Collateral brain damage, a potential source of cognitive impairment after selective surgery for control of mesial temporal lobe epilepsy

C Helmaetsdter, D Van Roost, H Clusmann, H Urbach, C E Elger, J Schramm

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METHODS

The study originally comprised 38 patients with left hemisphere language dominance who had been randomly assigned to selective amygdalo-hippocampectomy for mesial temporal lobe epilepsy, using either a transylvanian or a transcortical approach. Informed consent was obtained from the patients for randomisation and the study was approved by the ethics commission of the university clinics, Bonn. In our centre, SAH is generally indicated where there is a clinical diagnosis of mesial temporal lobe epilepsy and suspicion of mesial temporal sclerosis or atrrophy as the sole pathology.

Transsylvanian amygdalo-hippocampectomies are done through a pterional craniotomy of approximately 5 cm in diameter. After microsurgical dissection of the sylvian fissure (2.5–3 cm), the temporal horn of the lateral ventricle is entered through the temporal stem, thus enabling resection of the mesial structures (amygdala, hippocampus, parahippocampus). The collateral sulcus is the intended lateral resection border, while the area of maximum brain stem diameter is the dorsal border.

In transcortical amygdalo-hippocampectomies only the approach to the temporal horn is different: a 3 cm craniotomy is centred on the projection of the middle temporal gyrus. After a 2 cm corticotomy, the temporal horn is approached through the white matter with the aid of neuronavigation, followed by a hippocampal resection, as described above.

Three patients after left amygdalo-hippocampectomy had to be excluded from the because their magnetic resonance imaging (MRI) results were not available for review. One patient developed a postoperative space occupying intra-axial haematoma after left amygdalo-hippocampectomy, which was removed surgically. This patient was excluded because of persisting dysphasia and mild hemiparesis. There was no mortality in the series. Minor complications which did not lead to exclusion were evident in two patients with signs of meningeal inflammation, one patient with an asymptomatic small choroidal infarction, and one patient with some blood in the resection cavity, which did not require specific treatment. Visual field defects (contralateral upper quadrantanopsia), if present, were not encountered as complications. Thus 34 patients were evaluated for this study. Nineteen had a sylvian (nine left, 10 right) approach, and 15 a transcortical approach (five left, 10 right).

Abbreviations: AVLT, auditory verbal learning test; SAH, selective amygdalo-hippocampectomy; FLAIR, fluid attenuated inversion recovery

Despite advances in the pharmacological management of localization related epilepsy, seizures remain refractory to medical treatment in approximately 15–30% of patients. For these patients epilepsy surgery can be a successful treatment option. Epilepsy surgery, however, bears an undeniable risk of causing additional cognitive impairment. Temporal lobe resections still represent the most frequent type of surgery and, accompanying progress in neuroimaging and electroencephalographic monitoring, there is a “new wave” in epilepsy surgery away from standard en bloc resections towards tailored and highly selective approaches. Restricting the resection to already damaged and epileptogenic tissue was originally thought to spare unaffected brain areas and their associated brain functions. However, there have been contradictory findings relating to memory loss after left selective amygdalo-hippocampectomy (SAH). The same is true of studies comparing the outcome of selective surgery versus standard two thirds anterior temporal lobectomy. caused by the surgical approach. This turns out to be a potential source of postoperative cognitive impairment.

METHODS

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Verbal learning and memory were assessed preoperatively and three months after surgery by parallel versions of a serial word list learning test, which requires learning and immediate recall of a word list (A) of 15 words over five trials, delayed recall after distraction (learning a second list (B) in one trial) and after a delay, and recognition of list A items from among alternatives (German pendant of the auditory verbal learning test (AVLT)16). The chosen measures of “learning over five trials,” “loss of learned items in delayed free recall,” and “recognition memory (correct minus errors)” differentially assess aspects of verbal short term/working memory and verbal long term consolidation/retrieval, and reflect more temporo-cortical or temporo-mesial functioning, respectively.17

Figural memory was assessed using a revised version of a serial design list learning test which requires learning and reproduction of nine abstract designs.18 Each design consists of five lines of equal length, and the designs have to be reproduced using five wooden sticks. Learning over four trials was chosen as the dependent measure. This test has been shown to be sensitive to right temporal lobe function and surgery.19 20

