Published in final edited form as:

Anesthesiology. 2012 March ; 116(3): 603–612. doi:10.1097/ALN.0b013e318246ec0b.

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

Richard P. Kline, Ph.D., M.A.^{1,4} [Senior Research Scientist], Elizabeth Pirraglia, M.A.^{2,3} [Research Statistician], Hao Cheng, B.S.¹ [Medical student], Susan De Santi, Ph.D.^{2,3} [Adjunct Associate Professor], Yi Li, MD^{2,3} [Research Scientist/Radiologist], Michael Haile, M.D.^{1,4} [Research Assistant Professor], Mony J. de Leon, Ed.D.^{2,3} [Professor and Director, Center for Brain Health], Alex Bekker, M.D., Ph.D.^{1,4} [Professor], and Alzheimer's Disease Neuroimaging Initiative*

¹NYU Langone Medical Center, Dept Anesthesiology, NY, NY 10016

²NYU Langone Medical Center, Dept Psychiatry, 145 E. 32nd St, NY, NY 10016

³NYU Langone Medical Center, Center for Brain Health

⁴NYU Langone Medical Center, Center of Excellence on Brain Aging

Abstract

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

Materials and 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 inter-visit intervals for a surgical cohort (n=41) and a propensity matched non-surgical 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). 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 increased rates of atrophy for cortical gray matter and hippocampus, and lateral ventricle enlargement, as compared to non-surgical 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.

Dept Anesthesiology, NYU Langone Med Cntr, 550 First Ave, NY, NY 10016; 212-263-6155 (w), 917-226-4941 (Cell), 212-263-0664 (fax), Richard.kline@nyumc.org.

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data, but did not participate in the design, analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Introduction

There have been numerous reports of impairment of cognitive performance following surgery¹⁻⁴. 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 surgery¹. The presence of POCD is determined by the comparison of preoperative and postoperative cognitive performance using a battery of neuro-psychometric tests which assess memory and executive function²⁻³. A goal of the present study was to examine short-term longitudinal changes in brain volume and in cognition in elderly patients pre and post surgery in order to improve our understanding of the risk of POCD⁵.

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 groups⁶. It has recently been suggested that the baseline cognitive diagnosis, mild cognitive impairment (MCI), may also identify additional patient risk for postsurgical cognitive impairment⁷. 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's disease (AD) progression in subjects both with MCI⁸⁻⁹, and in cognitively normal elderly¹⁰. 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 obtaining significant results with fewer patients¹¹. 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 Neuro-imaging Initiative (ADNI) database were used to examine the interaction of aging, severity group (normal (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 Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). 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 non-profit organizations, as a \$60 million, 5-year public/private partnership. . The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co- investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 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 biological markers, as well as clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (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 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years.” For up-to-date information, see www.adni-info.org.

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 be willing and able to complete all study tests at baseline and for at least 3 years including two follow-up exams. Exclusion/inclusion criteria applied to patients in the ADNI study also apply 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. Additionally, the following illnesses/injuries constituted exclusions: Huntington's disease, brain tumor, normal pressure hydrocephalus, progressive supra-nuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, major depression or bipolar disorder, alcohol abuse and head trauma followed by neurologic deficits 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 etc.), and excluded based on negative key words (e.g. cataract, lasik etc.) 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 pre-surgical and postsurgical MRI, and that the follow-up (post surgical) MRI was within 5 to 9 months of the baseline pre-surgical 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 inter-visit interval.

The non-surgery group of 341 patients included subjects who were not flagged for key words and who did not have minor surgery. The non-surgical 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 Score, and Hachinski (vascular risk). The surgery subjects (n=41) were then matched 1:3 to the current non-surgical cohort (n=341) using the control subject's propensity to have surgery based on these variables. The propensity population for the non-surgery subjects was n=123 (51 stable NL, 72 MCI). For the non-surgery group, the first two MRI's 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 inter-visit intervals for a surgical cohort (n=41) and a

propensity matched non-surgical 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 progression¹². 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. (Freesurfer software is available at no charge at <http://surfer.nmr.mgh.harvard.edu>.)

Cognitive analysis

POCD was defined as a Z score change greater than -2 SD on 2 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 5 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 non-surgery groups were examined with t-tests; and, for categorical variables (e.g. gender) group differences were evaluated using Pearson chi-squared 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, non-surgical controls) in Repeated Measures ANCOVA between baseline and the 1st follow-up evaluation (to assess the initial effects of surgery), between the 1st and 2nd follow-up (to assess persistence of the surgery effect), and between baseline and 2nd 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 % change of the regional brain volume ratios. The annual percent change in the regional brain volume ratios between baseline and the 1st follow-up were used as independent variables in logistic regression analyses predicting surgery group. Statistical significance was defined as *p* values < .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 method¹³. 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 to controls were assessed using Pearson chi-squared 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 5 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 non-surgical 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, **bar graph**).

