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ARTICLES

Selective posterior callosotomy for drop attacks

A new approach sparing prefrontal connectivity

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ABSTRACT

Objective: To evaluate a novel approach to control epileptic drop attacks through a selective posterior callosotomy, sparing all prefrontal interconnectivity.

Methods: Thirty-six patients with refractory drop attacks had selective posterior callosotomy and prospective follow-up for >4 years. Falls, episodes of aggressive behavior, and IQ were quantified. Autonomy in activities of daily living, axial tonus, and speech generated a functional score ranging from 0 to 13. Subjective effect on patient well-being and caregiver burden was also assessed.

Results: Median monthly frequency of drop attacks decreased from 150 to 0.5. Thirty patients (83%) achieved either complete or >90% control of the falls. Need for constant supervision decreased from 90% to 36% of patients. All had estimated IQ below 85. Median functional score increased from 7 to 10 ($p = 0.03$). No patient had decrease in speech fluency or hemiparesis. Caregivers rated the effect of the procedure as excellent in 40% and as having greatly improved functioning in another 50%. Clinical, EEG, imaging, and cognitive variables did not correlate with outcome.

Conclusions: This cohort study with objective outcome assessment suggests that selective posterior callosotomy is safe and effective to control drop attacks, with functional and behavioral gains in patients with intellectual disability. Results are comparable to historical series of total callosotomy and suggest that anterior callosal fibers may be spared.

Classification of evidence: This study provides Class III evidence that selective posterior callosotomy reduces falls in patients with epileptic drop attacks. *Neurology*® 2016;87:1–7

GLOSSARY

ADL = activities of daily living; **IR** = interquartile range; **SSMA** = supplementary sensorimotor area.

Epileptic drop attacks are usually refractory to medication, and their association with sudden bilateral synchronization of ictal discharges provides a rationale for callosotomy.[1,2] The procedure is indicated when focal resection is not feasible and specifically targets the sudden falls, irrespective of the underlying etiology. Thus, clinical heterogeneity of candidates is the norm.

The pioneers in sectioning the callosum for seizure control performed total callosotomies,[1] but the procedure evolved to prioritize sectioning of the anterior fibers.[3,4] However, it is the posterior extent of the callosotomy that leads to better control of drop attacks and, most importantly, when anterior or anterior two-third sections fail, extension to total callosotomy consistently improves results.[5–7]

When evaluating a patient with a small lesion in the left premotor cortex and focal thinning of the isthmus of the corpus callosum (figure 1A), our attention was drawn to the possibility that motor fibers crossed more posteriorly than previously thought. We thus modified our approach and performed section of the posterior half of the callosum in 2 patients with drop attacks and bilateral centroparietal lesions, leaving the possibility of anterior extension to total callosotomy.

