The corpus callosum and recovery of working memory after epilepsy surgery

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SUMMARY

Objective: For patients with medically intractable focal epilepsy, the benefit of epilepsy surgery must be weighed against the risk of cognitive decline. Clinical factors such as age and presurgical cognitive level partially predict cognitive outcome; yet, little is known about the role of cross-hemispheric white matter pathways in supporting postsurgical recovery of cognitive function. The purpose of this study is to determine whether the presurgical corpus callosum (CC) midsagittal area is associated with pre- to postsurgical change following epilepsy surgery.

Methods: In this observational study, we retrospectively identified 24 adult patients from an epilepsy resection series who completed preoperative high-resolution T1-weighted magnetic resonance imaging (MRI) scans, as well as pre- and postsurgical neuropsychological testing. The total area and seven subregional areas of the CC were measured on the midsagittal MRI slice using an automated method. Standardized indices of auditory-verbal working memory and delayed memory were used to probe cognitive change from pre- to postsurgery. CC total and subregional areas were regressed on memory-change scores, after controlling for overall brain volume, age, presurgical memory scores, and duration of epilepsy.

Results: Patients had significantly reduced CC area relative to healthy controls. We found a positive relationship between CC area and change in working memory, but not delayed memory; specifically, the larger the CC, the greater the postsurgical improvement in working memory ($b = 0.523; p = 0.009$). Effects were strongest in posterior CC subregions. There was no relationship between CC area and presurgical memory scores.

Significance: Findings indicate that larger CC area, measured presurgically, is related to improvement in working memory abilities following epilepsy surgery. This suggests that transcallosal pathways may play an important, yet little understood, role in postsurgical recovery of cognitive functions.

KEY WORDS: Epilepsy, MRI, Corpus callosum, Short-term memory, Executive function, Neuronal plasticity.

For patients with medically intractable focal epilepsy, the best option for achieving seizure control is often surgical resection. However, the benefit of epilepsy surgery must be weighed against the risk of cognitive decline, which is commonly observed in the domains of language and long-term memory. Conversely, postsurgical gains in executive domains such as attention and working memory can be observed. Clinical (e.g., epilepsy duration, presurgical cognitive level) and demographic (e.g., age) factors predict postsurgical cognitive outcomes. Yet, little is known about...
the degree to which cross-hemispheric white matter pathways promote recovery of cognitive functions following epilepsy surgery.

Functional reorganization following epilepsy surgery is a phenomenon that has been widely reported. The spatial pattern of functional reorganization can be broadly classified as within the same hemisphere (ipsilesional) or to homologous regions in the contralateral hemisphere (contralesional). Reorganization of lateralized functions such as language and verbal memory is associated with intrahemispheric reorganization following left hemisphere resections, and accompanied by structural changes in ipsilesional white matter tracts. However, functional reorganization of bilaterally represented cognitive domains such as working memory may rely more on contralesional reorganization, facilitated by cross-hemispheric white matter tracts. This possibility has yet to be investigated.

Corpus callosum (CC) atrophy is common in the context of chronic epilepsy. Here, we test whether presurgical CC area is associated with changes in memory functions after epilepsy surgery. To quantify CC area, we apply a computational method that segments the CC from the midsagittal section of a whole brain T1-weighted magnetic resonance imaging (MRI) scan and calculates total and subregional CC area. CC area in patients with chronic treatment-resistant epilepsy (TRE) is compared to age-matched healthy controls to determine whether presurgical CC atrophy is present. Then, the linear relationship between presurgical CC area and change in auditory-verbal working memory and delayed memory from pre- to postsurgery is assessed. Our hypothesis is that the CC area will be associated with change in memory functions, independent of established predictors such as age, presurgical cognitive level, and epilepsy duration. Finally, we analyze seven distinct subregions of the CC to explore the spatial pattern of effects.

**Methods**

**Standard protocol and patient consents**

All patients consented to the use of their clinical records for the purpose of research, as well as for MRI scanning and neuropsychological testing. Study procedures were approved by the New York University Institutional Review Board.

**Participants**

For this observational, longitudinal study, we retrospectively identified consecutive participants with TRE from an epilepsy surgical series at the New York University Comprehensive Epilepsy Center, spanning from 2007 to 2013. Neuropsychological measurements were obtained longitudinally pre- and postsurgery and MRI was obtained cross-sectionally prior to surgery. The following criteria were used to select patients: (1) had a focal neocortical resection to treat medically refractory seizures; (2) completed a research MRI scan prior to surgery; (3) had clinical neuropsychological testing prior to surgery; (4) completed research neuropsychological testing following surgery; (5) were between the ages of 17 and 65 (to fall within the standardization sample range for the working memory index); (6) had at least a low average intellectual quotient score (IQ > 70); (7) had no history of significant head trauma or diffuse encephalopathy; and (8) no history of drug or alcohol dependence.