Repeated measures ANCOVA

Cortical GM—The interaction of evaluation period and surgery group was significant ($F_{1,159} = 5.3, p=.02$) between baseline and 1st 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 1st follow-up than the non-surgical controls. This was not found between the baseline and the 2nd follow-up nor was an interaction found between the 1st follow-up and 2nd follow-up.

LV—The interaction of evaluation and surgery group was significant ($F_{1,159} = 16.62, p<.001$) between baseline and 1st 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 1st follow-up than the non-surgical controls. The change in LV can be seen in paired images from a representative surgical patient (Figure. 2.). As above, no other interactions were found.

Hippocampus—The interaction of evaluation and surgery group was significant ($F_{1,159} = 12.76, p<.001$) between baseline and 1st 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 1st follow-up than the non-surgical controls. We display these changes graphically (see Figure 3.A) for hippocampal volume between baseline and 1st 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 ($F_{1,159} = 0.12, ns$).

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 non-surgical 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 non surgery controls [$\chi^2=5.4, p=.02, OR=1.09$ (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 non surgical controls [$\chi^2=8.4$, $p<.01$, 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 non surgical controls [$\chi^2=9.9$, $p<.01$, 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 non surgical controls.

Cognitive Tests

Incidence of POCD—We identified surgical subjects who crossed the cognitive threshold associated with POCD during the first interval (pre to post surgery). The distribution of POCD amongst the surgical cohort was similar to that expected from published values² (4/38; 10.5%). However, only one subject exceeded this cognitive threshold (measured across the 1st evaluation interval) for the much larger non-surgical control cohort (1/123; < 0.82%). The surgical 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. While there was not a significant difference in the slopes for surgical cohort versus non-surgical controls in the NL group, the MCI subjects with surgery showed a significantly greater decrease in scores compared to the MCI non-surgical controls ($F_{1,91}=7.81$, $p<.01$; see Figure 3.B). 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 interest¹⁴, 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 1 region of interest as potentially significant. As expected from previous studies, potential correlations were different based on the included severity groups¹⁵⁻¹⁶. 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 which 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 Figure. 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 cognition⁹. For example (see Figure 4.A), a mean 8.1% ($\pm 1.8\%$, SE) reduction in hippocampal volume

for MCI subjects (versus NL) can be compared to a 2.9% ($\pm 0.8\%$, SE) atrophy for surgical patients. Similar results were found for the other regions of interest (GM, LV; Figure 4, panel B and C, respectively; see caption). For GM, the mean change from NL to MCI is 3.5% ($\pm 0.8\%$, SE) versus a 1.39% (0.43%, SE) atrophy in the surgical group. For the LV volume, an enlargement of MCI versus NL of 15.9% ($\pm 8.9\%$, 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 studies¹⁷, we also calculated the mean difference of the annual percent change (95% confidence intervals; square brackets). Comparing the two atrophy rates for hippocampal volume – surgical versus non-surgical control groups – the mean difference in the annual % change was 3.7% [1.2, 6.3]; comparing annualized atrophy rates for GM volume gives a difference in annual % 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 non-surgery 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 occurred⁵. 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 hetero-modal regions can serve as diagnostic indicators. Atrophy occurs prior to 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 sensitivity²¹. 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 controls¹⁹; e.g., rostral medial temporal cortex had the largest thinning (0.4 mm; 14% versus older controls) with thinning in excess of 0.2 mm in the inferior temporal, temporal pole, inferior parietal, and superior frontal regions (8.1% to 11.6% change versus 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 progression²², 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 diagnosis⁹ predict increased risk of progression 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 framework²⁵ 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 non-trivial (20% to 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 progression¹⁶, and compared to our reported atrophy rates, atrophy for surgical patients would seem to have advanced by 1 to 2 years more than controls. From Figure 3A & 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 co-morbidity

