Surgery and Brain Atrophy in Cognitively Normal Elderly Subjects and Subjects Diagnosed with Mild Cognitive Impairment

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ABSTRACT

Background: Structural magnetic resonance imaging is used to longitudinally monitor the progression of Alzheimer disease from its presymptomatic to symptomatic phases. Using magnetic resonance imaging data from the Alzheimer's Disease Neuroimaging Initiative, we tested the hypothesis that surgery would impact brain parameters associated with progression of dementia.

What We Already Know about This Topic

- Structural magnetic resonance imaging is used to longitudinally monitor the progression of Alzheimer disease from its presymptomatic to symptomatic phases, but has not been applied to the setting of postoperative cognitive dysfunction

What This Article Tells Us That Is New

- Elderly subjects after surgery experienced an increased rate of brain atrophy during the initial evaluation interval, a time associated with risk for postoperative cognitive dysfunction

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Methods: Brain images from the neuroimaging initiative database were used to study normal volunteer subjects and patients with mild cognitive impairment for the age group 55 to 90 inclusive. We compared changes in regional brain anatomy for three visits that defined two intervisit intervals for a surgical cohort (n = 41) and a propensity matched nonsurgical control cohort (n = 123). The first interval for the surgical cohort contained the surgical date. Regional brain volumes were determined with Freesurfer and quantitatively described with J-image software (University of California at San Francisco, San Francisco, California). Statistical analysis used Repeated Measures ANCOVA (SPSS, v.18.0; Chicago, IL).

Results: We found that surgical patients, during the first follow-up interval (5–9 months), but not subsequently, had

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increased rates of atrophy for cortical gray matter and hippocampus, and lateral ventricle enlargement, as compared with nonsurgical controls. A composite score of five cognitive tests during this interval showed reduced performance for surgical patients with mild cognitive impairment.

Conclusions: Elderly subjects after surgery experienced an increased rate of brain atrophy during the initial evaluation interval, a time associated with enhanced risk for postoperative cognitive dysfunction. Although there was no difference in atrophy rate by diagnosis, subjects with mild cognitive impairment suffered greater subsequent cognitive effects.

T HERE have been numerous reports of impairment of cognitive performance following surgery.[1–4] However, it is not yet known which patients are at risk for post operative cognitive dysfunction (POCD).

POCD occurs in approximately 10% of elderly patients after noncardiac surgery.[1] The presence of POCD is determined by the comparison of preoperative and postoperative cognitive performance using a battery of neuropsychometric tests that assess memory and executive function.[2–3] A goal of the present study was to examine short-term longitudinal changes in brain volume and in cognition in elderly patients pre- and postsurgery in order to improve our understanding of the risk of POCD.[5]

Despite numerous reports describing cognitive decline after surgery, proponents have met with considerable criticism because the population considered most at risk for POCD is subject to various other cognitive risks, including progressive dementias, vascular insults, and the nonspecific impact of aging; it is also difficult to devise an appropriate control for the surgical groups.[6] It has recently been suggested that the baseline cognitive diagnosis, mild cognitive impairment (MCI), may also identify additional patient risk for postsurgical cognitive impairment.[7] MCI is a clinical term that includes individuals with impairment in one or more cognitive domains (typically various forms of memory) greater than would be expected for a person's age, but who are otherwise functionally intact and capable of living independently. This suggests the need for an independent, object measure of POCD risk.

Quantitative magnetic resonance imaging (MRI) is particularly useful in observing longitudinal brain changes in patients with degenerative diseases. This includes monitoring of Alzheimer disease (AD) progression in subjects both with MCI,[8–9] and in cognitively normal elderly.[10] However, it has not been applied to monitoring effects related to POCD. MRI may avoid some of the confounds associated with cognitive testing (currently the standard for tracking POCD), while also obtaining significant results with fewer patients.[11] Quantitative MRI can be obtained with good accuracy for both between and within subject measurements,

and can be reduced to continuous value parameters (*e.g.*, volume) for individual brain structures. Such images from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were used to examine the interaction of aging, severity group (normal, or NL, MCI, and AD), and surgery on the geriatric brain. We hypothesized that surgery would have a noticeable impact on brain parameters also associated with progression of dementia.

Materials and Methods

ADNI Database

Data used in this study was obtained from the ADNI database. ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-yr public/private partnership. The Principal Investigator of this initiative is Michael W. Weiner, M.D., Veterans Administration Medical Center and University of California – San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from more than 50 sites across the United States and Canada. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, and other biologic markers, as well as clinical and neuropsychological assessment, can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers for very early AD progression is intended to aid researchers and clinicians in the development of new treatments and to monitor their effectiveness. This would also have the effect of lessening the time and cost of clinical trials. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research: approximately 200 cognitively normal older individuals to be followed for 3 yr, 400 people with MCI to be followed for 3 yr, and 200 people with early AD to be followed for 2 yr.§§

Regulatory. The collection of data by ADNI was approved by the Institutional Review Boards of all participating institutions. Informed written consent was obtained from all participants. The New York University Medical Center Institutional Review Board takes the position that anonymous data from another institution (as in this case) is "not human subjects research."

