

## Can Neuropsychological Rehabilitation Determine the Candidacy for Epilepsy Surgery? Implications for Cognitive Reserve Theorizing

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### Abstract

**Objective:** The purpose of this study was to explore the effectiveness of a neuro-optimization intervention to determine the suitability for surgery in a patient suffering from left medial temporal lobe epilepsy (MTLE) and hippocampal sclerosis (HS). The rehabilitation program was aimed at amplifying cognitive resources and improving memory functioning, particularly in the non-dominant healthy hemisphere.

**Method:** A preoperative neuro-optimization program, inspired by the functional reserve model and the right hemisphere's verbal processing potential, was adopted. This neuro-optimization program targeted global cognitive and metacognitive enhancement with an emphasis on memory functions of the right temporal lobe, i.e., the functional upgrade of the healthy right hippocampus and related structures to assist memory after surgery.

**Results:** After a 32 weeks neuro-optimization program, the patient once again underwent intracarotid amobarbital test (IAT). This time his right hemisphere memory functioning yielded a borderline score, allowing us to consider surgery. Immediately after surgery, the patient was seizure free and did not show any clinically significant memory impairment. At six months post-surgery he had largely preserved memory optimization gains.

**Conclusion:** Preoperative optimization interventions aiming at enhancing cognition, in general and memory of the healthy hemisphere, in particular, may contribute to a positive memory outcome after left selective amygdalohippocampectomy.

**Keywords:** Medial temporal lobe epilepsy; Preoperative cognitive intervention; Neuro-optimization; Cognitive Reserve; Amygdalohippocampectomy

### Introduction

In the context of neurorehabilitation the concept of cognitive reserve, i.e., the inherent potential of the brain in order to cope with damage, represents a key concept. In the domain of MTLE surgery, the concept of cognitive reserve has been applied in two different models of hippocampal functioning, i.e. functional reserve vs. hippocampal adequacy, in relation to the risk for memory decrements following temporal lobectomy (TL). The hippocampal functional reserve model claims that the size of memory loss is related to the spare capacity of the contralateral temporal lobe to support memory functions after resection of the affected (ipsilateral) lobe. IAT injections contralateral to the side of epileptogenesis typically lead to memory impairment, whereas normal memory performance is seen in the healthy hemisphere following injections to the pathologic one [13,14,17,21,23,27,19]. Some researchers found no significant relationship between the functional reserve of the contralateral-healthy temporal lobe as assessed by the IAT and memory changes following TL.

On the other hand, there is rising evidence that the functional adequacy of the tissue to be resected determines the nature and extent of postoperative memory loss. It has been repeatedly observed that patients, whose mnemonic abilities were sufficiently intact before surgery, are adversely affected following TL [6,22,1,16]. In line with these findings, studies on memory functioning derived from IAT injections contralateral to the seizure focus indicated that patients with good memory before surgery were at much greater risk for memory loss than those who performed poor at baseline [2,10]. A weak point of the functional adequacy model, however, is that it does not predict mild material-specific memory deficits following TL. Although the contralateral temporal lobe alone does not determine the probability of memory loss following TL, this is not to say that its functional capacity should be ignored, especially if we consider ample clinical evidence documenting the devastating consequences for memory following bilateral hippocampal damage [24].

There is strong evidence of an inverse relation between the risk of postoperative memory impairments and the functional adequacy of the surgical temporal lobe, mostly seen with respect to verbal memory and left MTLE patients, rather than the functional reserve of the contralateral hemisphere [1,10,18,14,12].

In light of the above, we present the case of a patient with refractory left MTLE and hippocampal sclerosis, who participated in a 32 weeks

neuro-optimization program and improved memory performance of his healthy hemisphere as demonstrated in a following up IAT, enabling us to consider surgery.