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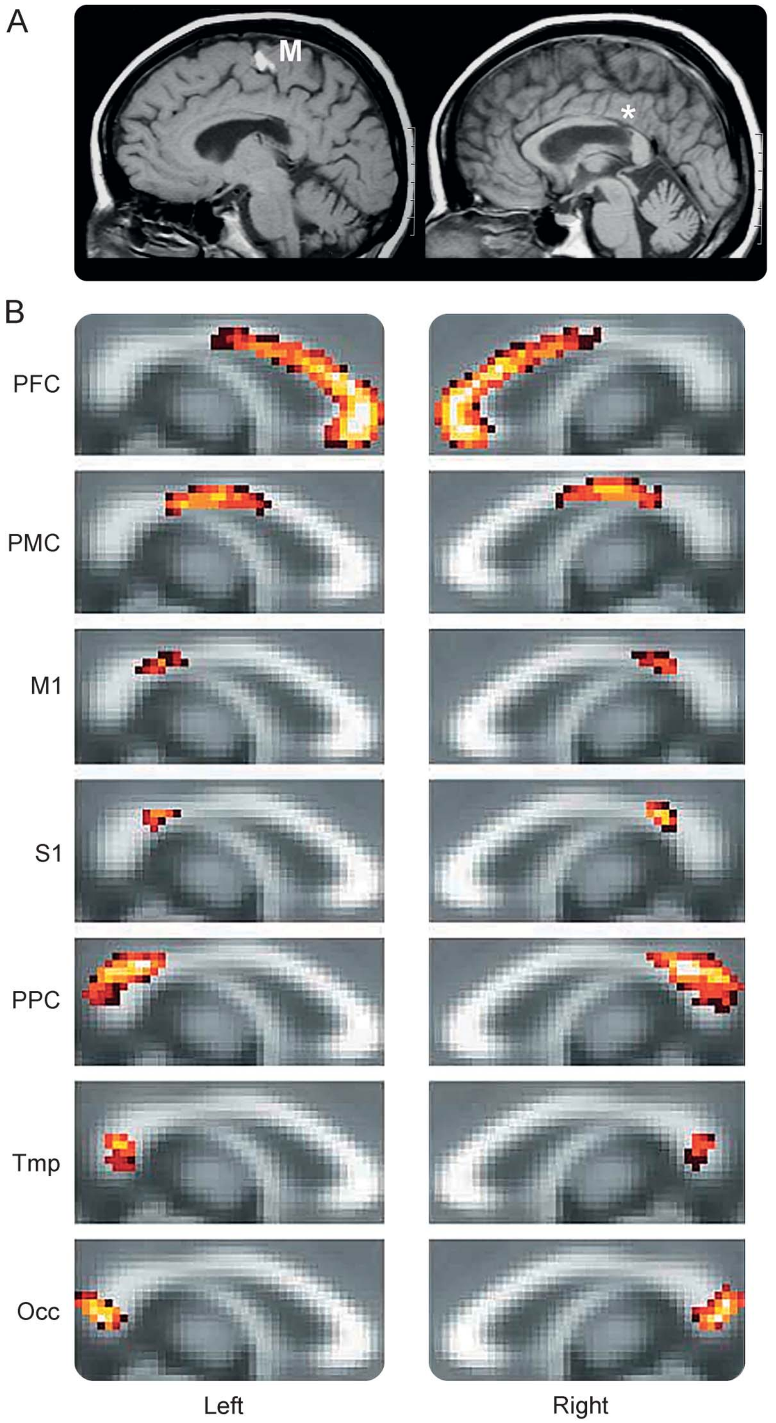
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 Imaging evidence that fibers from the premotor cortex and primary motor cortex cross through the posterior callosum



(A) Sagittal MRI section showing a small lesion in the border between the primary motor cortex (M) and supplementary motor area, accompanied by a focal thinning of the isthmus of the corpus callosum (asterisk). (B) Midsagittal group probability maps showing the location of cortical connections within the corpus callosum. Note that fibers from the PMC and primary motor cortex (M1) cross posterior to the midpoint of the callosum. Primary motor fibers indeed cross adjacent to the splenium. M1 = primary motor cortex; Occ = occipital; PFC = prefrontal cortex; PMC = premotor cortex; PPC = posterior parietal cortex; S1 = primary somatosensory cortex; Tmp = temporal. Panel B modified from Zarei et al.[9] with permission from the publisher, © 2006 John Wiley & Sons.

Both had sustained, complete control of the falls with posterior section only. This outcome came to be supported by anatomical[8] and imaging data[9,10] indicating that fibers from the premotor and primary motor cortex controlling axial and lower limb muscles indeed cross through the mid to posterior half of the callosum. Henceforth, we routinely offered selective posterior section to callosotomy candidates, based on the hypothesis that the improved results reported with total callosotomies were specifically related to section of the posterior fibers, rather than to the complete disconnection per se. Furthermore, because the disconnection syndrome reported with posterior callosotomy had limited effect on patients with normal cognition,[11,12] we further hypothesized that in a population with significant intellectual disability, it would be even less clinically relevant, particularly if prefrontal connectivity could be spared.[13,14]

We report a consecutive cohort of patients with disabling drop attacks and intellectual disability that underwent selective posterior callosotomy, sectioning the fibers that interconnect the motor cortices and display the fastest interhemispheric synchronization[9,10,15] (figure 1B).

METHODS This study addresses the long-term results of a novel approach to control epileptic drop attacks through selective posterior callosotomy, sparing prefrontal interconnectivity, through a cohort study providing Class III level of evidence. From April 1997 to October 2010, all patients with refractory drop attacks as the main disabling seizure type of symptomatic generalized or multifocal epilepsies underwent presurgical evaluation and selective posterior section of the corpus callosum at the Porto Alegre Epilepsy Surgery Program. The series comprises 36 patients prospectively followed for at least 4 years, with a median follow-up of 5.75 years (interquartile range [IR]: 8.9). Seven additional patients had only short follow-up. Demographic data are included in table e-1 at Neurology.org.