Subject Selection. Subject ages were between 55 and 90 (inclusive). Subjects must have been willing and able to complete all study tests at baseline and for at least 3 yr, including two follow-up exams. Exclusion/inclusion criteria applied to patients in the ADNI study also applied to subjects in this analysis. Those with MRI scans with evidence of infection, infarction, other focal lesions, or multiple lacunes in critical memory structures were excluded. In addition, the following illnesses/injuries constituted exclusions: Huntington's disease, brain tumor, normal pressure hydrocephalus, progressive supranuclear palsy, seizure disorder, subdural hema-

§§ For up-to-date information, see www.adni-info.org. Accessed November 2, 2011.

toma, multiple sclerosis, major depression or bipolar disorder, alcohol abuse, and head trauma followed by neurologic defaults or structural brain abnormalities. Other significant systemic illnesses or unstable medical conditions that would interfere with protocol compliance were also cause for exclusion.

The initial ADNI sample was 835 subjects with data available in the "Adverse Events/Hospitalizations–Log." Putative surgical patients were selected by searching the comment fields for positive key words (*e.g.*, surgery, thoracotomy, operative, among others), and excluded based on negative key words (*e.g.*, cataract, lasik), which pointed to no surgery or minor surgery. A group of 226 putative surgical subjects were thus identified. We screened manually for confirmation of surgery and date, resulting in a cohort of 119 confirmed surgical patients. We further required that each surgical patient had a presurgical and postsurgical MRI, and that the follow-up (postsurgical) MRI was within 5 to 9 months of the baseline presurgical MRI. That screened group included 66 subjects. At baseline, all demented subjects were excluded so the final surgical cohort contained 41 subjects (17 stable NL, 24 MCI). A subset of 31 surgical subjects (15 stable NL, 16 stable MCI) had a second MRI follow-up evaluation, defining a second intervisit interval.

The nonsurgery group of 341 patients included subjects who were not flagged for key words and who did not have minor surgery. The nonsurgical controls and surgical subjects were then matched utilizing a model that estimated the propensity of study participants to have surgery. This "propensity matching" procedure was based on the following available variables: age, sex, education, Apolipoprotein E status, months to follow-up 1, race, mini-mental state examination, Geriatric Depression Scale score, and Hachinski (vascular risk). The surgery subjects (n = 41) were then matched 1:3 to the current nonsurgical cohort (n = 341) using the control subject's propensity to have surgery based on these variables. The propensity population for the nonsurgery subjects was n = 123 (51 stable NL, 72 MCI). For the nonsurgery group, the first two MRIs that were within 5 and 9 months of each other were used as the baseline and follow-up.

Thus in summation, we compared changes in regional brain volume for three visits (evaluations) that defined two intervisit intervals for a surgical cohort (n = 41) and a propensity-matched nonsurgical control cohort (n = 123). The first interval for the surgical cohort contained the surgical date.

MRI and Image Analysis. We chose to examine whole brain gray matter (GM), whole brain white matter (WM), and lateral ventricle (LV) volumes as general measures of structural integrity. The hippocampal volume was examined as a specific memory-related region with relevance to AD. The GM volume does not include hippocampus. LV enlargement has been shown to parallel cognitive impairment during pro-

gression.[12] All MRI images were archived by ADNI, and the study volumes were acquired with Freesurfer software and analyzed with J-image by the ADNI Center at UCSF.##

Cognitive Analysis

POCD was defined as a Z score change greater than -2 SD on two or more cognitive tests. The test scores available included the digit symbol substitution test (assessing executive function and complex attention), digits span forward and backward (assessing verbal working memory), trails A (attention), and trails B (executive function).

Since an important part of the benefit of longitudinal imaging studies derives from comparison with the development of parallel cognitive changes, we used a Z score composite of the same five tests included in the POCD analysis for this longitudinal comparison. Memory tests, although quite relevant, were not assessed in this study because ADNI tests memory every 12 months, and therefore scores were not available for the time points of interest.