Insights to our rehabilitation program formulation were given by the proved ability of the right hemisphere to process lexical-semantic information and mediate verbal memory through its ability to process highly imageable words. This later notion is known as of imagery mediated verbal recall and constituted the basis for our right-hemisphere training program aimed at enhancing verbal mediation to support verbal memory after surgery. Jones [7], confirming Patten et al. [20], reported that both healthy individuals and left TLE patients improve their performance in a verbal paired-associate task by using the strategy of imagery mediated verbal recall, while right TLE patients do not. Accordingly, further evidence [8,9] suggested the critical role of the right temporal lobe in processing verbal material with high imageability, such as recalling concrete words. This is further corroborated by evidence that right TLE patients may face verbal memory difficulties when to be remembered material presents a strong imagery component [25].

The relatively limited literature in the domain of cognitive rehabilitation for epilepsy surgical patients has mainly focused on postoperative memory training [15,5,7], while there is only one study dealing with preoperative memory rehabilitation in patients with indication for surgery, which failed to find better memory outcomes as compared to postoperative interventions [11]. To our knowledge no studies to date have addressed preoperative cognitive rehabilitation in epilepsy patients for whom surgery is contraindicated with the aim to render them suitable surgical candidates.

## Case Report

At first assessment AG was 29 year old and had been referred by the treating neurologist for a neuropsychological evaluation as a likely candidate for epilepsy surgery. He is a right handed man with a negative family history for epilepsy. According to his personal history, at the age of three months he was hospitalized for 24 h, due to an episode of loss of consciousness which lasted about five to ten minutes; similar episodes were noted by his parents with a frequency of every five to six months. At the age of six, another episode of loss of consciousness occurred accompanied by fever, and that was the first time that encephalitis was diagnosed. Since then, teachers have described AG as distractible and unfocused, with concentration difficulties in class.

The epileptic episodes typically began with an unpleasant abdominal feeling, followed by obscuration of consciousness. Such episodes lasted for about 10-15 min with a frequency of one every 15 days, until the age of 17 years. At that age he was hospitalized, because of a secondary generalized seizure episode and placed on oxcarbazepine 300-300-300 mg. Since AG continued to have seizures, he was put on polytherapy (topiramate, valproic acid, lacosamide) and later on other medication regimens (i.e., phenobarbital, primidone, pregabalin, tiagabine hydrochloride, zonisamide, phenytoine, ethosuximide), but with no therapeutic effect.

At the time of evaluation, AG's ictal symptoms included looking around, mastication, tonic contractions of the right arm, simple

movements of left arm and aphasia. His seizures lasted about 1 min, followed by postictal blurring, drowsiness and sleep. The patient's MRI was suggestive of a left sided hippocampal sclerosis, while his electroencephalographic recordings (EEG) were not sufficiently specific to shed light on his pathology. Upon admission to the hospital, AG was receiving carbamazepine 700-600-700 mg, topiramate 25-0-50 mg, leviteracetam 1000-0-1000 mg, with a seizure frequency of 2-4 episodes per month.

## Cognitive rehabilitation program

The neuro-optimization intervention was divided into two parts: one aimed at enhancing the patient's global cognitive and meta-cognitive [26] functioning, with an emphasis on right hemisphere memory; the other part introduced the patient to the use of external aids and strategic compensatory approaches in dealing with everyday life tasks. The patient participated in the program for 1 h twice a week.

## Right hemisphere training

Imagery mediated verbal recall has been considered to enhance right hemisphere's contribution to verbal memory. As a result, the patient is instructed to form and memorize images of verbal material in order to remember (e.g. words) and later recall it by simply naming the stored image.

## Neurosurgical procedure

Our patient underwent a left temporal craniotomy. A transcortical selective amygdalohippocampectomy, including the parahippocampal gyrus, was performed, sparing the posterior one third of the hippocampus.

## Discussion

The aim of this work was to verify the effectiveness of a pre-surgery neuro-optimization program in amplifying cognitive resources and improving memory functioning, particularly in the non dominant healthy hemisphere, in order to contain the adverse effects of temporal resection.

