they signed an informed consent form. The methodology for this study was approved by our hospital's ethics committee.

2.2. Surgical technique

The surgical procedure used in this study has been described in detail in our previous paper.[13] The Leksell stereotactic system was used to plan a single trajectory along the long axis of the hippocampus, avoiding the ependymal surface of the ventricles. A percutaneous drill-hole was performed under local anesthesia at the entry point in the occipital region. The target point was placed in the amygdala. Thermo-coagulation of the amygdalohippocampal complex (AHC) and part of the parahippocampal gyrus, depending on the individual anatomy of the patient, was carried out using a string electrode with a 10 mm bold active tip. A mean of 26.4 lesions (17–38) were placed in each patient along the trajectory in AHC (Fig. 1). The local temperature was 75 °C or 88 °C, depending on the probe thickness.

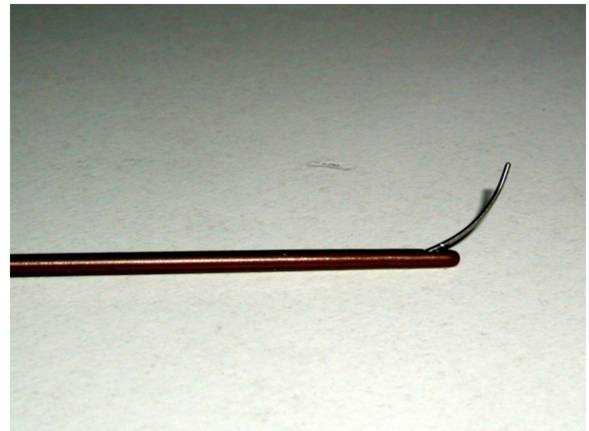

Fig. 1. Therapeutic electrode with a telescopic tip. During the procedure the active tip is exserted 8 mm from the guiding tube (external diameter 1.8 mm). After the coagulation is accomplished the tip is retracted, the guiding tube is rotated 45° and the tip is exserted again to make another lesion. After lesioning is complete in one position the probe is withdrawn by 55 mm and another series of thermolesions is performed.

We have reported the radiological results elsewhere.[13–15] For the purpose of this article, it may be important to mention that only part of the confluent lesion seen on MRI scans obtained on the day following surgery (Fig. 2a), was converted into a pseudocyst one year after operation (Fig. 2b).

2.3. Neuropsychological evaluation

All patients underwent neuropsychological assessment preoperatively and 12 months after surgery. They were tested in two sessions over two consecutive days, each lasting 60–90 min. During the first day a psychological interview was performed and WAIS-R presented. Memory, verbal functions and quality of life were assessed using WMS-R, a Verbal Fluency Test (standardized Czech versions) and a Quality of Life Questionnaire (Qolie-89) respectively, on the second day (the Qolie-89 and the Verbal Fluency Test were not used in this study). The patients were informed of the test results at the end of the session.

2.4. Statistics

We compared Full-Scale (FS-IQ), Verbal (VIQ) and Performance IQ (PIQ), all subtests of the WAIS-R, Global, Verbal and Visual Memory Quotients (MQ), and all WMS-R subtests in the pre- and postoperative sessions.

Changes at group level were assessed using paired *t*-tests. We also tried to estimate the operation benefit at an individual level and employed the Reliable Change Index (RCI) classification.[16,17]

Using this classification, patients were divided into groups according to whether they demonstrated a significant postoperative improvement when performing the task, deterioration or no change.