Statistical Analyses

Demographic and descriptive differences for continuous variables (*e.g.*, age) between the surgery and nonsurgery groups were examined with *t* tests; and, for categorical variables (*e.g.*, gender), group differences were evaluated using Pearson chi-square analyses. All regional brain volumes were summed over both hemispheres and adjusted for head size by using a ratio with the intracranial volume (ICV) as the denominator. Baseline differences in regional brain volume ratios were examined with ANCOVA with severity group (diagnosis; NL, MCI) and baseline age as covariates. Differences in the changes of regional brain volume ratios over time between groups were assessed by evaluating the interaction of evaluation (visit) and surgery group (surgical, nonsurgical controls) in Repeated Measures ANCOVA between baseline and the first follow-up evaluation (to assess the initial effects of surgery), between the first and second follow-up (to assess persistence of the surgery effect), and between baseline and second follow-up evaluation (to assess delayed effects). Age, baseline regional volume ratio, gender, Apolipoprotein E4 status, severity group, and months to follow-up evaluation were treated as confounds and included as covariates in the models. MCI and NL results were pooled after the interaction term was not significant for "severity" *versus* "evaluation." Significant results were confirmed with nonparametric (Mann–Whitney U) tests on the annual percent change of the regional brain volume ratios. The annual percent change in the regional brain volume ratios between baseline and the first follow-up were used as independent variables in logistic regression analyses predicting surgery group. Statistical significance was defined as $P \leq 0.05$. Multiple comparison corrections for the regional brain volume atrophy analysis using Repeated Measures ANCOVA, where there were multiple significant results, used the Holm–Bonferroni

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Freesurfer software is available at no charge at http://surfer.nmr.mgh.harvard.edu. Accessed November 2, 2011.

Table 1. Demographics and Baseline Statistics for Surgical and Nonsurgical Groups

	Nonsurgery	Surgery
n	123	41
Age	75.1 ± 6.3	75.3 ± 5.9
Education (years)	16.2 ± 2.8	16.2 ± 2.5
Months to follow up*	6.6 ± 0.5	6.5 ± 0.7
Intracranial volume (units of mm³)	1,544,316 ± 151,998	1,565,403 ± 154,102
% Female	49%	49%
% ApoE4+	48%	49%
% (n) normal	41% (51)	41% (17)

Values are mean ± SD or %.

* A significant difference ($P < 0.05$); found only for "months to follow up."

ApoE4+ = a positive ApoE4 status, a risk factor for Alzheimer disease.

Fig. 1. Baseline comparisons for region of interest volumes. The mean baseline volume ratios are shown for control (*red bars*) and surgery subjects (*blue bars*). The top panel (*A*) displays gray matter and white matter (vertical axis) as a proportion of intracranial volume. *Error bars* show 95% CIs of the mean. The bottom panel (*B*) is the same display for lateral ventricle and hippocampus. Note the difference in volumes as indicated by axis scale and bar size. ICV = intracranial volume.

method.[13] SPSS (version 18.0; Chicago, IL) was used for data analyses.

The POCD above and below the threshold of the Z scores for change in cognition with surgery compared with controls were assessed using Pearson chi-square analysis. The change in cognition was also examined in a Repeated Measures ANCOVA comparing the differences in slopes for the surgery and controls on the average Z scores for the five cognitive tests over the same time frames as the regional volume analysis.

Results

We examined 164 cases including 41 surgical cases and 123 propensity-matched nonsurgical controls. There were no significant differences between the surgery groups in demographic or descriptive variables (see table 1). There were no significant differences in the baseline regional brain volume ratios between the surgery groups, either pooled over severity group or within severity group (fig. 1).

Repeated Measures ANCOVA

Cortical GM. The interaction of evaluation period and surgery group was significant ($F_{1,159} = 5.3$, $P = 0.02$) between baseline and first follow-up, indicating that the slopes for the surgery groups were different with the surgical cohort showing a greater decrease in GM/ICV volume at the first follow-up than the nonsurgical controls. This was not found between the baseline and the second follow-up, nor was an interaction found between the first follow-up and second follow-up.

LV. The interaction of evaluation and surgery group was significant ($F_{1,159} = 16.62$, $P < 0.001$) between baseline and first follow-up, indicating that the LV/ICV slopes for
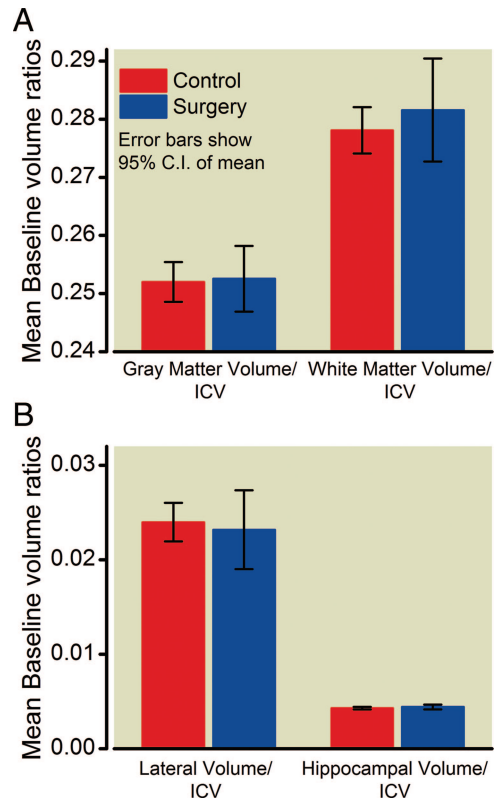
the surgery groups were different, with the surgical cohort showing a greater increase in ventricular volume at the first follow-up than the nonsurgical controls. The change in LV can be seen in paired images from a representative surgical patient (fig. 2). As above, no other interactions were found.

