ALZHEIMER’S-RELATED CORTICAL ATROPHY IS ASSOCIATED WITH POSTOPERATIVE DELIRIUM SEVERITY IN PERSONS WITHOUT DEMENTIA

Abbreviated title: Preclinical AD Cortical Thickness and Delirium

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DCA receives post-market institutional royalties for MRI inventions unrelated to the techniques used in this report. All other authors report no conflicts of interest.
ABSTRACT

Patients with dementia due to Alzheimer’s disease (AD) have increased risk of developing delirium. This study investigated the relationship between a magnetic resonance imaging (MRI)-derived biomarker for preclinical AD and postoperative delirium. Participants were older adults (≥70 years) without dementia who underwent preoperative MRI and elective surgery. Delirium incidence and severity were evaluated daily during hospitalization. Cortical thickness was averaged across a published set of a priori brain regions to derive a measure known as the “AD signature.” Logistic and linear regression was used, respectively, to test whether the AD signature was associated with delirium incidence in the entire sample (N=145) or with the severity of delirium among those who developed delirium (N=32). Thinner cortex in the AD signature did not predict incidence of delirium (odds ratio=1.16, p=.36), but was associated with greater delirium severity among those who developed delirium (b=-1.2, p=.02). These results suggest that thinner cortices, perhaps reflecting underlying neurodegeneration due to preclinical AD, may serve as a vulnerability factor that increases severity once delirium occurs.

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Keywords: delirium, cortical thickness, Alzheimer’s disease, biomarker, neurodegeneration, atrophy, preclinical Alzheimer’s disease, delirium severity
**Abbreviations:**

Aβ = beta-amyloid

AD = Alzheimer’s disease

ADL = activities of daily living

CAM = Confusion Assessment Method

CAM-S = Confusion Assessment-Severity

CSF = cerebrospinal fluid

GCP = General Cognitive Performance

IADL = instrumental activities of daily living

IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly

NIA-AA = National Institute of Aging/Alzheimer’s Association

OR = odds ratio

MCI = mild cognitive impairment; aMRI = amnestic mild cognitive impairment

MRI = magnetic resonance imaging

ROI = regions of interest

SAGES = Successful AGing after Elective Surgery

VIF = variance inflation factor
1. INTRODUCTION

Delirium is a well-characterized clinical disorder of attention and cognition, but its pathophysiology is not well understood. Although cognition and dementia are consistently identified as the leading risk factors for delirium (Fong et al., 2015; Jones et al., 2016) mechanisms contributing to this increased risk remain unclear. Alzheimer’s disease (AD), the most common cause of dementia, occurs as a continuum or trajectory of pathophysiological processes and clinical symptomatology, beginning up to two decades or more before clinical symptoms appear (Dubois et al., 2016). Preclinical AD refers to the stage of the AD trajectory that is characterized by accumulating AD-related pathological changes with only subtle, if any, cognitive changes (Dubois et al., 2016). Although compelling work has identified dementia as a major risk factor for delirium (Fong et al., 2015), considerably less is known about the relationship between delirium and preclinical AD. Given that preclinical AD represents an important window for potential interventions to slow or stop progression to dementia (Dubois et al., 2016), it is important to determine whether AD is a risk factor for delirium, not only at the dementia stage but also during the preclinical timeframe. Furthermore, a better understanding of the relationship between delirium and specific features of preclinical AD could improve our pathophysiological understanding of delirium and suggest a biological mechanism for the association between dementia and delirium.

The primary pathological features of AD are beta-amyloid (Aβ) plaques, neurofibrillary tangles, and neurodegeneration (Jack et al., 2016; Jack et al., 2013). In individuals without dementia, some studies have reported an association between cerebrospinal fluid (CSF) or plasma levels of Aβ and tau and delirium (Idland et al., 2016; van den Boogaard et al., 2011; Xie et al., 2014) while others have not (Witlox et al., 2011). Similarly, some magnetic resonance imaging (MRI) studies of regional brain volume and delirium have identified an association (Gunther et al., 2012; Shioiri et al., 2016) while others have not (Cavallari et al., 2015; Root et al., 2013). To date, brain volume studies in delirium research have used mostly exploratory methods rather than a priori-defined region-of-interest measures of brain regions vulnerable to AD pathology, making inferences about the connection to AD difficult or impossible.
We have previously shown that reduction of regional cortical thickness in a specific set of brain regions of interest (ROIs)—the “AD signature”—is a clinically and biologically valid measure in the prodromal and preclinical stages of AD that is associated with cognitive decline and progression to dementia (Bakkour et al., 2009; Bakkour et al., 2013; Dickerson et al., 2009; Dickerson et al., 2011a; Dickerson et al., 2011b, 2012, 2013; Putcha et al., 2011). Furthermore, AD signature cortical thickness has previously been shown to be a better predictor of progression from mild cognitive impairment (MCI) to AD compared to entorhinal (Bakkour et al., 2009) or hippocampal volume (Dickerson et al., 2013) and is closely associated with AD-like CSF characteristics (Dickerson et al., 2012). However, the AD signature has not yet been investigated as a predictor of delirium incidence or severity.