A complication in any longitudinal study is risk of mortality/morbidity²⁶. Subjects with diagnoses ranking high on the list of co-morbidity 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 years 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 damage²⁷. 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 post surgery - 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, due to their cumulative atrophy at the time of surgery. Furthermore, MCI subjects would presumably have less cognitive reserve and compensatory factors working to stabilize cognition²⁵. 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 standpoint⁶. In some instances, the presumed impact of surgery was the impact of the precipitating illness itself²⁹. Yet various factors commonly associated with surgery (e.g. elevated peripheral blood levels of IL-6³⁰, and chronic pain³¹) 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, etc - and recuperative requirements – decreased mobility etc) might interact with atrophy by way of neural plasticity mediated effects on GM/WM density³²⁻³³. 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 post surgical 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 to 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 reserve²⁷, whereby an individual with minor cortical atrophy is spared the symptoms of cognitive impairment by a postulated cortical redundancy – presumed a function of increased education²⁵. Such redundancy is difficult to measure a priori, and comparable education by no means guarantees comparable levels of reserve.

Another possible source of inhomogeneity 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 due to 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 network³⁷. Thus GM and WM atrophy occur with complex timing²², 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 year 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 epidemiological 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 well have long term relevance. Consider, for example, a recent epidemiological study³⁸ reporting a significant increase in

mortality in patients diagnosed with POCD at 3 months, an effect not evident until approximately 2 years post surgery. POCD at even one week after surgery was statistically associated 8 years later with early exit from the labor force, and the need for social support services³⁸.

Conclusion

In our cohort of elderly subjects, those having undergone surgery experienced a more pronounced atrophy in hippocampal and GM volume than did non-surgical (control) subjects over a similar time frame (5 to 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 (unpublished results); 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 risk⁵. 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.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Inc., Merck and Co., Inc., Novartis AG, Pfizer Inc, F. Hoffman-La Roche, Schering-Plough, Synarc, Inc., as well as non-profit partners the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129, K01 AG030514, and the Dana Foundation.

Funding Sources: Dr. Alex Bekker was funded by The New York University Medical Center Alzheimer's Disease Core Center, Grant No. AG08051-19; Foundation for Perioperative Research and Education (fppe.org). Dr. Mony J. De Leon was supported by the National Institutes of Health (NIH)-National Institute on Aging Grants AG13616, AG12101, AG036502, AG035137, AG008051, AG032554, and AG022374, NIH-National Center for Research Resources Grant 1 UL1 RR029893, and grants from the Alzheimer's Association.

References

1. Silverstein JH, Timberger M, Reich DL, Uysal S. Central nervous system dysfunction after noncardiac surgery and anesthesia in the elderly. *Anesthesiology*. 2007; 106:622–8. [PubMed: 17325520]
2. Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology*. 2007; 106:572–90. [PubMed: 17325517]
3. Bekker AY, Weeks EJ. Cognitive function after anaesthesia in the elderly. *Best Pract Res Clin Anaesthesiol*. 2003; 17:259–72. [PubMed: 12817919]
4. Maze M, Todd MM. Special issue on postoperative cognitive dysfunction: selected reports from the journal-sponsored symposium. *Anesthesiology*. 2007; 106:418–20. [PubMed: 17325497]