Hippocampus. The interaction of evaluation and surgery group was significant ($F_{1,159} = 12.76$, $P < 0.001$) between baseline and first follow-up, indicating that the hippocampus/ICV slopes for the surgery groups were significantly different, with the surgical cohort showing a greater decrease in hippocampus/ICV volume at the first follow-up than the nonsurgical controls. We display these changes graphically (see fig. 3A) for hippocampal volume between baseline and first follow-up. Slopes for NL and MCI are shown separately to illustrate that the atrophy starts at different baselines for the two diagnostic conditions. There is no difference in the rate of atrophy by severity group. Again, no other interactions were found.

Cortical WM. The interaction of evaluation and surgery group was not significant for any of the time frames examined ($F_{1,159} = 0.12$, ns).
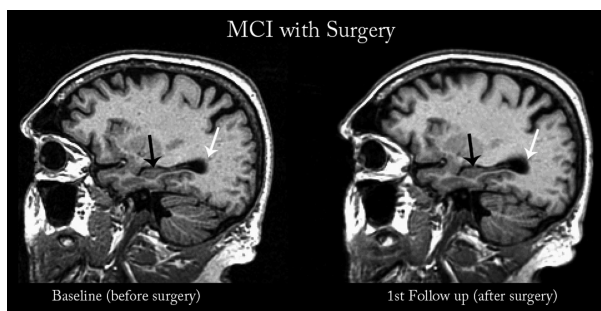
Fig. 2. Lateral ventricle volume changes in a surgical patient. Sample cortical magnetic resonance image pairs (baseline, first follow-up) show lateral ventricle enlargement subsequent to surgery for a mild cognitive impairment patient. The percent volume change for this particular subject from the pre- to postsurgical interval was 7.13%, about 33% greater than the average post surgery change. *White arrow* indicates lateral ventricle; *black arrow* indicates hippocampus. MCI = mild cognitive impairment.

Logistic Regression Analysis

This analysis was performed in propensity-matched cohorts, with the annual percent change in the regional brain volume ratios predicting surgery group membership and allowing us to assess the amount of separation between the surgical cohort and nonsurgical controls, in terms of changes in regional brain volume ratios.

GM. The annual percent change in GM/ICV yielded a significant separation between the surgical cohort and nonsurgery controls: chi-square = 5.4, $P = 0.02$, OR = 1.09 (95% CI: 1.01–1.17), specificity = 64% (79/123), sensitivity = 59% (24/41), overall accuracy = 63% (103/164).

LV. The annual percent change in the LV/ICV yielded a significant separation between the surgical cohort and nonsurgical controls: chi-square = 8.4, $P < 0.01$, OR = 1.06 (95% CI: 1.01–1.10), specificity = 65% (80/123), sensitivity = 71% (29/41), overall accuracy = 66% (109/123).

Hippocampus. The annual percent change in the hippocampus/ICV yielded a significant separation between the surgical cohort and nonsurgical controls: chi-square = 9.9, $P < 0.01$, OR = 1.07 (95% CI: 1.02–1.13), specificity = 71% (87/123), sensitivity = 54% (22/41), overall accuracy = 66% (109/123).

WM. The annual percent change in WM/ICV did not provide adequate separation between the surgical cohort and nonsurgical controls.

Cognitive Tests

Incidence of POCD. We identified surgical subjects who crossed the cognitive threshold associated with POCD during the first interval (pre- to postsurgery). The distribution of POCD among the surgical cohort was similar to that expected from published values[2] (4/38; 10.5%). However, only one subject exceeded this cognitive threshold (measured across the first evaluation interval) for the much larger nonsurgical control cohort (1/123; less than 0.82%). The surgi-

cal cohort has a significantly higher incidence ($\chi = 9.1$; $P = 0.01$; Fisher exact) of cognitive decline using this measure. We also note that all the POCD subjects in the surgical cohort were in the MCI group.

