

Potential role of a cognitive rehabilitation program following left temporal lobe epilepsy surgery

Reabilitação neuropsicológica em pacientes com epilepsia submetidos à lobectomia temporal dominante

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ABSTRACT

Research into memory and epilepsy has focused on measuring problems and exploring causes with limited attention directed at the role of neuropsychological rehabilitation in alleviating post-operative memory difficulties. **Objectives:** To assess the effects of a memory rehabilitation program in patients with left temporal lobe epilepsy following surgery. **Methods:** Twenty-four patients agreed to participate and 18 completed the study; nine received memory rehabilitation while nine had no input and were designated as controls. Verbal learning efficiency, naming abilities, memory subjective ratings, ecological activity measures and a language fMRI paradigm were used as outcome measures. **Results:** Improved verbal learning and naming test performance, increase in memory strategy use and improved self-perception were observed following the rehabilitation. Changes in fMRI activation patterns were seen in the rehabilitation group over the long term. **Conclusion:** The findings support the potential role of a cognitive rehabilitation program following left temporal lobe surgery.

Keywords: epilepsy, temporal lobe; memory; neurologic rehabilitation; anterior temporal lobectomy.

RESUMO

As publicações na área de epilepsia e memória se focam em mensurar prejuízos e investigar causas, com poucos dados sobre reabilitação neuropsicológica em pacientes pós-cirúrgicos. **Objetivos:** Avaliar os efeitos da reabilitação neuropsicológica em pacientes submetidos a lobectomia temporal dominante. **Métodos:** Vinte e quatro pacientes iniciaram o estudo, apenas dezoito o concluíram, dos quais 9 foram participantes de sessões de reabilitação com enfoque em memória. Todos os participantes foram avaliados quanto a autopercepção de dificuldades de memória; ao uso de estratégias para minimizar tais dificuldades; a habilidade de nomeação e a aprendizagem verbal e foram submetidos à ressonância magnética funcional. **Resultados:** Foi encontrado efeito significativo da reabilitação neuropsicológica na autopercepção de dificuldades de memória; no uso de estratégias compensatórias; na aprendizagem verbal e na nomeação. Alterações no padrão de ativação na RMf foram observadas no grupo submetido a reabilitação. **Conclusão:** A reabilitação neuropsicológica pode beneficiar pacientes submetidos a lobectomia temporal antero-mesial dominante com prejuízos de memória.

Palavras-chave: epilepsia do lobo temporal; memória; reabilitação neurológica; lobectomia temporal anterior.

Memory deficits in people with temporal lobe epilepsy (TLE) have been widely reported and memory decline is a well-established surgical outcome, particularly following dominant temporal lobe resections. Memory difficulties can have far ranging effects that affect academic and work performance but also can cause considerable personal distress. Research into memory and epilepsy has focused on measuring problems and exploring causes with limited attention directed to the role of neuropsychological rehabilitation¹. Cognitive rehabilitation comprises a range of techniques, and

research in patients with various brain injuries and pathologies has provided some support for its efficacy^{2,3,4,5,6,7}.

The evidence base for memory rehabilitation in epilepsy is limited particularly in temporal lobe surgical cases, a high-risk group. Well-controlled trials are few and data on generalization to daily activities and the persistence of effects are sparse^{1,8}. Existing reports have been encouraging^{8,9}. Unfortunately few studies describe the rehabilitation process sufficiently⁸, while for others memory rehabilitation forms part of a more extensive set of interventions such that it is impossible to identify specific effects¹⁰.

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Which features of the rehabilitation programs contribute to the cognitive gains reported and the mechanism of underlying these changes is uncertain but available evidence suggests it can be effective. If memory rehabilitation has positive effects then this would provide support for inclusion in surgical programs and further research is of considerable clinical relevance. This study aimed to assess the effectiveness of memory rehabilitation for left TLE patients following surgery and utilized an fMRI paradigm to assess for changes in brain function in association with rehabilitation.