Healthy control participants were recruited through community advertisement and gave consent to participate in this study. Control participants were excluded from analyses if they reported any prior history of neurologic disorders, psychiatric disorders, head injury, or substance abuse.

**Clinical variables**

Clinical data abstracted for all patients includes age at time of presurgical research scan, duration of epilepsy, handedness, side of surgery, resection lobe, years postsurgery, and whether participants had seizure recurrence postsurgery (yes/no).

**Memory indices**

The Wechsler Adult Intelligence Scale (WAIS-III or WAIS-IV)—Working Memory Index (WMI), and California Verbal Learning Test-II (CVLT-II) or Rey Auditory Verbal Learning Test (RAVLT) were acquired as part of a standard clinical neuropsychological work-up for epilepsy surgery and at least 6 months postsurgically for research.

The WMI comprises a digit span task, letter-number sequencing (WAIS-III), and/or mental arithmetic (WAIS-IV) task, which require mentally rehearsing and manipulating auditory-verbal information; therefore, the particular working memory index that we used is specific to auditory-verbal, rather than visuospatial, working memory abilities. Depending on the version of the WAIS administered (Third or Fourth Edition), test-retest reliability metrics for the WMI range from 0.85 to 0.92. WMI scores from the WAIS-III and WAIS-IV are strongly correlated (r = 0.87), thus supporting their combined analysis. To operationalize change in WMI scores from pre- to postsurgery, a change score was calculated and used as a dependent variable in subsequent analyses; (WMI-change score = postsurgical WMI – presurgical WMI). Lower numbers indicate worse postsurgical performance.

Either the CVLT-II or RAVLT was administered to patients pre- and postsurgically to probe verbal memory. In both tests, examinees are read a list of 15 (RAVLT) or 16 (CVLT-II) words and asked to recall them across a series of five learning trials. Retention and free recall are tested after a brief (5-min) and long (20-min) delay, followed by a yes/no recognition test. To utilize data from both tests, we used the standardized, age-corrected delayed recall t-scores as a measure of verbal delayed recall (DR). To operationalize
change in DR scores from pre- to postsurgery, a change score was calculated and used as a dependent variable in subsequent analyses: (DR-change score = postsurgical DR z-score — presurgical DR z-score). Lower numbers indicate worse postsurgical performance.

MRI and image analysis

\( T_1 \)-weighted three-dimensional (3D) magnetization prepared rapid gradient echo (MPRAGE) MRI studies were acquired from each participant prior to epilepsy surgery on a 3-Tesla Siemens Allegra research-dedicated scanner (voxel size = 1 × 1 × 1.33 mm\(^3\), echo time = 3.25 msec, repetition time = 2,530 msec, TI = 1,100 msec, flip angle = 7 degrees). The total CC cross-sectional area and seven CC subregional areas (according to the Witelson subdivision scheme\(^{16}\)) were delineated on the midsagittal slice and measured automatically using “yuki” (www.nitrc.org/projects/art), an automatic CC segmentation algorithm (Fig. 1).\(^{10,11}\) Brain volume was measured using “Brain Extraction Tool,” distributed as part of the FSL software package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET).\(^{17}\)

Statistics

The Shapiro-Wilk test was used to test for normality in all variables. Analysis of covariance (ANCOVA) was used to test for a group differences between patients and controls on the CC area and each subregion area, after controlling for overall brain volume. A hierarchical regression model was used to test for a linear relationship between each unit increase in CC total area or subregion area and pre- to postsurgical change in WMI and DR, after controlling for overall brain volume, age at surgery, presurgical WMI, z-score. Lower numbers indicate a large degree of individual variability in pre- to postsurgical WMI-change. To determine whether the degree of change in WMI scores could be categorized as reliable “decline” or “improvement,” the magnitude was compared to published 90% reliable change indices for the WAIS working memory index.\(^{18}\) We utilized reliable change indices (RCIs) established in an epilepsy cohort with a similar proportion of temporal to extratemporal cases.\(^{17}\) A decrease in performance by at least 17 points (−17) was required to be classified as “WMI-decline” and an increase of at least 13 points (+13) was required to be classified as “WMI-improvement” (90% confidence interval), over and above that observed in a similar cohort that did undergo epilepsy surgery. This criterion allows for a sensitive estimate of postoperative cognitive change that can be attributed to surgical intervention rather than ongoing seizures and medication use. Based on this criterion, 8% (N = 2) showed postsurgical improvement in WMI.