Longitudinal Measure of the Composite Cognitive Score. There was noted a significant interaction between severity group and surgery group in the repeated measures ANCOVA of the averaged cognitive Z scores from baseline to the first follow-up, so the severity groups were examined separately. Although there was not a significant difference in the slopes for surgical cohort *versus* nonsurgical controls in the NL group, the MCI subjects with surgery showed a significantly greater decrease in scores compared with the MCI nonsurgical controls ($F_{1,91} = 7.81$, $P < 0.01$; see fig. 3B). There were no significant differences in the surgery groups (either in the separate severity groups or pooled) between baseline and follow-up 2 or between follow-up 1 and follow-up 2.

We also examined correlations between changes in cognitive test results and changes in atrophy for various regions of interest,[14] and determined that we required a more extensive analysis using more complex models, better left for a subsequent study. Univariate analyses for the composite cognitive parameter identified both baseline and dynamic (annual percent change) volume measures from more than one region of interest as potentially significant. As expected from previous studies, potential correlations were different based on the included severity groups.[15–16] The patients enrolled at different time points in terms of age- or dementia-related progression; and therefore presented with different cognitive abilities and levels of atrophy at baseline. The cognitive score we used was a composite that didn't include primary memory tests. GM and WM are also composite scores, and GM represents multiple regions that are known to undergo atrophy with varying latencies.

Progressive Atrophy *versus* Acute Atrophy

To put these atrophy results in a more quantitative context, we compared (see fig. 4) mean baseline volumes for three severity groups (NL, MCI, MCI-AD; left 3 bars) on the same bar plot as the mean atrophy for surgical and control subjects during the first evaluation interval (right 2 bars). This allowed us to compare, from the same data set, atrophy associated with surgery to volume changes during transition between severity groups (*i.e.*, changes in diagnosis), where we know that there is a difference in cognition.[9] For example (see fig. 4A), a mean 8.1% (± 1.8%, SE) reduction in hippocampal volume for MCI subjects (*vs.* NL) can be compared to a 2.9% (±0.8%, SE) atrophy for surgical patients. Similar results were found for the other regions of interest (GM, LV; fig. 4B and C, respectively; see caption). For GM, the mean change from NL to MCI is 3.5% (± 0.8%, SE) *vs.* a 1.39% (0.43%, SE) atrophy in the surgical group. For the LV volume, an enlargement of MCI *versus* NL of 15.9% (±
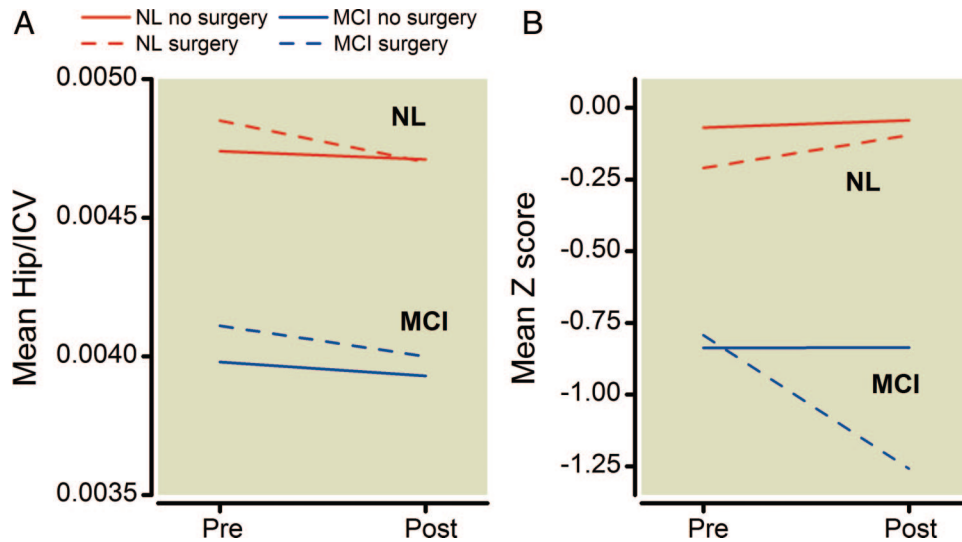
Fig. 3. Functions of severity group and surgery. (*A*) Atrophy of hippocampus as a function of severity group and surgery. Hippocampal volume is plotted on the vertical axis as a proportion of intracranial volume for two time-points (horizontal axis) that include: baseline (pre) and first follow-up (post). The *solid lines* are the control subjects and the *dashed lines* are the surgical subjects. Normal and mild cognitive impairment subjects are plotted separately. These plots illustrate that normal (*red lines*) and mild cognitive impairment (*blue lines*) subjects have the same atrophy rate, even though the latter subjects have a lower baseline atrophy level. (*B*) Reduced cognitive performance as a function of severity group and surgery. The cognitive score (mean composite Z score) is plotted on the vertical axis for two time-points (horizontal axis) including: baseline (pre) and first follow-up (post). The *solid lines* are the control subjects and the *dashed lines* are the surgical subjects. Normal subjects (*red lines*) subjects and subjects with mild cognitive impairment (*blue lines*) are plotted separately. Only the mild cognitive impairment surgical subjects show a worsening performance *versus* the nonsurgical controls. MCI = mild cognitive impairment; NL = normal.