Interictal prolonged video-EEG recordings determined whether discharges were predominantly generalized, multifocal, or significantly lateralized. Ictal recordings were analyzed as to symmetry and discharge pattern: polyspikes, polyspike slow waves, or diffuse attenuation following generalized spike-slow waves. MRI was performed in a 1.5T Siemens scanner (Siemens AG, Erlangen, Germany). Neuropsychological evaluation estimated IQ through subtests of the Wechsler Adult Intelligence Scale–Revised or Wechsler Intelligence Scale for Children. Patients were considered able to read simple sentences if they could read out loud "It is a beautiful day." All were stabilized on a combination of valproate, lamotrigine, and a benzodiazepine for at least 6 months before surgical decision[16] and were kept in this regimen after operation. Doses were allowed to change over the years, according to occasional relapses or side effects.

Pre- and postoperative epileptologic and functional evaluation. Relatives were interviewed to assess demographic and etiologic data, level of dependence in activities of daily living (ADL), need for constant supervision, and episodes of aggressive behavior. During the 3-month baseline period and following surgery, relatives were instructed to keep seizure diaries, taking note of drop attacks. They were not instructed to register other seizure types. Frequency of falls was analyzed in absolute numbers and also categorized as follows: at least daily, weekly, monthly, yearly, or less frequently than once a year.

Neurologic examination and parental reporting classified patients as dependent or independent for ADL, including praxis to feed, dress, and button (text e-1), and whether constant supervision was needed. Episodes of aggressiveness were categorized as occurring rarely, monthly, weekly, or daily. Ability to sustain the head and stand was rated as normal or abnormal. Gait could be independent or needing assistance and word articulation could be fluent, comprehensible, or incomprehensible. From these neurologic and functional data, we generated a composite functional score ranging from 0 to 13 points (text e-1).

Following operation, relatives were asked to register drop attacks and episodes of behavioral dyscontrol. They were also asked to rate the effect of the procedure as excellent, improved, unchanged, or worsened according to well-being of the patients and burden of the caregivers. Seizure, behavioral, and functional data were obtained prospectively after surgery, through outpatient visits every 6 to 12 months and telephone contact with the clinic between consultations. Most recent functional and behavioral data were assessed through a structured questionnaire by trained interviewers blinded to preoperative data.

Surgical procedure, postoperative antiepileptic drug management, and evaluation of outcome. Surgical technique is illustrated in figure e-1 and described in text e-2. Because section should include fibers originating from the premotor, supplementary sensorimotor area (SSMA), and primary motor cortex,[9] including those associated with ictal negative motor phenomena,[17,18] 50% to 60% of the callosum needed to be disconnected in the posterior-to-anterior axis, as judged by postoperative MRI (figure 2). Fibers interconnecting the frontal lobes anterior to the SSMA were spared.

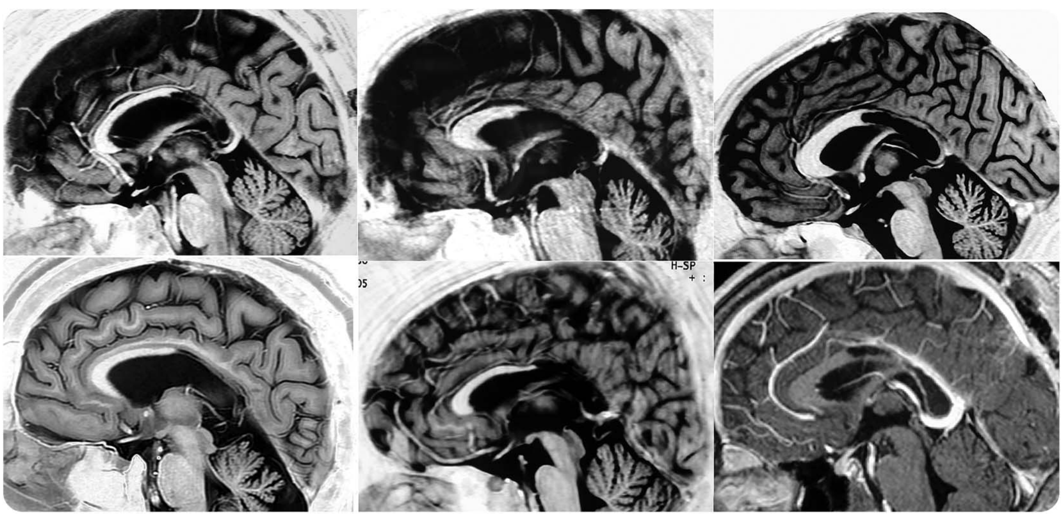
Standard protocol approvals, registrations, and patient consents. The study was performed in the setting of managing patients with very severe epilepsies. The procedure was explained in detail to relatives, including why selective posterior callosotomy was being offered, the expected seizure and functional outcomes, and a critical appraisal of the possible complications. All gave written informed consent to the procedure and to the publication of data. The study was approved by the institutional ethics committee.