5. Bekker A, Lee C, de Santi S, Pirraglia E, Zaslavsky A, Farber S, Haile M, de Leon MJ. Does mild cognitive impairment increase the risk of developing postoperative cognitive dysfunction? *Am J Surg.* 2010; 199:782–8. [PubMed: 20609722]
6. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS. Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. *Anesthesiology.* 2009; 111:964–70. [PubMed: 19786858]
7. Evered LA, Silbert BS, Scott DA, Maruff P, Ames D, Choong PF. Preexisting Cognitive Impairment and Mild Cognitive Impairment in Subjects Presenting for Total Hip Joint Replacement. *Anesthesiology.* 2011; 114:1297–1304. [PubMed: 21502855]
8. Devanand DP, Liu X, Tabert MH, Pradhaban G, Cuasay K, Bell K, de Leon MJ, Doty RL, Stern Y, Pelton GH. Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. *Biol Psychiatry.* 2008; 64:871–9. [PubMed: 18723162]
9. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR Jr, Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology.* 2010; 74:201–9. [PubMed: 20042704]
10. Mosconi L, Brys M, Glodzik-Sobanska L, De Santi S, Rusinek H, de Leon MJ. Early detection of Alzheimer's disease using neuroimaging. *Exp Gerontol.* 2007; 42:129–38. [PubMed: 16839732]
11. Nestor SM, Rupsingh R, Borrie M, Smith M, Accomazzi V, Wells JL, Fogarty J, Bartha R. Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. *Brain.* 2008; 131:2443–54. [PubMed: 18669512]
12. de Leon MJ, Ferris SH, Blau I, George AE, Reisberg B, Kricheff II, Gershon S. Correlations between computerised tomographic changes and behavioural deficits in senile dementia. *Lancet.* 1979; 2:859–60. [PubMed: 90961]
13. Holm S. A Simple Sequentially Rejective Multiple test procedure. *Scand J Stat.* 1979; 6:65–70.
14. Desikan RS, Fischl B, Cabral HJ, Kemper TL, Guttman CR, Blacker D, Hyman BT, Albert MS, Killiany RJ. MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD. *Neurology.* 2008; 71:819–25. [PubMed: 18672473]
15. Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD. Differential aging of the medial temporal lobe: a study of a five-year change. *Neurology.* 2004; 62:433–8. [PubMed: 14872026]
16. Rusinek H, De Santi S, Frid D, Tsui WH, Tarshish CY, Convit A, de Leon MJ. Regional brain atrophy rate predicts future cognitive decline: 6-year longitudinal MR imaging study of normal aging. *Radiology.* 2003; 229:691–6. [PubMed: 14657306]
17. Rodrigue KM, Raz N. Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. *J Neurosci.* 2004; 24:956–63. [PubMed: 14749440]
18. de Leon MJ, Convit A, Wolf OT, Tarshish CY, DeSanti S, Rusinek H, Tsui W, Kandil E, Scherer AJ, Roche A, Imossi A, Thorn E, Bobinski M, Caraos C, Lesbre P, Schlyer D, Poirier J, Reisberg B, Fowler J. Prediction of cognitive decline in normal elderly subjects with 2-[(18)F]fluoro-2-deoxy-D-glucose/poitrone-emission tomography (FDG/PET). *Proc Natl Acad Sci U S A.* 2001; 98:10966–71. [PubMed: 11526211]
19. Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, Grodstein F, Wright CI, Blacker D, Rosas HD, Sperling RA, Atri A, Growdon JH, Hyman BT, Morris JC, Fischl B, Buckner RL. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex.* 2009; 19:497–510. [PubMed: 18632739]
20. Fotenos AF, Mintun MA, Snyder AZ, Morris JC, Buckner RL. Brain volume decline in aging: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. *Arch Neurol.* 2008; 65:113–2. [PubMed: 18195148]
21. Wang X, Bauer W, Chiaia N, Dennis M, Gerken M, Hummel J, Kane J, Kenmuir C, Khuder S, Lane R, Mooney R, Bazeley P, Apkarian V, Wall J. Longitudinal MRI evaluations of human global cortical thickness over minutes to weeks. *Neurosci Lett.* 2008; 441:145–8. [PubMed: 18603368]

22. Whitwell JL, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, Petersen RC, Jack CR Jr. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain*. 2007; 130:1777–86. [PubMed: 17533169]
23. de Leon MJ, George AE, Stylopoulos LA, Smith G, Miller DC. Early marker for Alzheimer's disease: the atrophic hippocampus. *Lancet*. 1989; 2:672–3. [PubMed: 2570916]
24. Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, Rusinek H, Pelton GH, Honig LS, Mayeux R, Stern Y, Tabert MH, de Leon MJ. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. *Neurology*. 2007; 68:828–36. [PubMed: 17353470]
25. Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron*. 2004; 44:195–208. [PubMed: 15450170]
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40:373–83. [PubMed: 3558716]
27. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*. 2008; 108:18–30. [PubMed: 18156878]
28. Price CC, Garvan CW, Monk TG. Type and severity of cognitive decline in older adults after noncardiac surgery. *Anesthesiology*. 2008; 108:8–17. [PubMed: 18156877]
29. Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM. Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol*. 2008; 63:581–90. [PubMed: 18481292]
30. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. *Biol Psychiatry*. 2008; 64:484–90. [PubMed: 18514163]
31. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. *Prog Neurobiol*. 2009; 87:81–97. [PubMed: 18952143]
32. Keller TA, Just MA. Altering cortical connectivity: remediation-induced changes in the white matter of poor readers. *Neuron*. 2009; 64:624–31. [PubMed: 20005820]
33. Yasuda CL, Valise C, Saude AV, Pereira AR, Pereira FR, Ferreira Costa AL, Morita ME, Betting LE, Castellano G, Mantovani Guerreiro CA, Tedeschi H, de Oliveira E, Cendes F. Dynamic changes in white and gray matter volume are associated with outcome of surgical treatment in temporal lobe epilepsy. *NeuroImage*. 2010; 49:71–9. [PubMed: 19683060]
34. Whitwell JL, Jack CR Jr, Parisi JE, Knopman DS, Boeve BF, Petersen RC, Ferman TJ, Dickson DW, Josephs KA. Rates of cerebral atrophy differ in different degenerative pathologies. *Brain*. 2007; 130:1148–58. [PubMed: 17347250]
35. Villain N, Desgranges B, Viader F, de la Sayette V, Mezenge F, Landeau B, Baron JC, Eustache F, Chetelat G. Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. *J Neurosci*. 2008; 28:6174–81. [PubMed: 18550759]
36. Villain N, Fouquet M, Baron JC, Mezenge F, Landeau B, de La Sayette V, Viader F, Eustache F, Desgranges B, Chetelat G. Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. *Brain*. 2010; 133:3301–14. [PubMed: 20688814]
37. Zhang D, Raichle ME. Disease and the brain's dark energy. *Nat Rev Neurol*. 2010; 6:15–28. [PubMed: 20057496]
38. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology*. 2009; 110:548–55. [PubMed: 19225398]