8.9%, SE) can be compared to a 5.3% (0.9%, SE) enlargement for the surgical patients.

For comparison of atrophy values with those quoted in aging/dementia studies,[17] we also calculated the mean difference of the annual percent change (95% CIs; square brackets). Comparing the two atrophy rates for hippocampal volume, surgical *versus* nonsurgical control groups, the mean difference in the annual percent change was 3.7% (1.2, 6.3); comparing annualized atrophy rates for GM volume gives a difference in annual percent change of 2.2% (0.3, 4.0); and, comparing annualized enlargement rates for LV, there was a 4.4% greater rate (1.4, 7.5) for the surgery subjects.

Discussion

The analysis of ADNI image data suggests that surgical patients experience greater atrophy rates than nonsurgery patients. Of particular interest are the findings of increased brain changes by region, including: global GM (atrophy), hippocampus (atrophy), and LV (enlargement). Examining cognitive performance, we report a significant decrease in the composite cognitive score for the MCI surgery group during the same interval for which the atrophy occurred.[5] Differences by surgical group in both rate of atrophy and cognitive loss dissipates during the second follow-up interval.

Changes in Cortical Volume

Brain volume changes have been detected during various clinical and behavioral conditions. During the onset of AD,

one of the best studied of the neurodegenerative illnesses, changes in vulnerable limbic and heteromodal regions can serve as diagnostic indicators. Atrophy occurs before symptoms and becomes more pronounced as symptoms progress.[16,10,18–20] Because our sample contains both NL and MCI patients of advanced age, we assume a varied distribution of baseline atrophy.

Longitudinal MRI studies of cortical anatomy can be performed with great reproducibility and sensitivity.[21] Comparing normal subjects and those with cognitive impairment showed significant changes.[10,19] For example, cortical thinning was reported to average 5.2% greater in AD subjects than older controls[19]; *e.g.*, rostral medial temporal cortex had the largest thinning (0.4 mm; 14% *vs.* older controls) with thinning in excess of 0.2 mm in the inferior temporal, temporal pole, inferior parietal, and superior frontal regions (8.1–11.6% change *vs.* older controls). The primary visual cortex, seldom involved in AD, showed no significant thinning (0.03 mm, 2.2%).

We chose to examine cortical GM as a general measure, and hippocampus as a specific region of interest. Hippocampus is known to atrophy with age, over almost the entire course of AD progression,[22] and in response to environmental stressors. Since some areas of the cortex may not be affected by either baseline atrophy or surgical stress, global GM changes will not fully reflect the size of the changes in the most involved areas of the cortex. Both hippocampal atrophy[23–24] and MCI diagnosis[9] predict increased risk of pro-
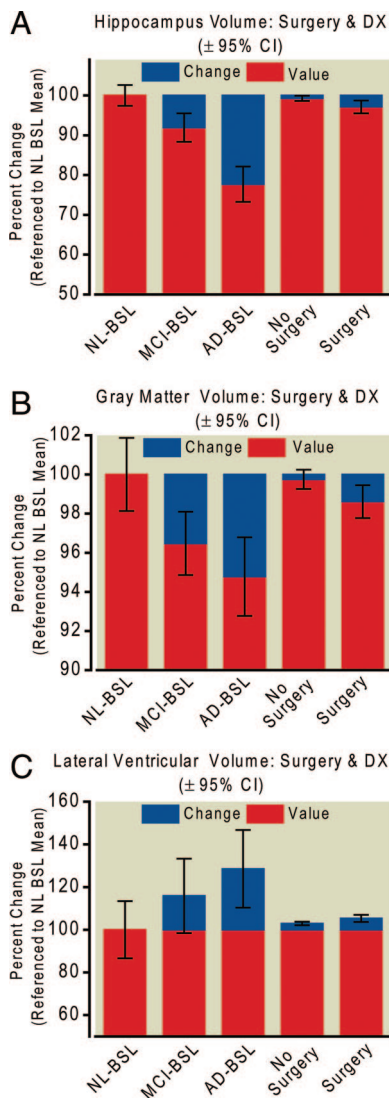
Fig. 4. Hippocampal, gray matter, and lateral ventricular volume change as a function of severity group and surgery. A graphical display is used to present the effects of severity group and surgery in a single bar graph. (*A*) Setting the normal hippocampal volume mean equal to 100, hippocampal volume measures for subjects with mild cognitive impairment (MCI) averaged 91.94% (± 1.82% SE; n = 62) of normal (100%; ± 1.30% SE; n = 68) at baseline; and MCI-AD subjects were 77.68% (± 2.27% SE, n = 34) of normal at baseline. MCI-AD subjects are MCI subjects who transitioned to Alzheimer disease during participation in the Alzheimer's Disease Neuroimaging Initiative. The average change in hippocampal volume atrophy for the surgical patients during the first interval was 2.86% (± 0.82%; n = 41) of the average normal hippocampal volume. The background atrophy (nonsurgical control patients) was 0.73% (± 0.32%; n = 123). (*B*) For the gray matter volume an atrophy *versus* normal (NL; 100 ± 0.95%) was seen of 3.52 ± 0.82% and 5.2 ± 1.03% from NL to MCI and NL to MCI-AD, respectively. The percent change for the first interval for surgery subjects was 1.39 ± 0.43% and for nonsurgical controls 0.25 ± 0.25%. (*C*) For the lateral ventricular volume an expansion *versus* NL (100 ± 6.83%) was seen of 15.87 ± 8.91% and 28.54 ± 9.28% from