High resolution MRI was undertaken a week after surgery, using a 1.5 Tesla system (Gyroscan ACS-NT, Philips Medical Systems, Best, Netherlands). Results of post-surgical MRI (axial and coronal FLAIR and T2 weighted fast spin echo images) were assessed by two independent examiners with respect to, first, the extent of hippocampal resection (defined negatively by measuring the distance from a line through the dorsal resection border to a line along the dorsal border of the quadrigeminal plate (fig 1A, 1B, left side); and second, the extent of post-surgical brain tissue signal changes along the transsylvian or transcortical path to the mesial temporal lobe (“collateral damage”), quantified by the mean diameter on coronal T2 weighted or FLAIR fast spin echo images (fig 1A, 1B, right side). “Collateral damage” was considered on the one hand as a continuous variable, ranging from 0 to 22 mm, and on the other as a dichotomous variable. Defining a diameter greater than the median (10 mm) as a significant lesion, 15 of the 34 patients were classified as showing greater collateral temporal cortical damage, and 19 as having lesser or no such damage.

Statistics
Data were analysed by repeated measurement analysis of covariance (MANCOVA), which included preoperative/postoperative memory testing as the “within subject” factor, and side of surgery, surgical approach, and the diameter of the MRI signal intensity changes (dichotomous variable) as between subject factors. The extent of the mesial resection was controlled by covariance analysis. A prediction model of memory outcome (difference score: post-pre) was calculated by backward multiple regression analysis ($p$ for removal $<0.1$). Regression analysis took into consideration baseline performance, side of surgery, surgical approach, and the diameter of the MRI signal intensity changes (dichotomous variable) as between subject factors. The extent of the mesial resection was controlled by covariance analysis. A prediction model of memory outcome (difference score: post-pre) was calculated by backward multiple regression analysis ($p$ for removal $<0.1$). Regression analysis took into consideration baseline performance, side of surgery, surgical approach, and the degree of the mesial resection, and the degree of signal intensity changes (continuous variable).

![Figure 1](http://jnnp.bmj.com/ on June 21, 2017 - Published by group.bmj.com)

**Figure 1**  (A) T2 weighted fast spin echo images in axial (left) and coronal (right) orientation after left amygdalo-hippocampectomy (transsylvian approach). The axial slice shows the measurement of the extent of hippocampal resection (11 mm). On the coronal slice only a small area of decent postoperative “damage” (9 mm in transverse diameter) can be seen adjacent to the sylvian fissure. (B) T2 weighted fast spin echo images in axial (left) and coronal (right) orientation after right transsylvian amygdalo-hippocampectomy with a much larger zone of postoperative alterations. The axial (left) image shows a similar extent of hippocampal resection (10 mm), but note the hypointense signal alterations in the right lateral temporal lobe. The quantification of “collateral damage” results in a 22 mm zone adjacent to the sylvian fissure.

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RESULTS
The patient groups (transsyllvian/transcortical) did not differ with respect to demographic variables (sex, age, intelligence quotient), clinical variables (age at onset, duration of epilepsy), seizure outcome (84% v 87% completely seizure-free), or the extent of the mesial resection (remaining hippocampus (mean (SD)), 1.8 (1.7) v 1.6 (1.8) cm). Surgical approaches were not associated with a different mean degree of “collateral cortical damage” (10 (7) mm v 9 (6) mm). With respect to verbal memory, multivariate analysis of variance revealed an effect of the MRI measure on postoperative memory change independent of the chosen approach (interaction effect: test repetition × collateral temporal damage, \(F = 3.4, p = 0.03\)). This effect was obtained only with respect to the more cortical aspects of verbal memory (learning/delayed recall, \(p < 0.001\); recognition, \(p = 0.05\)). In multivariate analysis of variance the observed interaction effect overshadowed the known effects of the side of surgery on verbal learning and memory. This effect became evident only in univariate analysis of variance and here only for verbal recognition memory (analysis of variance: \(F = 6.5, p = 0.01\)) (see also table 1).