Statistics. SPSS Statistics version 19 (IBM Corp., Armonk, NY) was used. Wilcoxon signed rank test for ordinal and continuous variables and the McNemar test for dichotomous variables were used. In addition, Poisson regression was applied for multivariate analyses.

RESULTS Twenty-four patients were male and 29 were right-handed. Mean age at epilepsy onset was 2.8 years (SD 3.5) and that of drop attacks 6.4 years (SD 4.6). Mean duration of epilepsy before operation was 18.1 years (SD 11.6) and age at surgery 21.5 years (SD 11.3).

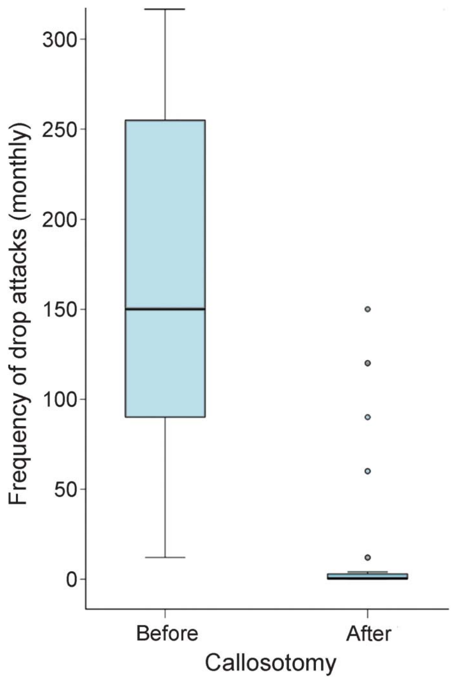
Control of drop attacks. Median preoperative frequency of drop attacks per month was 150 (IR: 187.5) and reduced to 0.5 (IR: 3.5) after posterior callosotomy (figures 3 and 4). Seventeen patients (47%) achieved complete control of the falls, often following a running down course over the first 3 months. In this subgroup, preoperative median monthly frequency of drop attacks was 180 (IR: 220). The other 19 patients who still had drop attacks following posterior callosotomy had a median of 150 falls (IR: 120) preoperatively and a median of 2 falls after operation (IR: 59.5). Thirteen of the latter 19 (68%) had a >90% reduction in the frequency of falls. Thus, 30 of 36 patients (83%) had complete or >90% control of drop attacks and only 6 patients (17%) were not significantly improved

Figure 2 Composite picture of postoperative MRIs in the midsagittal plane of 6 patients undergoing selective posterior callosotomy



The section on the right, bottom row, is a contrasted T1 image. All others are inversion recovery images.

Figure 3 Boxplot of median and interquartile range of pre- and postoperative frequency of drop attacks



Circles in the postoperative column represent individual patients. Note that all others are clustered within a median of 0.5.

by the procedure (figure 4). Preoperatively, 32 patients (89%) had daily falls and the other 4 fell at least once a week. Following selective posterior callosotomy, only 6 patients (17%) fell daily and 3 (8%) at least once a week ($p = 0.0001$) (figure e-2A). Need for constant supervision declined from 90% to 36% of patients after surgery. Five patients (14%) had a clinical and EEG picture compatible with the Lennox-Gastaut syndrome. Preoperative frequency of drop attacks did not differ in these patients compared to the other 31 ($p = 0.19$; text e-3), and surgical results were similar. Control of drop attacks according to MRI findings is shown in table e-2.

