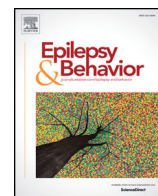




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## Red flags in epilepsy surgery: Identifying the patients who pay a high cognitive price for an unsuccessful surgical outcome

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## ABSTRACT

Preoperative estimates of cognitive and seizure outcome must be as accurate as possible if the candidate is to make an informed decision about epilepsy surgery. Significant declines in memory function are reported in approximately 30% of temporal lobe surgery patients. The percentage varies according to the ways in which a postoperative deterioration is defined but since the majority of outcome studies do not take into account the patient's capacity to deteriorate if they are functioning at or close to the floor of a memory test prior to surgery, the published percentages may be an underrepresentation of the true extent of memory decline following epilepsy surgery. We examined the cognitive 'cost' of epilepsy surgery in a consecutive series of 474 patients who underwent elective surgery for medically intractable epilepsy. All patients underwent a presurgical assessment prior to and 1 year after the surgery. Reliable change indices were used to identify significant postoperative memory decline. Postoperative outcome was dichotomized using the ILAE 2008 classification. All patients in class one were classified as seizure-free (67.5% of the sample). Excluding patients already functioning at or below the 2nd percentile on standardized memory tests, 37.8% experienced a significant postoperative decline in memory function. Twelve percent experienced the 'double hit' of significant postoperative memory decline and ongoing seizures following surgery. Patients with pathologies other than hippocampal sclerosis and with signs of limited cognitive reserve, both in terms of memory function and overall intellectual ability were most likely to suffer a double hit. Our results indicate that caution should be exercised when operating on these patients and preoperative counseling should be tailored to reflect the likely risk/benefit ratio of a temporal lobe resection for medically intractable epilepsy in this group.

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### 1. Introduction

Despite the remarkable advances in imaging and other presurgical evaluations over the past decade [1], only 60–70% of patients who undergo epilepsy surgery are seizure-free 1 year following surgery [2]. This percentage has not changed in line with the technological advances [3]. This proportion drops to below 50% in series who have been followed up over longer periods [2,4]. One explanation often put forward for the static nature of outcome statistics is that centers are now operating on more 'difficult' patients. Having got used to the 30%–40% margin of failure, this continues to be the convention, even as the characteristics of the patient group change. While this may be an acceptable approach in terms of the physical risk/benefit ratios of undergoing a surgical procedure; in epilepsy surgery, the patient has often paid a considerable cognitive 'price' for their postoperative outcome whether it is successful or not.

The decision to proceed to epilepsy surgery is a complex one. Prospective candidates need to weigh up the chances of being seizure-free or of having a significant reduction in their seizures against the inherent risks of the procedure [5]. The risks of stroke, infection, a permanent neurological deficit, or a worsening of seizure control following epilepsy surgery are small [6]. However, the risk of a significant decline in memory function following surgery falls into a different class of risk that prospective candidates must consider. Unlike a stroke or other untoward complication, a decline in memory function does not necessarily mean that something has 'gone wrong' with the procedure, rather it can be viewed as part of the expected outcome. The risks are different for each candidate, dependent upon their clinical characteristics but for some candidates, the chances of experiencing a significant decline in memory function are high, greater than 50% [7]. In these circumstances, a postoperative decline in cognitive function could be considered as the likely 'cost' the candidate will pay for surgery, rather than a possible risk [5]. Thus, in the surgical decision making process, the chances of a postoperative decline in cognitive function can be thought of as the likely price the candidate will pay for the chance of being seizure-free. This price is attached to the surgery, not the outcome. It is imperative that

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the clinicians' estimates of both the likely cognitive 'cost' and the chance of being seizure-free are as accurate as possible if the candidate is to make an informed decision about an elective surgical procedure. These estimates are typically made on base rates of decline reported in the literature.

There is a large existing literature on the predictors of poor seizure outcome following surgery and a separate literature on the factors associated with postoperative memory decline in epilepsy surgery candidates [8]. We have previously published extensive data from our own series on these outcomes [4,9,10]. This study focuses on the identification of patients who pay a high cognitive price for an unsuccessful surgical outcome. These are a distinct group of patients who deserve special attention. Surgery may be an acceptable treatment option for some patients if there is a low risk of cognitive morbidity, even if it fails to completely control seizures. For other patients, cognitive morbidity may be a price they are prepared to pay for a good chance of seizure freedom. The clinical issues associated with these suboptimal outcomes are very different to the patients who pay a high cognitive price for an unsuccessful surgical outcome.