METHODS

Participants

Patients with epilepsy, who had undergone selective left temporal lobe surgery at least six months previously, were recruited. Participants were at least 16 years old and were right handed. No participant had a learning disability (IQ < 70) or a psychiatric history or any evidence of anti-epileptic drug toxicity.

Sixty-two patients met the study criteria but only 24 agreed to participate.

Thirteen people were assigned to the active treatment program (the rehabilitation group) and 11 to the control group. Unfortunately, participant selection was not random, as those in the control group were people who were unable to commit to the time and travel requirements of the treatment program.

Written informed consent was obtained from all participants. This study was approved by the ethics committee (process number 9968/2009).

Eighteen people completed the study, nine in the rehabilitation group and nine in the control group. Six patients did not complete the entire program, four in the rehabilitation group and two in the control group. Five failed to attend one of the appointments for the fMRI scan and the cognitive reassessment. The reasons for discontinuing the program prematurely were lack of time due to starting a new job (n = 1), other personal commitments (n = 2), depression (n = 1) and lack of resources for traveling to the hospital (n = 2).

There were no significant differences between the control and rehabilitation groups on demographic or epilepsy related variables (Table 1). Both groups experienced good surgery outcomes (Engel I and II).

Procedure

At the study onset, both groups completed tests of memory, naming, a memory complaints questionnaire and an ecological memory measure. Each participant also underwent an fMRI study.

The rehabilitation group then received eight cognitive rehabilitation sessions, delivered on an individual basis, once a week for two months. Thirty days following the completion

Table 1. Demographic and clinical characteristics of the rehabilitation and control groups.

Variable	Control	Rehabilitation
Gender		
Male/Female	4/5	4/5
Age (years)	44 (14)	41 (14.4)
Education (years)	7.2 (29)	7.9 (32)
Occupation		
Employed	5	2
Unemployed	3	6
Student	1	1
IQ	86.44 (9.7)	85.11 (5.4)
Age of epilepsy onset	10.44 (5.43)	9.7 (5.98)
Years since surgery	5.2 (4.2)	5.3 (4.5)
Engel		
I	6	7
II	3	2
Anti-epileptic drugs		
Carbamazepine	8	9
Clobazam	1	0
Lamotrigine	1	2

Note: Values are means (SD) unless otherwise noted. IQ: intelligent quotient.

of the program, they had a second fMRI study and repeated the cognitive tests and questionnaire.

The control group underwent cognitive retesting and a second fMRI study at an interval of two months but received no rehabilitation. During these two months, they were not seen at the hospital.

A third fMRI was scheduled for both groups two months after the reassessment; however, this was only possible for the rehabilitation group.

Cognitive rehabilitation sessions

Weekly sessions lasted one hour. Topics covered psycho-education about memory, and taught rehabilitation techniques focusing on attention, memory and word-finding problems. Cognitive strategies included self-monitoring and encoding level intervention, such as semantic elaboration, prospective memory training and visual imagery¹¹. Instruction was given in the use of external memory aids such as notes and diaries. Strategies and exercises were derived from those advocated by proponents of memory rehabilitation¹¹. Also, homework was given at the end of each session and checked at the beginning of the next session (Table 2).

At the beginning of the second and of the third sessions, a relative or living companion attended a session on the use of memory strategies and aids in order to provide support in the home setting when needed.

Table 2. Rehabilitation sessions content.

Report:	explain the aims of the sessions; check the patients' complaints; establish goals; explain the relevance of the commitment to the sessions and timing.
Psycho-education:	how memory works, epilepsy and memory (drugs, surgery); age and mood influencing memory; types of memory; awareness of memory function.
Self-monitoring:	to assist participants to assess their memory in everyday settings and to apply techniques taught.
External memory aids:	a range of memory aids was shown and selected on an individual basis (diaries, calendars, lists, notes, pill dispensers, alarms, wipe and clean memo boards, computers).
Internal strategies:	how to actively work with information to make it more memorable; paying attention and reducing distractions; chunking to organise large information to remember making associations (semantic elaboration); make a story with new information; mental pictures of the information to be remembered (visual imagery); semantic elaboration (determines what property objects to be remembered have in common); PQRS to increase the recall of written information; retrieval strategies (alphabetical searching; retracing events, retrospection).
Practise:	exercises in the use of strategies were incorporated in the sessions.
Homework:	to get the best of the strategies taught; whether they were useful and if changes had to be made; homework was given in the end of each session. Adjustments to the use of strategies or other difficulties were discussed. Participants were encouraged to practice regularly and to try out strategies in daily life.