Neurologic, behavioral, and functional effect. Table e-3 lists pre- and postoperative autonomy in ADL. No patient had significant dyspraxia or worsened in any ADL or in the ability to sustain the head and stand. Median functional score increased from 7 to 10 postoperatively ($p = 0.03$) (figure e-3A). No patient had akinetic mutism, decrease in speech fluency, hemiparesis, or other complications that could be attributed to the procedure. Nine patients (25%) were able to read simple sentences before operation and continued to read afterward.

Preoperatively, bouts of aggressive behavior occurred at least once a week in 16 patients (44%) but in only 5 (14%) after operation. Overall, 15 (43%) had significant reduction in aggression and only 4 (11%) worsened. Caregivers rated the procedure as having had an excellent result in 40% of patients and having greatly improved functionality in another 50%. Only one patient was judged as worsened (figure e-3B). Four patients had venous air embolism detected with Doppler, and correction measures were performed without postoperative clinical consequences. All patients were ambulatory on the second postoperative day.

Electrographic, imaging, and cognitive findings. These findings are summarized in table e-4 and detailed in text e-3. There was no significant relationship between cognitive, electrographic, or imaging abnormalities and degree of control of drop attacks. Postoperatively, 10 of the 23 patients (43%) with predominantly generalized EEG discharges changed to a predominantly lateralized pattern. The other 13 patients, with predominantly multifocal or distinctly lateralized discharges in the preoperative EEG, did not have notable EEG changes.

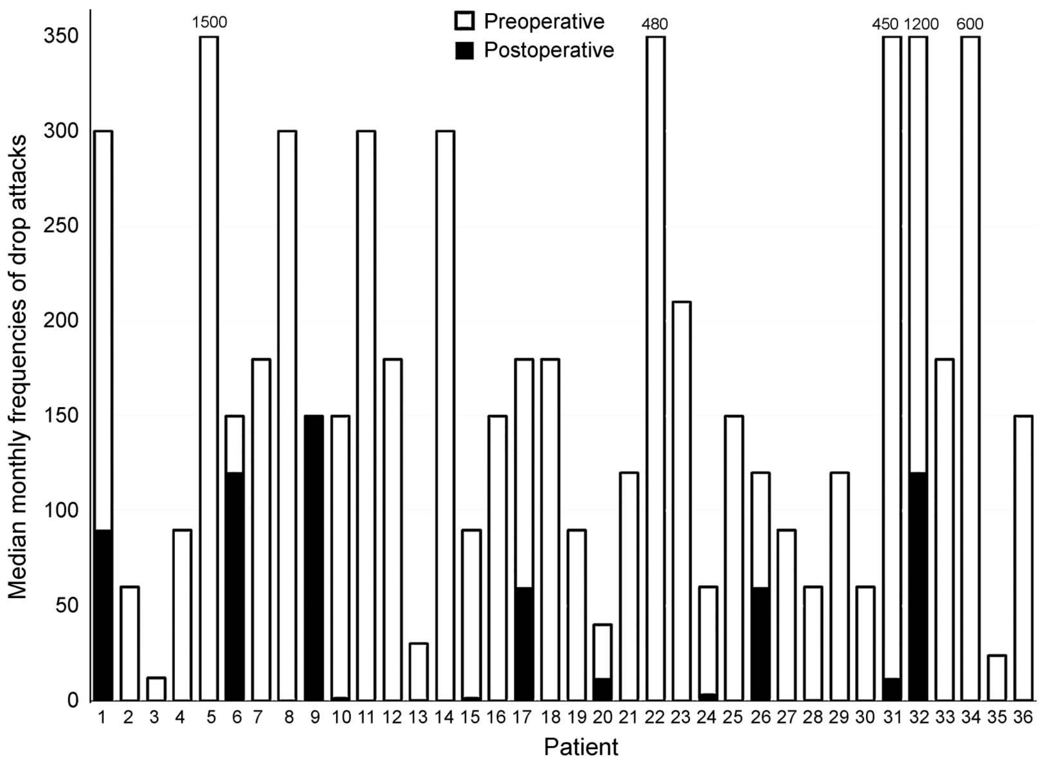
Multivariate analysis. Included in the multivariate analysis were those variables with a $p < 0.20$ in the bivariate analysis: imaging findings, age at seizure onset, epilepsy duration, and variability of the composite functional score. Only the latter remained significantly correlated with seizure outcome (relative risk = 1.25; 95% confidence interval: 1.02–1.54; $p = 0.034$) (figure e-2B).