We used test–retest reliability coefficients for each test score from which the standard error (SE) of difference was derived. From this we calculated a 95% confidence interval (CI) for the change. Score changes which fell within the specific CI would represent changes that could occur by chance 95% of the time. Score changes outside the CI would represent a statistically reliable change that would occur <2.5% of the time in patients without surgical intervention. The RCI classification is based on the extent of the

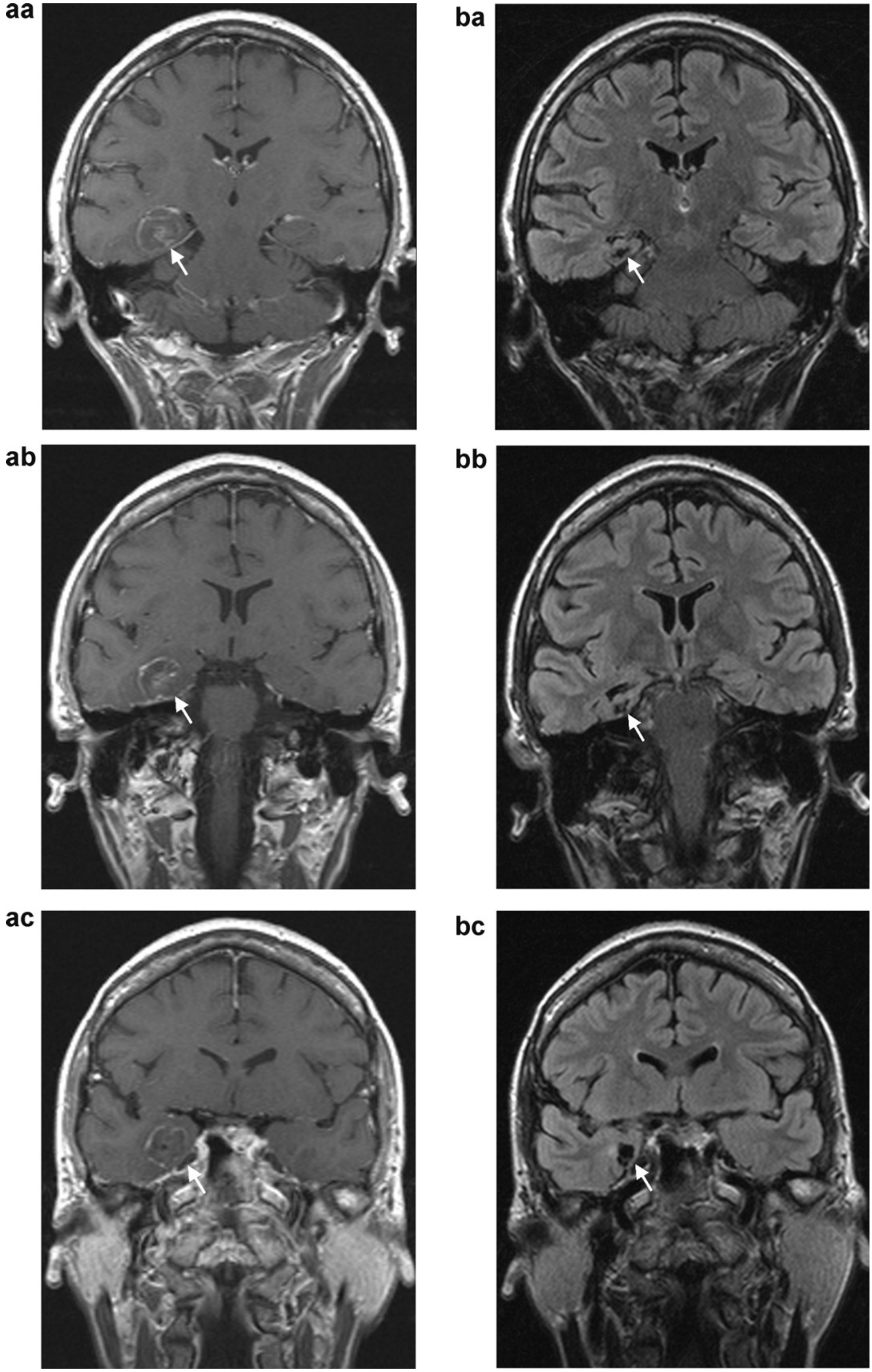

Fig. 2. Coronar sections, FLAIR weighted MR images on the second day after operation (a) and 1 year postoperatively (b). Coronal sections, FLAIR weighted MR images on the second day after operation (a) and 1 year postoperatively (b) (arrows). Post-contrast enhancement in the right hippocampus, amygdala and parahippocampal gyrus alongside a slight vasogenic oedema caused by breakdown of the blood–brain barrier could be seen shortly after operation (a). 1 year after operation a small pseudocyst formation, atrophy and collateral hyperintensity (presumably gliosis) are present in the target area (b).

individual change, while both the general variance of the data and instrument reliability are also considered.