AG showed a slight improvement in memory for abstract words and pictures, and a larger and stable improvement in (RAVLT) delayed recall, as well as in his higher level attention and executive functions (TMT-B). This improvement is consistent with our initial hypothesis predicting that contralateral temporal functions strengthening can effectively support memory after surgery.

To sum up, our patient's post surgery overall memory profile was slightly lower than his post rehabilitation one (before surgery), but still considerably higher with respect to his baseline performance (pre-rehabilitation performance).

Among others, our intervention led to improved right hemisphere memory functioning, as shown by patient's post-rehabilitation IAT, making patient suitable candidate for surgery (Table 1).

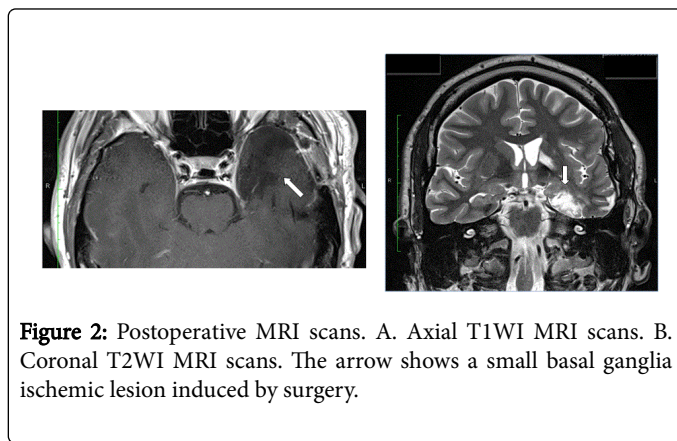
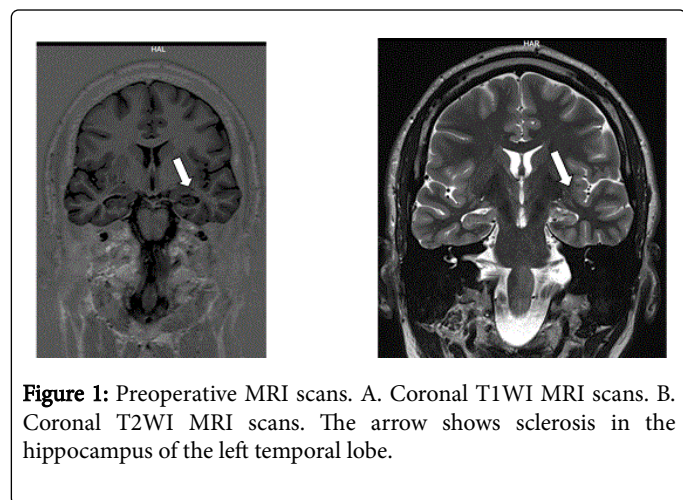
		Normative group			Baseline			6 months post-treatment			6 months post-surgery		
		n	Mean	SD	AG's Score	t-value*	p-value	AG's Score	t-value	p-value	AG's Score	t-value*	p-value
Rivermead Behavioural Memory Test	First Names	144	1.861	0.4521	2	0.306	0.38	2	0.306	0.38	1	-1.898	0.03
	Last Names	144	1.771	0.588	0	-3	0.002	2	0.388	0.349	2	0.388	0.349
	Personal Belongings	144	1.729	0.582	5	5.601	0	8	10.738	0	6	7.313	0
	Appointments	144	1.681	0.5374	2	0.592	0.277	3	2.446	0.008	4	4.3	0
	Picture Recognition	144	9.583	1.2928	5	-3.53	0	8	-1.22	0.112	7	-1.991	0.024
	Story Immediate Recall	136	13.941	4.0318	2	-2.95	0.001	7	-1.715	0.044	7	-1.715	0.044
	Story Delayed Recall	136	11.772	5.0398	1.5	-2.03	0.022	4	-1.536	0.063	4.5	-1.438	0.076
	Face Recognition	144	4.354	1.2653	9	3.659	0	9	3.659	0	8	2.872	0.002
	Route Immediate Recall	144	4.743	0.7266	11	8.582	0	12	9.953	0	11	8.582	0
	Route Delayed Recall	144	4.729	0.75	8	4.346	0	11	8.332	0	9	5.675	0
	Messages Immediate Recall	144	2.785	0.4605	6	6.957	0	5	4.793	0	6	6.957	0
	Messages Delayed Recall	144	2.771	0.4836	5	4.593	0	5	4.593	0	6	6.654	0
	Orientation	144	8.701	0.8535	9	0.349	0.364	9	0.349	0.364	9	0.349	0.364
	Date	144	0.889	0.3154	1	0.351	0.363	1	0.351	0.363	1	0.351	0.363
	Total Memory Scaled Score	144	21.285	3.6483	13	-2.26	0.013	24	0.742	0.23	22	0.195	0.423
	Abstract Words												
	1st Trial	10	8.3	1.3375				1	-5.204	0	2	-4.491	0.001
	2nd Trial	10	9.5	0.9718				2	-7.358	0	4	-5.396	0
	3rd Trial	10	9.7	1.8886				2	-3.887	0.002	7	-1.363	0.103
	4th Trial	10	10.2	1.3166				3	-5.214	0	5	-3.766	0.002
	Delayed Recall (60')	10	11.1	1.6633				0	-6.363	0	3	-4.643	0.001
	Abstract Figures												
	1st Trial	10	8.4	1.075				2	-5.676	0	3	-4.789	0
	2nd Trial	10	8.3	0.9487				2	-6.332	0	4	-4.322	0.001
	3rd Trial	10	9.9	0.9944				3	-6.616	0	6	-3.739	0.002
	4th Trial	10	9.7	1.567				4	-3.468	0.003	8	-1.034	0.164

