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The effect of quantitative and qualitative antiepileptic drug changes on cognitive recovery after epilepsy surgery

Christoph Helmstaedter *, Christian Erich Elger, Juri-Alexander Witt

University of Bonn, Department of Epileptology, Germany

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ABSTRACT

Purpose: Epilepsy surgery is associated with a risk of cognitive deterioration, but improvement has also been reported. Improvements have mostly been attributed to seizure control, neglecting changes in drug treatment during the observation period. We evaluated whether changes of antiepileptic treatment affect cognitive outcome one year after epilepsy surgery.
Methods: This retrospective study evaluated the impact of quantitative and qualitative antiepileptic drug changes on postoperative outcome on cognition (executive functions, episodic memory) and mood in 116 epilepsy surgery patients, controlling the results for seizure outcome (seizure free yes/no) and site of surgery (87 temporal lobe, 29 extratemporal lobe resections).
Results: At baseline, 60% of all patients showed impairment in executive functions, 54% in memory, 49% in mood. Postoperatively, 65% of the patients were seizure free. Executive functions, memory, and mood improved in 22%, 10%, and 32%, respectively, and deteriorated in 15%, 21%, and 11%. Drugs were changed quantitatively (change of drug load) and qualitatively (optimization in regard to side effect profiles). According to MANCOVA and individual level analyses, executive functions changed significantly with altered drug load. This was confirmed by partial correlations when controlling for seizure outcome. Memory outcome was more strongly determined by site of surgery. Mood improved non-specifically. However, qualitative drug change had some positive effect on postoperative memory and mood.
Conclusion: The data highlight the relevance of AED changes for cognitive outcome after epilepsy surgery. Drug load reduction and selection of drugs with favorable side effect profiles significantly release cognitive functions thereby supporting recovery after epilepsy surgery.

1. Introduction

Epilepsy surgery is a well-established and successful treatment option for patients with pharmacoresistant structural, i.e. focal symptomatic, epilepsies [1]. Epilepsy surgery, however, is associated with a risk of causing cognitive deterioration [2]. Major determinants of postoperative performance change are (1.) the preoperative cognitive status, i.e. the patients' reserve capacity which can be estimated by baseline performance, education, intelligence, age, and hemisphere dominance, and (2.) the functional importance and contribution of the tissues and fibre tracts to be resected and, connected to this, the preoperative pathological status and the type and extent of the surgical resection [3]. As a third factor seizure control, i.e. recovery from epilepsy after successful surgery has been discussed as a determinant of cognitive outcome. In our previous longitudinal follow-up study in surgically versus medically treated patients with temporal lobe epilepsy we observed longer-term improvements of executive and memory functions, particularly when seizures were successfully controlled (seizure freedom and percentual reduction of seizure frequency) [4]. In our study and in a study by Hermann and Seidenberg dating back to 1995 this improvement was interpreted as the result of a postoperative release of functions secondarily affected by inhibition through epileptic dysfunction before surgery [4,5].

An issue which has rarely been explicitly addressed in this context is the effect of the change of the antiepileptic medication from before to after surgery on cognition [6]. It is important to note that in the present evaluation "change" is understood as a change of the drug load or change of individual substances and not as postoperative discontinuation of the medication. As for drug withdrawal/discontinuation in seizure free medically treated

* Corresponding author at: Department of Epileptology, University of Bonn, Sigmund Freud Str. 25, 53105 Bonn, Germany. Tel.: +49 228 287 16108; fax: +49 228 287 90 16108.
E-mail address: C.Helmstaedter@uni-bonn.de (C. Helmstaedter).

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patients, there is evidence from older and more recent studies that this leads to an improvement of cognitive functions [7–11]. In addition there are two epilepsy surgery studies which described improvement of intelligence in children after epilepsy surgery, particularly when drugs had been discontinued [12,13]. Skirrow and colleagues concluded that "cessation of antiepileptic medication was the strongest predictor of postoperative IQ increase, even after exclusion of patients with continuing seizures, which lends support for the concerns about the potential impact of long-term AED use [. . ..] on cognitive development" [12].

With this background, the aim of the present study was to evaluate the effect of antiepileptic drug changes versus seizure control on cognitive outcome in adult patients after epilepsy surgery, particularly on executive functions.

In order to address this question the major selection criterion for the evaluated group of patients who had undergone epilepsy surgery was the pre- and postoperative use of the assessment tool EpiTrack, a brief test of executive functions and working memory, which has been designed and validated for the monitoring AED-induced cognitive side effects [14–16]. In addition, and as a control condition, we considered changes in memory and mood.