Outcome measures

Objective cognitive outcomes.

The Boston Naming Test¹² was used to assess retrieval from semantic memory. The subject is required to name 60 items of increasing difficulty, presented as line drawings. The score used was the total number of items named correctly, considering spontaneous response plus semantic cues.

The Rey Auditory Verbal Learning Test¹³ was used to assess verbal learning and recall. The subject is read a list of 15 words over five trials. On each trial, they have to recall as many words as they can. In this study, the total number of words recalled over the learning trials was used as the measure of the memory performance (maximum score = 75).

The Ecological Activity was adapted from the Five Daily Living Test, part of the Neuropsychological Assessment Battery¹⁴. This test assesses memory in a context that simulates performance in everyday life. The subject has to remember what and where in the test room the examiner hides an object. The subject is also given a name to remember, e.g. Carolina Paiva. One point is given for each correct answer resulting in a maximum score of four points. The total score was used in the analysis.

Subjective memory outcomes.

The Self Report Memory Questionnaire² was used to assess the self-perception of memory and the strategies used by the subject in everyday settings. It consists of 28 items; 24 items concern the experience of memory failures encountered in daily life and the remaining four the use of memory support strategies. The questionnaire produces a maximum score of 96 points for the first 24 questions – four points for each correct answer; the higher the score, the poorer the memory self-perception; and 20 points for the remaining four questions (five points for each answer; the higher the score, more strategies the subject uses). The scores were analysed separately.

fMRI

A fluency paradigm to assess language networks pre- and post-rehabilitation provided a generic measure of brain activation involving the semantic processing system. Posterior temporal regions within a larger antero-posterior-basal temporal network have been identified in the process of word retrieval in TLE¹⁵ and word finding difficulties have been found to correlate with resting-state metabolism of the postero-infero-temporo-basal region (BA 20-37), the posterior part of superior temporal gyrus (BA39) and inferior parietal lobule (BA40)¹⁵. Several studies have demonstrated that verbal fluency paradigms are sensitive to detecting impaired functioning of the prefrontal cortex and brain interconnections, particularly of the left hemisphere¹⁶.

fMRI task

Participants underwent out-of-scanner training to maximize task compliance. The task used followed a blocked experimental design and all the stimuli were presented via a digital sound recorder. Patients were asked to think silently of as many words as possible starting with a specified letter (M, A, E, C and S- LET task)¹⁷. The whole paradigm consisted of nine blocks: five resting periods and four activations, in 30 second blocks. During the resting period the subjects were instructed to think of a “blank wall”.

fMRI acquisition

The MRI data acquisition was performed on a Philips Achieva 3T XSERIES scanner. Structural T1-weighted images were obtained using a standard gradient-echo sequence MPRAGE (TR = 6 ms, TE = 3 ms, matrix 256 x 256, FOV = 256mm, 1mm slice). One set of functional echo-planar images were acquired (TR/TE = 3000/30ms, FOV 230mm, voxel vol 1.79 x 1.79 x 4.00mm³, matrix dimension = 128 x 128). Functional images were processed using the software Brain

Voyager™ QX (version 2.0) Brain Innovation, Maastricht, The Netherlands (Goebel et al., 2006)¹⁸. The fMRI data sets were obtained in EPI-BOLD sequences and were co-registered with high-spatial resolution images (3D gradient-echo T1-weighted sequence) covering both brain hemispheres. Preprocessing consisted of 3D movement correction, a 4-mm FWHM Gaussian spatial filter, and a temporal high-pass filter.