DISCUSSION

Traditionally, callosotomy targets the anterior third, half, or two-thirds of the corpus callosum, thus primarily disconnecting the frontal lobes.[2–5] However, variable extensions of anterior callosotomy frequently fail to control drop attacks and results consistently improve following additional posterior section.[5–7] This raises the possibility that fibers crossing through the posterior callosum may be specifically relevant to epileptic falls, as suggested by anatomical, imaging, and neurophysiologic data.[8,9,15] In our consecutive cohort of patients undergoing selective posterior callosotomy, results compared favorably with historical series of total callosotomy,[7,19,20] suggesting that disconnecting the prefrontal regions may not be necessary for control of drop attacks. The favorable results with posterior sections in our initial patients led us to systematically propose this procedure. Because the results challenge long-held views on surgical strategy and cognitive risks, we included only patients with 4 or more years of follow-up.

Our study has a number of limitations. First, pre- and postsurgical frequencies of drop attacks were not documented through video-EEG monitoring. Seizure diaries may underestimate these, because atonic, tonic, or myoclonic attacks potentially leading to falls may occur when patients are not standing. However, although a placebo effect could occur in the early

Figure 4 **Median monthly frequencies of drop attacks before and after selective posterior callosotomy in each of the 36 patients**



Frequencies above 350 are specifically indicated.

postoperative period, it is unlikely that it would persist for many years after the procedure. Second, this is a cohort study analyzing seizure outcome in an uncontrolled fashion. We tried to enhance the reliability of the findings by following patients closely, restricting the analysis only to drop attacks—the seizure type most unlikely to be missed by caregivers—and having final outcome data collected by interviewers blinded to preoperative findings. As in most series, preoperative frequency of drop attacks was high, and it would probably be artificial to compare results following surgery with a "control" group of patients on a waiting list, as has been the case with temporal lobectomy.[21] Third, we devised a pragmatic functional score based on simple ADL representing the difficulties faced by patients and caregivers. Although it has not been validated, it addressed the major question regarding a posterior disconnection, namely, whether it would compromise functional integration at a level that would negatively interfere with the daily lives of patients with intellectual disability. The fact that functional scores increased after surgery suggests that, in this population, selective posterior callosotomy is functionally safe.

Callosotomy is offered to patients with diffuse brain dysfunction who cannot have a focal resection and usually involves the anterior third,[3,4] anterior half,[19] anterior two-thirds,[4,7] everything but the splenium[22] or the totality of the callosum.[5,7,23] The idea to shift the paradigm toward selective posterior callosotomy was supported by the consistent improvement of control of generalized seizures when anterior sections are extended to complete sections.[19] A recent report from the Mayo Clinic showed complete control of drop attacks in 13 of 22 patients (60%) who had 1- or 2-stage complete callosotomy but in only 8 of 33 (24%) in whom only the anterior two-thirds of the callosum was sectioned.[7] Of note, 5 of the latter had extension into complete section and 4 (80%) became free of drop attacks. In the study reporting the best results, 1-stage total callosotomy completely controlled drop attacks in 25 of 34 patients and led to a >90% improvement in 6 others.[20]

Compared to data pooled from a systematic review[24] including studies reporting specifically on control of drop attacks with variable extents of anterior and total callosotomy in children,[6,25–28] our patients were twice as old and epilepsy duration and postoperative follow-up were twice as long (table e-1). Although our series was not restricted to pediatric patients, it is interesting to note that the rate of at least >90% reduction in the frequency of drop attacks was almost exactly the same in our patients undergoing *selective posterior callosotomy* and in the patients undergoing *total callosotomy* pooled from this review (83.3% vs 83.5%). Moreover, the selective posterior approach appears more efficacious than different extensions of anterior sections in adults.[22,23] In the updated Montreal Neurological Institute series of anterior callosotomy, only 38% of patients were completely free of falls and 34% had a >75% response.[4]