3. Results

3.1. Surgical results

At last follow-up, 23 (74.2%) patients were Engel class I, 5 (16.1%) Class II, 1 (3.2%) Class III and 2 (6.5%) Class IV. Postoperatively, 16 patients reported headaches and 10 of these had signs of meningeal irritation (nuchal rigidity, Kernig's sign, Brudzinski's sign). These symptoms rapidly resolved after symptomatic treatment. We feel that proper postoperative care with preventive administration of antibiotics and painkillers and bed rest is important as patients who were transported to another hospital after the procedure experienced a slightly elevated rate of adverse events.[13] Aseptic meningitis, a small asymptomatic subdural hematoma and a small asymptomatic intracerebral hematoma in the electrode trajectory were diagnosed, each in one patient. All these patients recovered without any permanent sequelae. In one patient, an electrode fragment was found in the hippocampus. Although he was asymptomatic, postoperative MRI control could not be performed. Due to the postoperative persistence of seizures (II A, II A and IV A) one repeated SAHE and 2 anteromesial temporal lobectomies were performed with a I A outcome for all.

3.2. WMS-R and WAIS-R scores

The following tables summarize our results. Tables 1 and 2 show test–retest means, SD and mean performance changes, test–retest reliabilities and significance levels for the whole group. Changes in memory outcome are presented in Table 1 (WMS) while intellectual outcome is illustrated in Table 2 (WAIS-R). Significant differences are outlined in bold print in Table 2. Table 3 shows intraindividual changes according to reliable change indices for both memory and intelligence. Thus, no significant memory changes could be demonstrated in Table 1 and significant improvement in Full-scale, Verbal and Performance IQ scores can be seen in Table 2.

3.3. Memory outcome

In the group as a whole there were no statistically reliable changes in Global, Verbal and Visual MQ ($p = 0.635$; 0.318 and 0.855 respectively) and all other memory subtests.

At an individual level (Table 3 and supplementary material Table A3), 3 (10%) patients showed significant improvement in global memory performance, 1 (4%) patient deteriorated and 25 (86%) did not change. 1 patient (3%) demonstrated reliable improvement and none showed deterioration in their verbal memory performance, while 28 (97%) were unchanged. In visual memory performance, there was one patient with reliable deterioration, none improved and 29 (97%) of patients were unchanged. Reliable improvement in attention was shown in 4 (13%), deterioration in 1 (3%) and no change in 25 (84%) patients. A relatively high rate of reliable deterioration (4 patients, 17.5%), but also the highest rate of reliable improvement (4 patients, 17.5%), were observed in Delayed recall.

The patient who deteriorated in global memory (No. 8) was a right-handed, left-sided speech and memory dominant person, operated on her left. She did not have MTS and was not rendered seizure-free (Engel IIIB).

All those who improved in global memory were operated on the non-dominant side. 2 were right-handed left-side language dominant, operated on their right, 1 left-handed operated on the left side. According to the Wada test, memory results were inconclusive in the left-hander. Memory was localized in the right temporal lobe in one of the right-handers. This patient (No. 30) also improved in verbal memory. Interestingly, based on the Wada test, surgery may not have been recommended to him (because he failed the memory tests after a right-sided injection and the operation was planned, and finally performed, on the right side). In all those whose global memory improved (Nos. 6, 22, 30), MTS was diagnosed and their postoperative course was favorable (Engel IC, IA and IB, respectively).

The patient who showed significantly deterioration in visual memory (No. 17) was a right-handed person with left-sided speech and memory dominance who was operated on the left side. He had left-sided MTS and was Engel Class IB. Preoperative memory performance of both deteriorated patients was above average.