Statistical analysis

All data were analysed using SPSS 15.0 version (SPSS Inc., Chicago, IL, USA). First the Kolmogorov-Smirnov, Shapiro-Wilk and χ^2 tests at a 5% significance level were performed and the normal distribution hypothesis was rejected. Due to the small sample size, data was then analysed using non-parametric statistics: Mann-Whitney U tests for comparisons between groups and Wilcoxon tests for within group comparisons. Verbal learning and naming test scores and subjective memory questionnaire indices assessed one month after the completion of the rehabilitation program were the endpoints for analysis. The significance level was set at $p < 0.05$.

To determine the significance of changes in performance, each participant was classified as improved or not based on reliable change indices derived from normative data available from the Rey Auditory Verbal Learning Test and Boston Naming Test^{18,19,20}.

The fMRI temporal series were analysed statistically using a general linear model with the evolution of each voxel being compared to a modelled reference function. In order to extend statistical inferences to the group level, the statistical maps of all subjects were registered to standard space and the significance of activation at each condition was nonparametrically evaluated using the paired Wilcoxon test for two related samples at 5% significance level for both voxels and cluster levels. The difference in the activation between the first and the second scan, between the second and the third, and between the first and the third scans were the indices used for the analysis. Threshold maps ($p < 0.01$) were superimposed on the structural images for anatomic reference.

RESULTS

Objective cognitive outcomes

There were no statistically significant differences between the groups on the first assessment for the objective cognitive measures.

Significant improvements were recorded following the rehabilitation program for verbal learning ($W = 2.38$; $p = 0.02$); naming ($W = 2.32$; $p = 0.02$) and on the Ecological Activity measure ($W = 2.34$; $p = 0.02$). For the control group, improved performance was recorded only on the Ecological Activity measure ($W = 2$; $p = 0.05$) (Table 3).

Three participants in the rehabilitation group were classified as having improved memory on a basis of reliable change indices for verbal learning versus one participant in the control group. On the Boston Naming Test, two individuals were classified as having a meaningful improvement in naming versus none in the control group.

Subjective memory outcomes

The two groups were matched at the initial assessment on measures of self-perception and in the use of support strategies. Both subjective memory measures indicated improvements in the rehabilitation group (self perception: $W = 2.67$; $p = 0.008$ /strategies used: $W = 2.67$; $p = 0.008$). No changes were recorded for the control group (Table 3).

fMRI

There were no significant differences between the groups in activation patterns during the verbal fluency paradigm for the first fMRI scan. There were no changes between the first and the second scans for the rehabilitation group, but changes from the first to the third scan were observed in the right anterior prefrontal cortex ($W = 1.96$; $p = 0.05$), pars opercularis of Broca's area in left hemisphere ($W = 2.67$; $p = 0.01$), and in the right inferior prefrontal gyrus ($W = 2.43$ $p = 0.02$). When the second scan was compared to the third scan there were changes in the right dorsal anterior cingulate cortex ($W = 2.07$; $p = 0.04$) and in the left angular gyrus ($W = 2.21$; $p = 0.027$) (Figure).

Table 3. Control and rehabilitation group outcome measures.

Variable	Control		Rehabilitation	
	Pre	Post	Pre	Post
Objective measures				
Boston naming test	37.4 (7)	37.3 (6.1)	38.3 (11.6)	42.8 (8.2)
Rey auditory verbal learning test	44.7 (9.1)	45.8 (7.9)	45.4 (7.4)	48.7(6)
Ecological activity (median/range)	1 / 0-2	1/1-2	1/1-3	2/1-3
Subjective measures				
Memory self perception	40.7(11.9)	41.9(13)	43.2(13.6)	37.9(13.7)
Strategies used	9.8 (3.4)	10 (3.6)	8.2 (1.6)	12.9 (2.5)

Note. Values are means (SD) unless otherwise noted.