RESULTS

Sample characteristics

Twenty-four patients (13 male) met study criteria. Healthy control participants were matched to patients by age (±5 years). Patient and control characteristics are summarized in Table 1. Details regarding Wada test results and surgery for each patient are provided in Table S1.

Group differences on the working memory index (WMI)

Presurgical WMI scores were significantly lower in patients than controls (\( t_{46} = -4.1; p = 0.0002; \) See Table 2). This difference remained significant after controlling for years of education (\( F_{1,45} = 9.01; p = 0.0044 \)), which were lower in TRE patients than controls (see Table 1). The left TRE group had reduced WMI scores relative to controls (\( t_{36} = -2.27; p = 0.03 \)), as did the right TRE group (\( t_{36} = -3.94; p = 0.0004 \)), and the temporal lobe only group (\( t_{39} = -3.96; p = 0.0003 \)); the extratemporal lobe group had marginally reduced WMI scores relative to controls (\( t_{29} = -1.964; p = 0.059 \)). There was no difference in presurgical WMI scores between patients with right or left TRE (\( t_{23} = 1.3; p = 0.18 \)) or between patients with temporal and extratemporal TRE (\( t_{22} = -0.95; p = 0.35 \)); therefore, these groups are combined in all further analyses.

Pairwise t-tests showed that WMI scores in TRE patients did not differ from pre- to postsurgery (\( t_{23} = -0.27; p = 0.79 \)); however, WMI-change scores ranged from −29 to 34, indicating a large degree of individual variability in pre- to postsurgical WMI-change. To determine whether the degree of change in WMI scores could be categorized as reliable “decline” or “improvement,” the magnitude was compared to published 90% reliable change indices for the WAIS working memory index.\(^{18}\) We utilized reliable change indices (RCIs) established in an epilepsy cohort with a similar proportion of temporal to extratemporal cases.\(^{17}\) A decrease in performance by at least 17 points (−17) was required to be classified as “WMI-decline” and an increase of at least 13 points (+13) was required to be classified as “WMI-improvement” (90% confidence interval), over and above that observed in a similar cohort that did undergo epilepsy surgery. This criterion allows for a sensitive estimate of postoperative cognitive change that can be attributed to surgical intervention rather than ongoing seizures and medication use. Based on this criterion, 8% (N = 2) showed postsurgical improvement in WMI.
showed no change (N = 20), and 8% (N = 2) showed decline.

There was no significant difference in WMI-change between patients with a temporal versus an extratemporal lobe resection (t_{22} = -0.25; p = 0.8). In addition, there was no difference in WMI-change between patients who had a recurrence in seizures versus those who became seizure free postsurgery (t_{22} = -0.5; p = 0.64).

**Group differences on verbal delayed recall (DR)**

Presurgical DR scores from the CVLT-II and RAVLT did not differ in the TRE group (t_{21} = -0.157; p = 0.877), which supports their combination in subsequent analyses. Presurgical DR \(z\)-scores were lower in patients than controls (t_{46} = -2.703; p = 0.01; see Table 2). This difference remained significant after controlling for years of education (F_{1,45} = 4.16; p = 0.047). Within specific patient subgroups, the left TRE group had reduced DR scores relative to controls (t_{32} = -2.45; p = 0.02), as did the right TRE group (t_{36} = -2.032; p = 0.05), and the temporal lobe only group (t_{39} = -2.398; p = 0.02); the extratemporal lobe group had marginally reduced DR scores relative to controls (t_{29} = -1.9; p = 0.06). There was no difference in presurgical DR scores between patients with right or left TRE (t_{22} = -0.538; p = 0.74) or between patients with temporal and extratemporal TRE (t_{22} = 0.116; p = 0.91); therefore, these groups are combined in all further analyses.

**Is there evidence of CC atrophy in patients with focal TRE relative to controls?**

CC cross-sectional area was normally distributed (Shapiro-Wilk statistic = 0.977; p = 0.462). Patients with TRE had smaller CC area (mean 615.92 mm\(^2\), SD 76.45 mm\(^2\)), relative to controls (mean 676.97 mm\(^2\), SD 83.89 mm\(^2\); t_{46} = -2.635; p = 0.01. Group differences remained after controlling for overall brain volume (F_{2,48} = 6.21;
Is corpus callosum cross-sectional area associated with WMI change in patients with TRE?