Delayed recall significantly deteriorated in one left-hander operated on the left side and 3 right-handers operated on the right. Among those who improved were 2 ambidexterous, 1 left-handed and 1 right-handed patient, all operated on the left side.

3.4. Intellectual outcome

There was a small, but statistically significant improvement in Verbal, Performance and Global intellectual performance ($p = 0.001$, 0.002 and 0.004 respectively) in our group of patients. Patients showed significant improvement in Subtests Information ($p = 0.028$), Vocabulary ($p = 0.018$) and Object Assembly ($p < 0.0001$).

At an individual level (Table 3 and supplementary material Table A4), 5 (17%) patients improved in Global intellectual performance, and 83% of patients remained unchanged. Verbal IQ improved in 4 (14%) patients and Performance IQ in 4 (13%) patients; no deterioration was found.

The pattern of patients with intellectual gain after surgery is not clear. 4 left- and 1 right-sided patients had improved FS-IQ (Nos. 7, 21, 22, 29, 30) and their seizure outcome was favorable (4 with IA

Table 1
The WMS-R scores – Global, Verbal and Visual Memory Quotients and all subtests.

WMS-R	Before surgery	1 year after surgery	Mean change	Test–retest reliability	Significance level *p*
Global MQ	92.7 (17.7)	93.8 (17.3)	−1.13	0.81	0.635
Verbal MQ	90.0 (19.1)	92.5 (17.9)	−2.50	0.77	0.318
Visual MQ	97.8 (15.4)	98.2 (11.9)	−0.39	0.70	0.855
Attention	81.13 (18.97)	81.10 (17.30)	0.03	0.90	0.990
Delayed recall	89.33 (14.10)	91.54 (25.04)	−0.46	0.77	0.648
Figural memory	6.65 (1.50)	6.74 (1.37)	−0.10	0.44	0.708
Logical Memory I	21.07 (9.32)	23.65 (8.16)	−2.58	0.74	0.067
Visual Paired Associates I	12.16 (4.20)	11.1 (3.96)	1.07	0.58	0.072
Verbal Paired Associates I	16.03 (6.27)	15.71 (5.92)	0.32	0.60	0.710
Visual Reproduction I	34.07 (4.65)	35.00 (3.97)	−0.94	0.59	0.107
Logical Memory II	16.46 (7.75)	21.33 (19.3)	−4.88	0.75	0.255
Visual Paired Associates II	5.17 (1.13)	8.83 (19.72)	−3.67	0.59	0.379

Table 2
Test–retest means, SD, mean difference score, test–retest reliability and significance level of the *t*-test.

WAIS-R	Before surgery	1 year after surgery	Mean change	Test–retest reliability	Significance level *p*
Full-Scale IQ	89.8 (12.9)	94.5 (14.5)	−3.69	0.94	**0.001**
Verbal IQ	90.9 (12.7)	93.5 (14.7)	−2.62	0.96	**0.002**
Performance IQ	89.9 (13.8)	94.2 (14.4)	−4.33	0.90	**0.004**
Information	7.83 (3.12)	8.59 (3.76)	−0.76	0.86	**0.028**
Digit span	7.27 (3.36)	7.33 (3.14)	−0.07	0.83	0.883
Vocabulary	8.47 (2.66)	9.00 (2.98)	−0.53	0.91	**0.018**
Arithmetic	9.35 (3.19)	9.62 (3.41)	−0.28	0.80	0.433
Comprehension	9.04 (2.38)	9.35 (2.55)	−0.31	0.65	0.403
Similarities	8.53 (2.21)	9.10 (3.13)	−0.57	0.65	0.271
Picture completion	8.48 (2.68)	8.83 (2.69)	−0.36	0.74	0.329
Picture arrangement	8.36 (2.01)	8.46 (1.76)	−0.10	0.58	0.777
Block design	10.26 (3.78)	10.90 (3.26)	−0.65	0.91	0.053
Object assembly	7.50 (2.81)	8.87 (3.04)	−1.37	0.81	**0.000**
Digit symbol	8.48 (2.80)	9.16 (2.34)	−0.68	0.90	0.055

Significant differences ($p < 0.05$) are outlined in bold print.

and 1 with IB). VIQ improvement (Nos. 2, 22, 30, 31) was seen twice after left- and twice after right-sided procedures. Seizure outcome was good for 3 patients (IC, IA and IB, respectively) and poor (Engel Class IVB) for 1. PIQ improved in 3 left- and 1 right-sided operated patients and seizure outcome was consistently good (3 with IA and 1 with IB).