The aims of this study were the following:

1. To determine the proportion of patients who are not seizure-free and who experience a significant postoperative decline in memory function following surgery (double loss).
2. To identify the preoperative factors associated with double loss following surgery.

## 2. Methods

### 2.1. Participants

The participants in this study were a consecutive series of patients who had undergone elective temporal lobe surgery for medically intractable epilepsy at the National Hospital, Queen Square from 1992 to 2015 who had completed the standard clinical neuropsychological assessment prior to surgery and 1 year after their operation. Patients were excluded if English was not their first language, and they were assessed via an interpreter. All patients are routinely followed-up at 1 year.

Complete pre- and postoperative neuropsychological data were available for 474 patients ( $n = 217$  RTL;  $n = 257$  LTL). The mean age of the patients at the time of the preoperative assessment was 33.4 years (range: 16–66 years, s.d. 9.9) with a mean age of onset of 12.0 years (range: 0–54 years, s.d. 9.6). The clinical and demographic characteristics of the sample are presented in Table 1.

### 2.2. Neuropsychological tests

Scores from the List Learning and Design Learning tasks from the Adult Memory and Information processing Battery (AMIPB) and the British Memory and Information Processing Battery (BMIPB) were used as measures of memory function [11,12]. The structure of the

AMIPB and BMIPB memory tests is identical. However, the BMIPB is a restandardization of the original AMIPB test norms. These tests have been shown previously to be sensitive to mesial temporal dysfunction and temporal lobe surgery [13,14]. In the list learning task, the patient is presented with a list of 15 unrelated words to learn, over 5 trials (max 75). A second list is then presented as a distractor before the patient is required to return to the first list and recall as many as they can, without further exposure. The structure of the design learning test parallels that of the list learning test. The patient is presented with an abstract design with nine components and asked to reproduce it over 5 trials (max 45). A second design is then presented as a distractor, before the patient is required to reproduce the first design again without further exposure.

### 2.3. Outcome measures

The raw scores from the verbal learning and visual learning tasks were converted to z scores for the purposes of the statistical analyses.

### 2.4. Memory decline

Previous studies of postoperative memory decline in patients with epilepsy surgery may have underestimated the true prevalence of significant deterioration by including patients who already function at or close to the floor of traditional neuropsychological tests prior to surgery. While these patients may demonstrate decline in function on behavioural measures, this will not be detected on formal psychometric tests as the patients are already functioning at the floor of the test, and further decline will not be evident using robust measure change for example, reliable change indices, [8,9]. The inclusion of patients who already function at or close to the floor of a clinical test and cannot deteriorate further, will distort the true rate of postoperative deterioration, returning a lower percentage than is likely to be the true rate. Capacity for postoperative decline was, therefore, determined by a preoperative score at or above the 2nd percentile according to published norms of the test.

A significant memory decline was defined using previously determined reliable change indices for each task [7]. A postoperative score lower than the preoperative score by the RCI 80% or greater was classified as a significant postoperative decline in memory function.

Postoperative outcome was determined using the ILAE 2001 classification [15]. Seizure outcome was dichotomized for the statistical analyses. Patients in the ILAE classification class one were classified as seizure-free, other outcomes were classified as not seizure-free.

### 2.5. Statistical analyses

#### 2.5.1. Predictors of 'double loss' following surgery

Logistic regression analyses were used to identify predictors of a postoperative 'double loss'. A double loss was defined as a significant

**Table 1**  
Clinical and demographic characteristics of the participants.

	RTL (n = 217)	LTL (n = 257)	Whole group n = 474
Age	34.5 (9.9)	32.5 (9.8)	
Gender	102 male 115 female	118 male 139 female	220 male 254 female
Age at seizure onset	12.8 (9.7)	11.4 (9.7)	
Preoperative verbal IQ	94.3 (14.5)	91.5 (12.2)	92.8 (13.3)
Preoperative performance IQ	96.2 (16.2)	98.1 (14.4)	97.2 (15.2)
MRI characteristics	N = 8 NAD N = 149 HS N = 60 Other	N = 10 NAD N = 192 HS N = 55 Other	n = 18 NAD n = 341 HS n = 115 Other
Seizure outcome	144 seizure-free (66%)	176 seizure-free (68%)	320 seizure-free (67.5%)

HS – hippocampal sclerosis.

NAD – no abnormalities detected.

Other – other pathology including cortical dysplasia, DNET, cavernoma, glioma, and other structural lesions.

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