gression to AD. However, it is not known whether hippocampus atrophy induced by environmental stressors (*e.g.*, surgery) incorporates the same mechanisms and/or risk of progression as the atrophy studied during incipient AD. In terms of understanding age- and dementia-related progression, it seems prudent to assume a multiple factor framework[25] such that atrophy is only one of several causal factors driving progression of cognitive symptoms.

From figure 4, it is evident that the atrophy associated with surgery is a nontrivial (20–40%) portion of that encountered in going between the severity levels (NL, MCI, MCI-AD). Based on the time patients remain at each severity level, or on the average atrophy rates during progression,[16] and compared with our reported atrophy rates, atrophy for surgical patients would seem to have advanced by 1 to 2 yr more than controls. From figures 3A and B, we can see that the changes in the composite cognitive parameter as a function of hippocampal atrophy are larger in relation to surgery, than in relation to changed severity group levels (diagnosis).

Surgery, POCD, and Comorbidity

A complication in any longitudinal study is risk of mortality/morbidity.[26] Subjects with diagnoses ranking high on the list of comorbidity risk, as well as diagnosed AD or evidence for cognitive progression (leading to a diagnostic severity change), were all excluded from this study at the time of ADNI enrollment. This should imply a relatively homogeneous group at the time of enrollment. However, despite the enrollment restrictions, some 15% of the initial enrollees wound up requiring surgery within 3 yr of joining the study.

Attempts have been made to classify surgeries in terms of postoperative cognitive risks. One might assume that type and duration of surgery, incidence of complications, coronary-pulmonary bypass, hypotension, and blood loss would be predictors of POCD risk. However, the only POCD risk factors proven significant in a recent report were: years of education, age, and history of cerebral vascular accident with no residual damage.[27] The limited availability of detailed surgical information for patients in our study, as well as the uncertain weighting of risk factors, discourages us from using a more complex stratification. However, we have found a distinct suggestion of MCI subject vulnerability to cognitive impairment postsurgery, both in the higher relative risk of a POCD-like change and the significant change in the composite cognitive parameter during the first evaluation interval. Although the increased rate of hippocampal atrophy, for example, is not different for MCI and NL patients, there already is considerable baseline atrophy for the MCI subjects. Thus surgery-associated atrophy may be more problematic for MCI subjects, because of their cumulative atrophy at the

NL to MCI and NL to MCI-AD, respectively. The percent change for the first interval for surgery subjects was 5.33 ± 0.85% and for nonsurgical controls 2.93 ± 0.41%. AD = Alzheimer disease; BSL = baseline; DX = direct expansion; MCI = mild cognitive impairment; NL = normal.

time of surgery. Furthermore, MCI subjects would presumably have less cognitive reserve and compensatory factors working to stabilize cognition.[25] Since MCI subjects are already at higher risk for conversion to AD, care must be taken in attributing their outcome to POCD alone.

Numerous studies have reported a relationship between surgery and cognitive impairment.[2,27–28] However, caution should be used in considering causality, because both surgery and cognitive impairment share common features, *e.g.*, age dependence and the involvement of inflammatory processes. Furthermore, developing a trial protocol randomized to surgery is difficult from a regulatory standpoint.[6] In some instances, the presumed impact of surgery was the impact of the precipitating illness itself.[29] Yet various factors commonly associated with surgery (*e.g.*, increased peripheral blood levels of interleukin-6[30] and chronic pain[31]) have been shown to cause GM atrophy in the absence of aging or surgery. Behavioral changes related to surgery (potentially reflecting both therapeutic impact, elimination of chronic pain, increased mobility, among others, and recuperative requirements, such as decreased mobility) might interact with atrophy by way of neural plasticity-mediated effects on GM/WM density.[32–33] Neural plasticity may be relevant to our finding of potential recovery from atrophy during the second follow-up interval, where we no longer find atrophy on average. However, it is important to keep in mind that recovery from atrophy doesn't necessarily lead to recovery of function.