Gender, age of onset, presence of risk factors, seizure frequency and epilepsy duration did not differ in those with significant memory or intellectual changes and mean group values.

4. Discussion

Mesial temporal structures (hippocampus, perirhinal area, entorhinal area, parahippocampus) and the temporal neocortex are key areas supporting memory (beside extratemporal structures such as the thalamus, lateral frontal cortex and associative cortices).[18] This system cooperates with the neocortex to establish and maintain long-term memory. The aim of surgery for MTLE is the removal of the mesiotemporal areas (amygdala, hippocampus, and parahippocampal gyrus). It follows that severe problems in memory may result. The consequences of surgical intervention on the cognitive functions of patients with MTLE remain controversial. ATL may result in material-specific memory impairment, typically verbal memory decline following left[19] and visual memory decline after right[20] temporal lobe resection. Although most surgical epilepsy patients do not notice post-operative changes in their memory function,[21] a small proportion of patients do experience negative effects in their everyday life.[22] Verbal memory functions are particularly at risk after left-sided resections in patients with mild mesial temporal sclerosis and normal presurgical verbal memory.[23] However, some studies have shown that successful surgery can stop or reverse the cognitive decline caused by intractable epilepsy. Results of other studies provide evidence for further decline of verbal memory functions up to 2 years after left-sided operations, which does not worsen thereafter.[24,25] However, some studies found progressive memory impairment even later after the operation.[3,26] Most studies (although not all) find improved verbal memory after left-sided selective amygdalohippocampectomy compared with anteromesial temporal resection.[9]

Several approaches have been developed to avoid unnecessary damage to the lateral temporal neocortex – namely transsylvian, subtemporal, and transcortical (trans-middle temporal gyrus) selective AHE. Some authors report no significant postoperative decline of verbal memory or even a slight improvement on the language-dominant side.[27,28] Others advocate amygdalohippocampectomy in patients who fail the contralateral Wada test. Nevertheless, there is evidence that some neuropsychological consequences may be due to collateral damage even in these selective approaches.[29] Furthermore, some authors claim that even limited approaches can lead to memory impairments.[30]

We developed SAHE to avoid any damage to the temporal lobe neocortex and white matter tracts. We have shown that it is safe and efficient with respect to seizure outcome in our previous work. The aim of the present study was to show the neuropsychological results of this procedure. Notably, it can be repeated or the patient can be referred to conventional surgery in case of failure.

Cognitive outcome after resective surgery can be affected by numerous variables, e.g. antiepileptic drugs administration, baseline test values, seizure outcome, etc. We did not change the antiepileptic drug regimen in any of our patients postoperatively. Volume reduction of mesial temporal structures varies widely and is regionally complex and we therefore chose to correlate volume reduction and neuropsychological outcome in a later work.

Our main finding is that at the group level our patients showed slight intellectual improvement and no memory change. We would like to stress that there were more improved than deteriorated patients in both the memory and intelligence domains. It is worth noting that we did not find any case of significant worsening of verbal memory.

The lack of postoperative memory improvement on the group level could be due to the destruction of nonpathological functional tissue[31] as SAHE attacks the same structures as conventional epilepsy surgery methods. One cannot expect consistent functional improvement after the destruction of a structure responsible for this function. As group statistics are of limited value,[32] and due to the small sample size, we should like to take the opportunity to discuss possible reasons for postoperative gains and losses in individual patients, where our results are also consistent with

Table 3
Intra-individual changes according to reliable change indices.