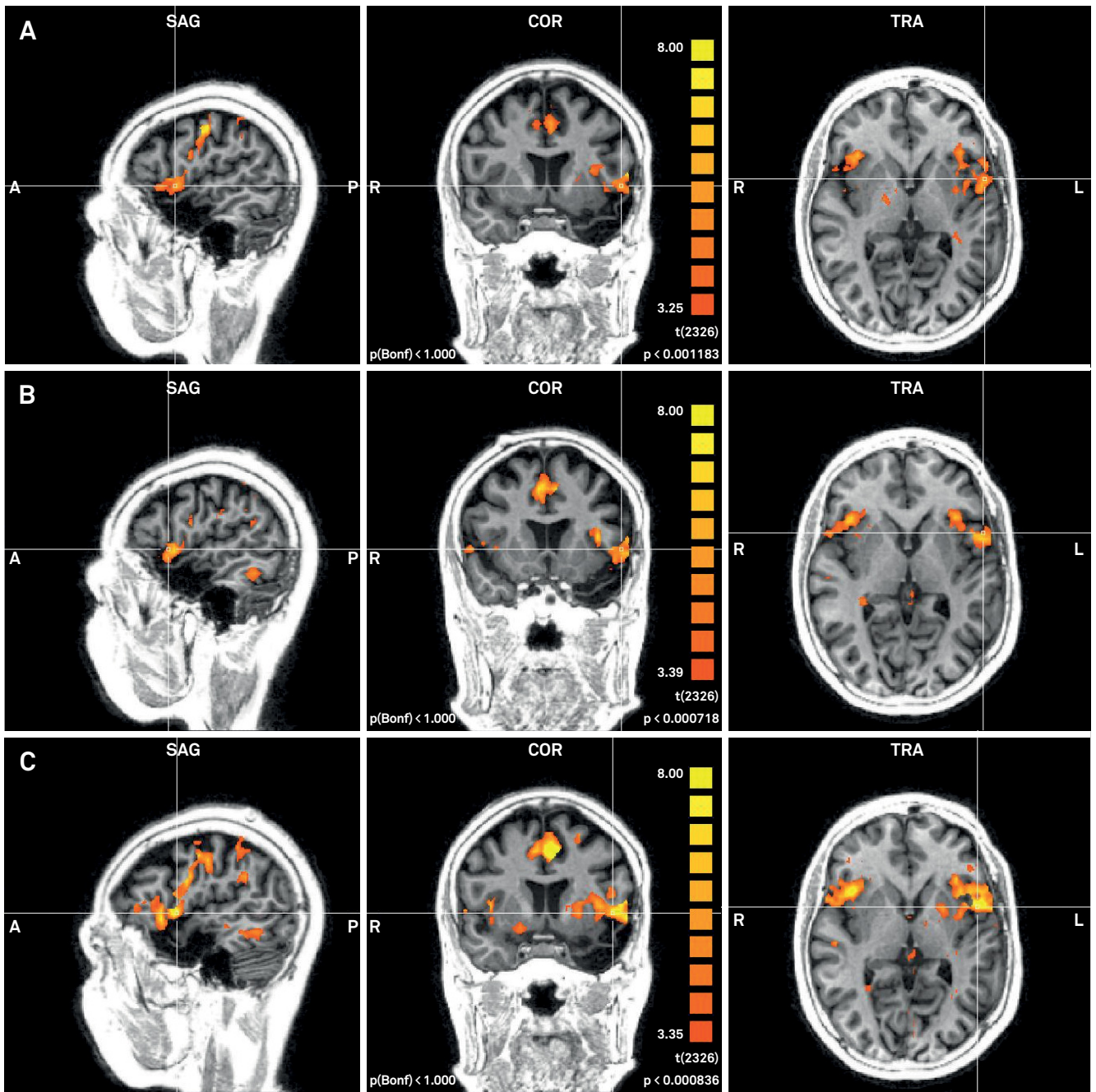


Figure. Activation pattern of language areas during fMRI word generation task in the rehabilitation group. A: before the intervention; B: one month after the program; C: three months after the program.