In this study, surgeries by type and incidence include: joint/limb repair (12; hip, shoulder, knee, wrist, ankle, foot), joint replacement (7; hip, shoulder, knee), tumor resection (7; breast, prostate, skin, pituitary, thyroid), gynecological (3; hysterectomy), ENT (3; ear, nose and throat), urological (2), vascular (2), spinal (2), abdominal (1; hernia), and ophthalmologic (1; excluding cataract). There is no reason to assume that these patients were spared the normal inflammatory or behavioral impact experienced due to the pre- or postsurgical clinical condition. Yet, using the propensity-matched control sample, there was no baseline difference in brain volume (GM, WM, or hippocampus) for the surgery compared with control subjects, either pooled or stratified by severity group.

Relation between Surgery and Baseline Factors

It is complicated to correlate atrophy with altered cognitive performance. For example, the fact that the risk of POCD varies inversely with years of education is generally attributed to cognitive reserve,[27] whereby an individual with minor cortical atrophy is spared the symptoms of cognitive impairment by a postulated cortical redundancy, presumed a function of increased education.[25] Such redundancy is difficult to measure *a priori*, and comparable education by no means guarantees comparable levels of reserve.

Another possible source of homogeneity in the relationship between atrophy and cognition is variation in baseline atrophy

in specific GM regions with known involvement in AD progression, *e.g.*, medial temporal lobe. GM baseline atrophy can be because of various configurations of change in subregions.[22,34] Furthermore, as hypothesized in the dissociation hypothesis,[35–36] atrophy of GM can lead to atrophy of enervating WM, and atrophy at any site can alter behavior in an entire network.[37] Thus GM and WM atrophy occur with complex timing,[22] not synchronized yet not independent.

Among the mechanistic questions posed by the atrophy measurement are whether: 1) we are seeing a simple speeding up of ongoing progression encountered at baseline; 2) there is a selective, and perhaps synergistic, interaction of surgical stressors with other forms of atrophy; 3) surgery-related effects are independent of those associated with normal progression of dementia; or whether, 4) attainment of threshold levels of atrophy induce irreversible changes in other risk factors. In any case, there is no reason to believe that predicting potential effects of surgery are any less complex than defining risks for progressive dementias themselves.

Long-term Effects

An obvious question is whether atrophy associated with surgery may alter progression of dementia.

It is difficult to explore long-term effects from a short-term study. For example, extending our analysis from 6 months to 1 yr reduced the available surgery cohort from 41 to 31. Extensions to even longer time periods would lead to a further loss of sample size and power.

Analysis of the second follow-up interval did not show a statistically significant continuation of atrophy. The components of change in the second interval include some subjects with improved volume (recovery from atrophy), some with no change, and some with continued atrophy. Since a fairly small increase in risk of progression is important from a public health standpoint, we would only have to show that a small proportion of the subjects with continuing atrophy had increased risk of conversion to AD for an important epidemiologic result. However, a surgically related increase in the annual MCI to AD conversion rate in our study from 16.5% to 20% would only result in a single extra AD patient, a change unlikely to be resolved.

However, although the surgically related effect on rate of cortical atrophy may be temporary, transient changes in the postoperative period may have long-term relevance. Consider, for example, a recent epidemiologic study[38] reporting a significant increase in mortality in patients diagnosed with POCD at 3 months, an effect not evident until approximately 2 yr postsurgery. POCD at even 1 week after surgery was statistically associated 8 yr later with early exit from the labor force, and the need for social support services.[38]

Conclusion

In our cohort of elderly subjects, those having undergone surgery experienced a more pronounced atrophy in hippocampal and GM volume than did nonsurgical (control)

subjects over a similar time frame (5–9 months). We were not able, in exploring the second follow-up time interval, to find a persistent effect of surgery on rate of atrophy. There are individual subjects who continue to atrophy at an enhanced rate, but we cannot detect effects on their outcome within the limited time frame of the data using standard survival analysis; and we cannot rule out atrophy related to progressive dementia.

The cognitive change found from our composite measure was also limited to the first time interval, which is consistent with the early and transient occurrence of POCD (3 months) often reported in the literature. That significant cognitive changes accompanying atrophy were seen in the MCI surgery subjects suggests that their baseline atrophy may put them at increased risk.[5] Thus our study more readily supports the notion of a transient POCD event associated with surgical patients, than it contributes to the analysis of risk factors leading to dementia progression. These questions suggest the need for a more comprehensive examination of surgery, cognition, and atrophy.

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