There was no significant relationship between presurgical WMI scores and CC area in the TRE group ($r = 0.28; p = 0.89$). This remained the case after controlling for brain volume, age at time of scanning, and duration of epilepsy ($\beta = 0.038; p = 0.872$). However, presurgical CC area was strongly associated with a change in WMI scores from pre- to postsurgery ($r = 0.557; p = 0.005$). This relationship remained significant after controlling for brain volume, age at time of scanning, duration of epilepsy, and presurgical WMI scores ($\beta = 0.523; p = 0.009$). These more established predictors accounted for 19% of the variance in WMI change, whereas CC area contributed an additional 25.9% of the variance. Anterior CC subregions W1–W3 did not contribute incremental variance to WMI change after controlling for established predictors; however, the more posterior subregions W4–W7 were each independently associated with WMI change: (see Fig. 3B [W4: $\beta = 0.478; p = 0.023$]; [W5: $\beta = 0.522; p = 0.013$]; [W6: $\beta = 0.589; p = 0.002$], and [W7: $\beta = 0.595; p = 0.005$]).

Is corpus callosum cross-sectional area associated with DR change in patients with TRE?

There was no significant relationship between presurgical DR $z$-scores and CC area in the TRE group ($r = 0.005; p = 0.981$). This remained the case after controlling for brain volume, age at time of scanning, and duration of epilepsy ($\beta = -0.21; p = 0.924$). In addition, there was no relationship between presurgical CC area and DR-change scores ($r = -0.024; p = 0.912$). This null finding remained after controlling for brain volume, age at time of scanning, duration of epilepsy, and presurgical DR scores ($\beta = -0.04; p = 0.86$). Given the absence of a relationship between overall CC area and DR, we did not further investigate CC subregions.

**Discussion**

Our results demonstrate that a larger presurgical CC is associated with improvement in auditory-verbal working memory, but not delayed memory, following epilepsy surgery. Quantitative measurement revealed smaller presurgical CC area in patients with treatment-resistant epilepsy (TRE), relative to controls, after controlling for overall brain volume. Variation in CC area was associated with pre- to postsurgical change in working memory, after controlling for established predictors of cognitive outcome, such as age and level of cognitive functioning.\(^3\)\(^5\) This was not the case for longer-term retention of verbal information; there was no relationship between CC area and pre- to postsurgical change in delayed verbal memory. Thus, CC area has the potential to offer additional prognostic information for surgical decision-making, independent of established demographic and clinical predictors, but only for specific cognitive domains. Results suggest that the risk of working
memory decline in populations considered to be at risk (i.e., older age, higher intellectual functioning) may be mitigated by strong cross-hemispheric connectivity or conversely, that the possibility of improvement in working memory may be attenuated in the context of CC atrophy.

Our finding of lower CC area in TRE patients supports prior findings of CC atrophy in the context of chronic, medically refractory seizures,9,19–21 and extends these findings by defining the spatial pattern of atrophy. We show that the mid to posterior subregions of the CC are smaller in TRE patients relative to controls, which is consistent with what has been found in a temporal lobe epilepsy only sample.22 Although this might reflect the large number of patients with temporal lobe epilepsy in our sample, we found no differences between temporal and extratemporal patients in CC area or the area of CC subregions. This suggests that posterior CC atrophy might also be a factor to consider in extratemporal lobe epilepsy; however, a larger sample is needed to detect subtle effects of seizure onset localization on CC atrophy.

A positive relationship between posterior callosal size and overall intelligence in adults with epilepsy has been replicated across several studies.23–25 However, the same relationship has not been found between CC area and language or memory functions,24 which is consistent with what we observed in our presurgical data. This suggests that prior to surgery, the efficiency of working memory and long-term memory functions does not appear to be related to CC size. In contrast, we found that a change in working memory abilities from pre- to postsurgery is strongly associated with CC size, indicating that transcallosal pathways play an important, yet little understood, role in postsurgical recovery of working memory functions.

Posterior CC subregions showed the strongest relationship with pre- to postsurgical change in working memory. Postmortem and in vivo diffusion tensor imaging tract-tracing studies demonstrate that bi-hemispheric occipital, parietal, and temporal lobe pathways traverse the more posterior isthmus of the CC and pathways connecting frontal cortical regions traverse anterior CC regions.16,26,27 Bilateral frontoparietal network involvement in working memory is commonly appreciated28; however, mesial and lateral temporal regions also play a role,29,30 with evidence of bilateral temporal involvement in healthy controls4 and temporal lobe epilepsy patients.31 In a longitudinal investigation of changes in functional MRI–blood oxygen level dependent (fMRI–BOLD) activity during a visuospatial working memory task administered pre– and post–anterior temporal lobectomy, postsurgical improvement was associated with increased (task-positive) parietal lobe activity, as well as with increased ipsilateral and contralateral deactivation (task-negative) of hippocampal activity.4 This suggests that both temporal and parietal network reorganization are critical to postsurgical recovery of working memory functions; however, it remains unclear whether transcallosal pathways might have facilitated the contralateral network reorganization that was demonstrated.