	Improvement *N* (%)	No change *N* (%)	Deterioration *N* (%)
WMS-R			
Global MQ	3 (10)	25 (86)	1 (4)
Verbal MQ	1 (3)	28 (97)	0 (0)
Visual MQ	0 (0)	29 (97)	1(3)
Attention	4 (13)	25 (84)	1 (3)
Delayed recall	4 (17.5)	15 (65)	4 (17.5)
WAIS-R			
Full-Scale IQ	5 (17)	24 (83)	0 (0)
Verbal IQ	4 (14)	25 (86)	0 (0)
Performance IQ	4 (13)	26 (87)	0 (0)

Some patients did not complete all the subtests pre- or postoperatively.

previously published microsurgical amygdalohippocampectomy studies.

In the patient (No. 8) whose global memory deteriorated, there were several unfavorable prognostic factors. She was operated on her speech- and memory-dominant side, her preoperative memory was above average and she was non-lesional. In this situation invasive recording might have been considered prior to surgery.[33] However, a similar cumulative presence of negative prognostic factors was present in our other non-lesional right-sided patient (No. 12), who is Engel IB and without cognitive deficit. This illustrates the well-known fact that operating on the speech-dominant side is always risky and preoperative brain MRI is critical for the selection of these patients.[34] This case also shows that decline in memory function is associated with a poor surgical outcome.[35] In all patients who improved in global memory (1 of them also improved in verbal memory) after the operation, their preoperative memory function decreased in comparison to the norm on the operated side. They had been lesional, were operated on the non-dominant side and their postoperative course was favorable. This is in agreement with published data that operating on the language non-dominant hemisphere might improve memory functions.[36] Taken together, these findings are consistent with the "functional adequacy" model.[37]

The cause of visual memory deterioration in one patient (No. 17) is unclear as she was operated on her left side and seizure outcome was favorable (IB). It seems that no predictive model can be 100% accurate.

The cause of postoperatively improved IQ is not clear. However, this is a consistent finding in most studies.[36] In some previous reports,[24,32] the long-term positive course in the IQ variables was interpreted as being due to practice effects. This could be the case in our study, even though we used the reliable change indices method in the interpretation of our results which should eliminate these effects. Even using this instrument we cannot exclude the possibility that test–retest effect played some role. Interestingly, although most patients who improved intellectually after the procedure had favorable seizure outcomes, intellectual improvement occasionally also occurred in surgical failures.

Significant improvement was found in some subtests in WAIS-R (Information, Vocabulary and Object Assembly). We did not specifically evaluate remote memory (episodic and semantic), but these subtests do sample a range of remote memory. It is therefore possible that SAHE, by sparing temporal neocortical structures and their connections to other cortical regions, could improve some aspects of intellectual performance and remote memory functions.

Because most studies[9] show a certain deterioration in verbal memory at group level, even after left-sided selective amygdalohippocampectomy, our conclusion is that SAHE may be a more suitable alternative to standard epileptosurgical procedures in terms of neurocognitive outcomes.

Our study has several limitations:

(1) The number of treated patients is too small and the number of comparisons of various parameters extremely large (increasing the risk of false positive findings).
(2) The length of postoperative observation is quite short. We cannot draw any conclusions with regard to the accelerated memory loss reported in some studies.
(3) The neuropsychological battery is limited and mostly focused on anterograde memory. Therefore, no conclusion can be made regarding remote and long-term memory, for example, which could be of particular relevance to our topic.
(4) Most of our patients were left-sided. This could be an advantage as most concerns regarding temporal lobe epilepsy surgery deal with dominant side surgery. But it certainly is a bias reflecting physicians' worries about verbal memory expressed in patient/physician communication.
(5) We do not have a control group of open surgery patients and untreated patients (to confirm the test–retest effects). Our cohort is also not entirely homogenous, although MTLE has been diagnosed in all patients.

Further randomized studies (ideally comparing SAHE with transsylvian[7] or subtemporal[38] selective amygdalohippocampectomy, where improvements in certain aspects of verbal memory have been found) and extended observational periods using a wider range of neuropsychological methods are needed.

Conflict of interest statement

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

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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2012.02.008.

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