Differences between the surgical approaches only marginally disfavoured the transcortical approach. Regression analysis showed that only the degree of signal intensity changes (\(t = 3.5, p < 0.01\)) together with the preoperative baseline performance (\(t = 2.6, p < 0.05\)) remained in the regression model and explained about 40% of the postoperative change in verbal learning (\(F = 9.6, p < 0.01\)). The respective correlation between the degree of signal intensity changes and postoperative change in verbal learning is shown in fig 2. Performance in the more mesial function of verbal memory consolidation/retrieval (delayed free recall) was not affected by the degree of collateral damage, but in multiple regression analysis the expected effect of the side of surgery became evident (\(t = 2.3, p < 0.05\)); according to this, greater losses were observed after left sided surgery. Together with the baseline performance (\(t = 5.9, p < 0.001\)), the side of surgery explained 54% of the variance in performance changes in this measure (\(F = 18.1, p < 0.001\)). Greater losses in recognition memory, which also reflects mesial and cortical aspects of memory, were observed after left sided resections (\(t = 3.6, p < 0.01\)), with greater collateral damage (\(t = 3.0, p < 0.01\)), with continuance of seizures (\(t = 2.6, p < 0.05\)), and with better baseline performance (\(t = 2.0, p < 0.1\)). Together, these variables explained 48% of the variance in recognition memory change (\(F = 6.3, p = 0.001\)).

With respect to figural memory, multivariate analysis of variance indicated a significant two way interaction (test repetition × side of surgery, \(F = 5.2, p = 0.03\)) and a significant three way interaction (test repetition × side of surgery × collateral damage, \(F = 5.9, p = 0.02\)). Patients with right sided surgery showed greater losses in design learning than patients with left sided surgery, particularly when there was evidence of collateral cortical damage (table 1). According to regression analysis, right sided surgery (\(t = 3.0, p = 0.005\)), better baseline performance (\(t = 2.0, p = 0.04\)), continuing seizures (\(t = 2.1, p = 0.04\)), and older age (\(t = 1.7, p = 0.09\)) were predictive of greater losses in design learning. Altogether the remaining variables explained 43% of variance.

![Figure 2](http://jnnp.bmj.com/content/137/4/325/F2)

Figure 2 Regression showing a significant relation between the extent (diameter) of the collateral temporal cortical damage indicated by postoperative magnetic resonance imaging signal intensity changes and the postoperative change in verbal learning, independent of the surgical approach and the side of surgery (\(r = \text{Pearson's correlation coefficient}, p = \text{two tailed significance}\)). Negative values on the y axis represent losses, positive values gains in the absolute number of words learned over five trials.

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<th>Table 1 Pre- and postoperative memory as a function of side of surgery and collateral damage</th>
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Values are mean (SD).
*Raw scores.
CD+, collateral cortical damage >10 mm; CD−, collateral cortical damage <11 mm; LTLE, left temporal lobe excision; RTLE, right temporal lobe excision.
DISCUSSION

Our results replicate the known specific effect of left sided selective surgery on verbal long term consolidation/retrieval, which appears to be associated with left temporo-mesial structures. Right sided surgery, in contrast, had a negative effect, particularly on design list learning. SAH in patients with mesial temporal lobe epilepsy with hippocampal sclerosis as the sole pathology was originally intended to spare the unaffected temporal cortex and associated functions. However, as in our recent study on SAH, we observed not only losses in verbal consolidation/retrieval but also in verbal learning and recognition memory. In addition a significant correlation between collateral cortical damage and changes in verbal learning and recognition was evident, indicating an effect of temporal cortical damage from the surgical approach, particularly on the short term and working memory aspects of verbal memory performance. The effect on verbal learning appeared to be non-specific, as it was observed independently of the side of surgery and the surgical approach (transsylvian vs transcorital). This is consistent with findings that the short term and working memory aspects of verbal memory can be impaired nonspecifically by lesions of different location and lateralisation if these affect receptive or executive components of memory processing. With design list learning we were never able to differentiate mesial from cortical damage qualitatively. However, the present data indicate that right sided temporal collateral cortical damage has a negative effect on this performance.

We are aware that, in contrast to our previous studies on SAH, a rather short follow up interval was chosen in this study, so recovery from surgical damage can still be expected. The short interval was originally chosen in order to find out as quickly as possible whether a transcorital surgical approach has disadvantages over the transsylvian approach. The difference between the approaches was marginal and non-significant, although this may change with larger and more balanced groups. Furthermore it should be noted that more detailed information and more exact assessment of the collateral damage can be achieved using three dimensional analyses were not available in the patients evaluated here.

The decisive message of the present study, however, is that epilepsy surgery—even if stereotyped resections are planned—is not a neuropsychological “black box” in the operational sense of the word. Damage caused by the surgical approach appears to be a potential source of postoperative memory impairment, which should be considered in the discussion of the advantages/disadvantages of different neurosurgical approaches, and we hope the present findings contribute to an understanding of the contradictory findings in previous reports.

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Competing interests: none declared

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