Figure 1. Baseline comparisons for region of interest volumes

The mean baseline volume ratios are shown for control (open bars) and surgery subjects (filled bars). The top panel displays gray matter and white matter (vertical axis) as a proportion of intracranial volume (ICV). Error bars show 95% confidence intervals of the mean. The bottom panel is the same display for lateral ventricle and hippocampus. Note the difference in volumes as indicated by axis scale and bar size.

Figure 2. Lateral Ventricle volume changes in a surgical patient

Sample cortical magnetic resonance image pairs (baseline, 1st follow up) show lateral ventricle enlargement subsequent to surgery for a mild cognitive impairment (MCI) patient. The % volume change for this particular subject from the pre to post surgical interval was 7.13% (about 33% greater than the average post surgery change). White arrow indicates lateral ventricle. Black arrow indicates hippocampus.

Figure 3.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 2 time points (horizontal axis) which include: baseline and 1st follow up. The solid lines are the control subjects and the dashed lines are the surgical subjects. NL (normal) and MCI (mild cognitive impairment) subjects are plotted separately. These plots illustrate that NL and MCI subjects have the same atrophy rate, even though MCI subjects have a lower baseline atrophy level.

Figure 3.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 2 time points (horizontal axis) including: baseline and 1st follow up. The solid lines are the control subjects and the dashed lines are the surgical subjects. Normal (NL) subjects and subjects with mild cognitive impairment (MCI) are plotted separately. Only the MCI surgical subjects show a worsening performance versus the non-surgical controls.

Figure 4. A, B & C – 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. **[Fig. 4.A]** Setting the normal Hippocampal volume mean (top panel) equal to 100, Hippocampal volume measures for MCI subjects averaged 91.94 % ($\pm 1.82\%$ SE; n=62) of normal ($100\% \pm 1.30\%$ SE; n=68) at baseline; and MCI-AD subjects were 77.68 % ($\pm 2.27\%$ SE, n=34) of normal at baseline. MCI-AD subjects are MCI subjects who transitioned to AD 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 % ($\pm 0.82\%$; n=41) of the average normal Hippocampal volume. The background atrophy (non-surgical control patients) was 0.73% ($\pm 0.32\%$; n=123). **[Fig. 4.B]** For the gray matter (GM) volume (middle panel) an atrophy versus normal (NL; $100 \pm 0.95\%$) was seen of $3.52 \pm 0.82\%$ and $5.2 \pm 1.03\%$ from NL to MCI and NL to MCI-AD respectively. The percent change for the first interval for surgery subjects was $1.39 \pm 0.43\%$ and for non-surgical controls $0.25 \pm 0.25\%$. **[Fig. 4.C]** For the LV volume (bottom panel) an expansion versus NL ($100 \pm 6.83\%$) was seen of $15.87 \pm 8.91\%$ and $28.54 \pm 9.28\%$ from NL to MCI and NL to MCI AD respectively. The percent change for the first interval for surgery subjects was $5.33 \pm 0.85\%$ and for non-surgical controls $2.93 \pm 0.41\%$.

Table 1

Demographics and baseline statistics for surgical and non surgical groups

	No Surgery	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 (mm ³)	1,544,316 ± 151,998	1,565,403 ± 154,102
% Female	49%	49%
% ApoE4+	48%	49%
%(n) NL	41% (51)	41% (17)

Values are mean ± SD or %.

* indicates a significant difference ($p < .05$); found only for “months to follow up”. ApoE4+ implies a positive ApoE4 status, a risk factor for Alzheimer's disease. Units for intracranial volume (ICV) are cubic millimeters (mm³). NL - normal.