Delayed Recall (60')	10	10.8	1.6193					0	-6.359	0	5	-3.415	0.004
Trail Making Test - Part B	35	88.46	38.04	170'	2.114	0.021	150'	1.595	0.06	122'	0.869	0.195	
Verbal Fluency													
Semantic	28	33.9	6.3	32	-0.3	0.385	41	1.107	0.139	36	0.328	0.373	
Phonological	28	26.7	6.9	22	-0.67	0.254	16	-1.524	0.07	23	-0.527	0.301	
RAVLT													
Trial 1	25	7.5	1.6	6	-0.92	0.183	6	-0.919	0.183	7	-0.306	0.381	
Trial 2	25	9.6	1.8	10	0.218	0.415	10	0.218	0.415	7	-1.416	0.085	
Trial 3	25	11.7	1.9	10	-0.88	0.194	10	-0.877	0.194	8	-1.91	0.034	
Trial 4	25	12.6	2.3	10	-1.11	0.14	10	-1.108	0.14	7	-2.388	0.013	
Trial 5	25	13.2	1.4	9	-2.94	0.004	9	-2.942	0.004	9	-2.942	0.004	
Total Score	25	54.3	8.4	45	-1.09	0.144	45	-1.086	0.144	38	-1.903	0.035	
Delayed Recall (20')	25	11.1	2.5	1	-3.96	0	1	-3.962	0	3	-3.177	0.002	
IAT				40/100			70/100						

**Table 1:** Comparisons of neuropsychological performance of AG patient with control groups performed at baseline, 6 months post-treatment and 6 months post-surgery using the procedure of Crawford and Garthwaite [27] for comparing a single case with a control population. All comparisons were made using a one-tailed level of significance\*.

Our case points to the important clinical implications stemming from the notions of cognitive reserve and functional hemispheric asymmetry, in order to plan preoperative rehabilitation programs before epilepsy surgery.

Further neuropsychological research in the context of epilepsy surgery is required to address the complex concept of reserve and how the brain responds to preoperative rehabilitation challenges (Figure 1) and (Figure 2).



### Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

## Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Informed Patient Consent

The patient has consented to submission of this case report to the journal.

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