One possible role for the CC in supporting postsurgical recovery of working memory function is through coordination of bilateral temporal, frontal, and parietal cortical activity during working memory tasks; however, the absence of a relationship between presurgical CC area and working memory in our data does not support this. Another possibility is that posterior transcallosal pathways play a unique role
in facilitating contralateral reorganization of auditory-verbal working memory functions. Postsurgical resilience or recovery of cognitive functions can be explained by functional redundancies (i.e., multiple cortical representation of the same function) in bi-hemispheric homologous regions that are largely co-innervated or inhibited by transcallosal pathways, but can be released (disinhibited) in the context of chronic seizures, pathology, or surgical resection. In rats, reorganization of sensorimotor function following experimental occlusion of the middle cerebral artery is facilitated by intact transcallosal pathways and attenuated by CC atrophy. In humans, similar findings of contralateral attention and motor reorganization following stroke suggest acute unmasking of redundant sites in the contralateral hemisphere via transcallosal pathways. Thus, evidence from animal and human data support the CC as an important structure for facilitating contralateral reorganization of function following epilepsy surgery.

The absence of a relationship between CC area and change in delayed verbal memory suggests that transcallosal pathways may not be critical to recovery of long-term memory functions, such as memory consolidation, retention, or retrieval. Longitudinal fMRI investigation of memory functions pre- and post–anterior temporal lobe surgery supports a greater role for ipsilateral, rather than contralateral, mesial temporal regions in memory reorganization.6 Lateralization of cognitive functions could be a factor in explaining the degree to which postsurgical reorganization relies on transcallosal pathways. For example, strongly lateralized functions such as language may rely more on ipsilateral reorganization following anterior temporal lobectomy, as has been demonstrated, whereas bilaterally represented functions such as working memory may rely more on transcallosal pathways to support contralateral reorganization. Future longitudinal investigations of structural and functional changes pre- and postsurgery are needed to directly investigate whether CC size might be related to contralateral changes in fMRI-BOLD activity during working memory, but not delayed memory, tasks.

Limitations

Limitations of the current study include heterogeneity of seizure focus and surgical resection in the patient group. Although there were no significant differences between the temporal and extratemporal groups on presurgical CC area, WMI, or DR scores, supporting their combination in final analyses, the small size of patient subgroups may have reduced our ability to identify subtle localization-related differences. This may also explain why we did not observe greater verbal memory decline in the left hemisphere or temporal lobe only group. However, findings of verbal memory decline following epilepsy surgery vary. Although decline in delayed memory is commonly reported after left anterior temporal lobe resection, memory stability or a gradual return to presurgical level of memory functioning is also reported. This variability suggests the need to identify predictive factors. Although our findings did not support CC area as a potential explanatory factor for DR-change, other “brain reserve” factors such as the structural and functional integrity of the ipsilateral hemisphere should continue to be explored. In sum, although our TRE group was heterogenous in terms of surgical location, the consistency of the relationship between CC area and WMI-change is promising for generalization to the TRE population. This is especially critical because increasingly more extratemporal patients are being referred for epilepsy surgery.

Conclusion

The current study provides evidence that a larger corpus callosum, measured presurgically, is associated with stability or improvement in auditory-verbal working memory following epilepsy surgery. The relationship between CC area and WMI-change was independent of overall brain volume, suggesting that the CC may play a specific role in supporting postsurgical recovery of cognitive functions. Thus, the structural integrity of the CC may be an important factor to consider in surgical planning.

A considerable advantage of our method is that the MRI scan used in this analysis is easily obtainable on any current clinical MRI scanner. Future studies should apply a similar methodology for measuring CC area to a set of clinically acquired T1-weighted scans to test application in a clinical setting. A standardized acquisition protocol would be optimal to ensure that variability due to different acquisition parameters is eliminated. Acquisition of a postsurgical MRI scan proximal to the time of postoperative cognitive testing would be ideal to evaluate the degree to which changes in morphometric features explain changes in cognitive performance. Finally, future studies should determine whether CC area offers prognostic value by comparing the predicted to observed WMI scores in an independent sample. In sum, results from this study support an important role for the CC in recovery of working memory following epilepsy surgery; however, additional research is needed to determine the mechanisms underlying this effect and its prognostic relevance in surgical planning.

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Disclosure

None of the authors have any conflicts of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Additional Supporting Information may be found in the online version of this article: Table S1. Wada test results and surgery description for TRE patients.