The study explicitly did not aim to evaluate the effects of different types of surgery on cognition. However, since a mixed group of patients was evaluated, and since temporal and extratemporal epilepsies differentially affect memory and executive functions [17] this factor was controlled for in the analysis of the effects of drug changes versus the effects of seizure control.

2. Methods

2.1. Patients

A total of 116 patients was included who had undergone epilepsy surgery with preoperative baseline and one year postoperative follow up evaluation employing both the EpiTrack and standard tests of learning and memory. Most patients also had pre- and postoperative assessment of mood/depression.

Of the 116 patients included, 87 suffered from temporal lobe epilepsy (TLE), and 29 patients from extratemporal lobe epilepsy (ETLE, 20 frontal, 9 posterior).

Gender (49% female), education (56% > 10 years), preoperative IQ (29% between IQ 60 and 85), and side of surgery (54% left) were equally distributed in the patient subgroups. The mean age of the patients was 37.0 ± 12.7 years. Patients with ETLE were younger than those with TLE ($F = 9.0$, $p < 0.01$) (see Table 1).

2.2. Quantitative and qualitative parameters of AED treatment

Antiepileptic treatment was assessed by consideration of the number of concurrent antiepileptic drugs before and after surgery, as well as by the pre- and postoperative total drug load based on the defined daily dose (DDD). DDD was calculated according to the ATC index of the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) reported for the drugs in use (www.whocc.no\ddd\definition_and_general_considera/). For polytherapy, DDD of the individual concurrent drugs were summed up. As recently demonstrated, both measures of drug load show a good correlation to EpiTrack performance [18].

In addition, for each drug, withdrawal and new introduction were listed in order to have qualitative information about which drugs had been changed apart from simply calculating numbers of AED or DDD total drug load.

2.3. Neuropsychological assessment

The diagnostic measures of interest were executive functions, learning and memory, as well as mood which had been assessed before surgery (baseline T1), and again at a standard postoperative retest-interval of 12 months (follow-up T2). For executive functions and memory parallel test versions were applied before and after surgery.

Table 1
Patient characteristics.

		All patients	Temporal (TLE)	Extratemporal (ETLE)	TLE vs. ETLE Chi 2/Anova significance
N		116	87 (75%)	29 (25%)	
Female sex	%	49%	51%	45%	n.s.
Age	m/sd	37.0 (12.7)	39.0 (12.0)	31.2 (12.9)	$F = 9.0^{**}$
Education >10yrs.	%	56%	55%	41%	n.s.
IQ <85 but >60	%	29%	29%	29%	n.s.
Left-sided surgery	%	54%	52%	62%	n.s.
Seizures/month					
T1	m/sd	19.2 (47.0)	8.4 (13.0)	54.8 (86.8)	$F = 20.7^{***}$
T2	m/sd	1.2 (3.7)	1.0 (2.6)	1.9 (6.1)	n.s.
% Seizure reduction	m/sd	79.6 (74.0)	74.9 (83.8)	93.7 (24.7)	n.s.
Seizure free	%	65%	63%	69%	n.s.
Number of AED					
T1	m/sd	2.4 (0.8)	2.2 (0.7)	2.7 (0.8)	$F = 9.1^{**}$
T2	m/sd	2.1 (0.6)	2.0 (0.4)	2.1 (0.6)	n.s.
ΔAED T2 – T1	m/sd	−0.26 (0.8)	−0.2 (0.8)	−0.6 (0.7)	$F = 5.4^{*}$
DDD					
T1	m/sd	3.1 (1.9)	2.9 (1.8)	3.7 (2.0)	n.s.
T2	m/sd	2.8 (1.2)	2.8 (1.2)	2.9 (1.2)	n.s
ΔDDD T2 – T1	m/sd	−0.3 (1.7)	−0.1 (1.7)	−0.8 (1.9)	n.s.
Antidepressants/AD					
AD at T1 [10/116]	%	9%	9%	7%	n.s.
AD at T2 [16/116]	%	14%	15%	10%	n.s.
AD at T1 = 16	*n*	↓ 6	↓ 4	↓ 2	$Chi2 = 6.3^{*}$
No AD at T1 = 100		↑ 12	↑ 9	↑ 3	

* $p < 0.05$ AED antiepileptic drugs ↑ introduced ↓ withdrawn.
** $p < 0.01$ AD antidepressants ↑ introduced ↓ withdrawn.
*** $p < 0.001$ DDD daily defined dose.