Activation pattern changes for the control group were observed from the first to the second scan in the primary somatosensory cortex ($W = 2.03$; $p = 0.04$) and the left fusiform gyrus ($W = 2.38$; $p = 0.02$). Unfortunately, a third scan was not undertaken for technical reasons (Table 4).

DISCUSSION

Following a cognitive rehabilitation program, participants who were all post left temporal lobe surgery, showed improvements in memory and naming test scores and in

Table 4. Brain area activation.

Group	Brain area	W	p-value
Control group			
scan 1x2	Primary somatosensory cortex	-2.03	0.05*
	Dorsal anterior cingulate cortex	-2.38	0.02*
Rehab group			
scan 1x3	Anterior prefrontal cortex	-1.96	0.05*
1x3	Pars opercularis	-2.7	0.01*
1x3	Inferior prefrontal gyrus	-2.43	0.02*
2x3	Dorsal anterior cingulate cortex	-2.07	0.04*
2x3	Superior temporal gyrus	-2.21	0.03*

* $p \leq 0.05$.

subjective ratings which, with the exception of one test score but with a very small significance ($p = 0.05$), were not observed in the controls. All but one individual, classified as demonstrating meaningful change based on reliable change indices, had received the memory training program. Changes in verbal fluency fMRI activation patterns were recorded following rehabilitation, but at the longer-term follow up.

Our findings support those reported by Jones et al.²¹ and Koorenhof et al.²² of improvements in verbal learning in left TLE surgery patients following strategy training. Bresson et al.²³, in presurgical cases, demonstrated improved verbal learning in association with training in the use of semantic strategies. Training-related improvements in objective measures of memory have been reported after group-based memory training⁸.

We also found gains on a naming test following rehabilitation. Word-finding difficulties are a common complaint of people with TLE and naming decline has been observed in up to 60% of patients undergoing left anterior temporal lobe surgery²⁴ and yet has rarely been the target of rehabilitation in epilepsy. Gess et al.²⁵ report on a patient who demonstrated the benefit of errorless learning on naming performance after temporal surgery. Minkina et al.²⁶ reported naming improvements in a TLE patient after proper name retrieval training.

Participants in the rehabilitation group reported an increased use of memory strategies and a more positive perception of their memory. This suggests possible generalization from the program to daily life. Increased use of compensation strategies has previously been reported^{23,24,27}. Improvements in subjective ratings of memory after cognitive training have been identified in a few studies^{9,22,24}. We did not have any indication of the impact on quality of life and daily living skills and this is a shortcoming of the study.

Two months following the rehabilitation program, changes were recorded in left hemisphere networks involved in language, memory and attention and in right hemisphere networks involved in motivation^{28,29,30} that had not been apparent a month after completion. These changes may indicate a delayed positive impact of the rehabilitation program but this remains speculative due to the lack of a third scan in the controls. Changes in fMRI activation patterns observed in the controls were different and were apparent on the second scan and involved activation in the primary somatosensory cortex and the fusiform gyrus.

Our study has limitations. Participants were not randomly allocated: the control group consisted of patients who were unable to commit to the weekly rehabilitation sessions. We did not find differences in key demographic variables or initial cognitive performance levels but we cannot rule out that there were other possible differences between the groups. Our sample size was small and fell below our target set based on effect size analysis. Larger sample sizes would be required to have adequate power to detect change and to enable parametric analyses and consideration of predictor variables. However, performance changes were observed with the smaller numbers and we were also able to consider individual differences using reliable change indices. The lack of a third scan in the control group was a major limitation, which complicates the interpretation of the fMRI results.

However, this study provides support for the role of memory rehabilitation post-left temporal lobe surgery and the fMRI results are suggestive of accompanying changes in brain networks underlying the gains observed following rehabilitation. Our findings, we believe, are encouraging and indicate that rehabilitation should be considered as part of the surgical evaluation and preparation.

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