The fact that results with posterior section are comparable to those of historical series of complete disconnections (and particularly to *completed* callosotomies following unsuccessful anterior sections) suggests that fibers crossing in the posterior half of the callosum are key to drop attacks. It also suggests that it is not interhemispheric synchronization of epileptic discharges per se, but rather the synchronization of the fibers originating in the motor and premotor cortex, including the negative motor cortex,[17] that are relevant to the mechanism of falls. This is supported by the lack of correlation between the persistence of bisynchronous discharges on postoperative EEG and control of drop attacks in our and other studies.[20]

There are few reports of patients undergoing selective posterior callosotomy to control drop attacks and the rationale was not stated.[13,19] However, anatomical and histologic data do suggest a solid rationale for the posterior section,[9,15] and tractography studies confirm that fibers originating in the premotor, SSMA, and primary motor cortex cross around and posterior to the isthmus of the corpus callosum up to the borders of the splenium.[9] Furthermore, the majority of large fibers (>5 μm) cross posteriorly in the corpus callosum, whereas 70% of the fibers in the genu are 10 times thinner.[15] Therefore, resections of the anterior third, half, and two-thirds of the callosum miss most fast conducting fibers, the subsequent section of which in 2-stage total callosotomies predictably improves outcome.

The interhemispheric traffic of visual, tactile, and auditory information is fundamental to integrate environmental stimuli with specialized posterior association cortices supporting language, gnosis, and praxis.[11,29–31] Based on an extensive literature, we assumed there was a disconnection syndrome when sectioning the posterior callosum. However, recent accounts of the long-term functional follow-up of patients undergoing total callosotomies describe how little effect such disconnections may have outside the laboratory setting.[12,32] Thus, we opted for an assessment of the effect of such disconnection in ADL and showed that this is of minor significance in patients with intellectual disabilities, as suggested by improved postoperative scores in our straightforward functionality index. There was also a correlation between continued freedom from drop attacks and functional score, suggesting that control of falls is important for gains in functionality. These results suggest that in patients with generalized or multifocal epilepsies, uncontrolled drop attacks and intellectual disability, a pragmatic view of the posterior disconnection syndrome may be appropriate and should not preclude the option for selective posterior callosal section.

Although usually transient, akinetic mutism, ataxia, and poor sphincter control can follow anterior callosotomy and increase morbidity in the postoperative period.[33] Such abnormalities were not seen in our patients. Although we did not directly compare patients with total vs selective posterior callosotomy, data on the role of prefrontal connectivity, particularly the integration between stimulus-related semantic and episodic information,[13] suggest that patients may benefit from sparing prefrontal fibers, providing control of drop attacks is similar. Furthermore, the favorable functional outcome reported by the caregivers is in line with the view by Gazzaniga et al.[34] that whatever commissural fibers remain intact may be sufficient for interhemispheric transfer of information, supporting the sparing approach. Finally, the most common surgical complications of callosotomies, including hemiparesis, language disturbances, and ataxia, are often related to manipulation of the pericallosal arteries and cingulate gyrus, which is obviated by selective posterior callosotomy.

In a systematic review, variable extensions of callosotomies led to higher control of drop attacks than vagus nerve stimulation.[35] Our results further suggest that selective posterior callosotomy is likely to be even more efficacious and safe than the combined results of different extensions of callosal section, thus providing potential additional advantage over vagus nerve stimulation.

Finally, despite the overall good results, selective posterior callosotomy was still ineffective in approximately 20% of patients, suggesting heterogeneous epileptogenic mechanisms leading to falls. Future studies with larger patient samples may be powered to detect specific subgroups with more or less favorable prognoses.

AUTHOR CONTRIBUTIONS

Design, data collection, management, analysis and interpretation of the data, as well as preparation, review, and approval of the manuscript were under the control and responsibility of the authors. E.P. and A.P. designed the study, coordinated data collection, and wrote the first draft of the manuscript. M.P. obtained and interpreted all neuropsychological data, and wrote parts of the manuscript. J.R.H. and R.S. obtained and interpreted imaging data, and wrote parts of the manuscript. T.F., L.P., R.S. collected all data. W.M. organized the data bank and the statistics. N.A., J.C.C., M.H., and T.T. critically reviewed the manuscript and directly influenced the final format of the submission.

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DISCLOSURE

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