In this study, we address this gap in scientific understanding by examining the AD signature preoperatively in a group of older adults who underwent elective non-cardiac surgery and who were assessed daily for post-operative delirium. We hypothesized that individuals exhibiting evidence of preclinical AD (reduced cortical thickness in the AD signature regions) prior to surgery would be at greatest risk of delirium and that among those with delirium, thinner cortices in the AD signature would be associated with worse delirium severity.

2. METHODS

2.1. Study sample

The Successful AGing after Elective Surgery (SAGES) study is an ongoing prospective cohort study (enrollment from June 2010 and August 2013) of 560 adults aged 70 years or older who underwent elective major non-cardiac surgery and who did not have dementia at baseline. Approximately one third of SAGES participants were recruited to undergo MRI one month before surgery. The neuroimaging subset did not differ from the rest of the SAGES cohort on various relevant characteristics including age, sex, education, and surgery type. Details of the SAGES study including inclusion and exclusion criteria have been described previously (Cavallari et al., 2016; Schmitt et al., 2012). Briefly, subjects were recruited through regular review of operating room schedules for eligible elective surgeries. Inclusion
criteria included age ≥70 years old, English speaking, and undergoing elective surgery at Beth Israel Deaconess Medical Center (BIDMC) or Brigham and Women’s Hospital (BWH). Exclusion criteria included diagnosis of dementia as assessed by initial medical record screening or reported by the patient; cognitive impairment as defined by a score ≤69 or its education-adjusted equivalent on the Modified Mini-Mental State Examination during the baseline interview or by neuropsychological testing; terminal disease; total blindness; severe deafness; and alcohol intake >5 drinks per day (men) or >4 drinks per day (women). Additional exclusion criteria for MRI included contraindications to 3-T MRI, such as pacemakers, certain stents, and implants. Written informed consent was obtained from all participants according to procedures approved by the institutional review boards of BIDMC and BWH, the two study hospitals, and Hebrew SeniorLife, the study coordinating center, all located in Boston, Massachusetts.

2.2. Neuroimaging protocol

For this study, all participants who had undergone MRI scans prior to surgery (N=145, n=32 with delirium) were included. We analyzed the magnetization-prepared fast gradient-echo 3D anatomical T1-weighted imaging (TR 7.9 ms, TE 3.2 ms, 15° flip angle, 32 kHz bandwidth, coronal acquisition plane with 24×19 cm field of view, 0.94 mm in-plane resolution, 1.4 mm slices, preparation time of 1100 ms with repeated saturation at the beginning of the saturation period, and an adiabatic inversion pulse 500ms before imaging), collected at the BIDMC Radiology Department on a 3T HDxt MRI (General Electric Medical Systems) scanner using a standard 8-channel head coil (Cavallari et al., 2015).

2.2.1. Cortical atrophy signatures

T1 image volumes were examined quantitatively by a cortical surface-based reconstruction and analysis of cortical thickness, using a hypothesis-driven approach as described in multiple previous publications (Bakkour et al., 2009; Dickerson et al., 2009; Dickerson et al., 2011b, 2013). Briefly, we utilized nine ROIs (Figure 1) previously determined to be associated with AD, i.e. the cortical “AD signature” (Bakkour et al., 2009; Dickerson et al., 2009). The bilateral ROIs include: medial temporal
cortex, inferior temporal gyrus, temporal pole, angular gyrus, superior frontal gyrus, superior parietal lobe, supramarginal gyrus, precuneus, and middle frontal gyrus. The AD-signature, a continuous measure of the average thickness of all nine ROIs, was used as the primary diagnostic biomarker.

Following standard procedure, selected coronal slices of each automated segmentation were visually inspected, and scans with errors in processing of the structures of interest were identified. The distribution of the quantitative volumetric data and a review of scans at either tail of the distribution and outliers were examined in greater detail. In the present analysis, no scans were identified with important errors of reconstruction of cortical surfaces.

2.3. Assessment of delirium and preoperative cognitive function

Delirium incidence and severity were assessed using a structured battery on each postoperative day. Cognitive function was assessed at baseline prior to surgery.

2.3.1. Delirium Incidence

Delirium incidence was diagnosed using the Confusion Assessment Method (CAM) (Wei et al., 2008) diagnostic algorithm, supplemented with a validated chart review method (Inouye et al., 2005) to detect delirium presence or absence for each patient. The CAM was rated based on information from patient interviews including a brief cognitive screen (orientation, short-term recall, sustained attention), the Delirium Symptom Interview (Albert et al., 1992), and information related to acute changes in mental status noted by nurses or family members (Schmitt et al., 2015). Study interviewers underwent intensive training and standardization (Inouye, 2003). The CAM has high sensitivity (94%) and specificity (89%) for delirium and moderate to high interrater reliability (kappa 0.7–1.0) across studies. The chart-based delirium instrument has a sensitivity of 74% and specificity of 83% (Inouye et al., 2005). The CAM plus chart combined approach is the preferred method for detecting delirium since it maximizes sensitivity; while the CAM detects the majority of delirium cases, the additional chart review increases sensitivity by
identifying delirium throughout the 24-hour period (Saczynski et al., 2014).

2.3.2. **Delirium severity**

Delirium severity was determined using the CAM-Severity (CAM-S) long form, which is based on the 10 features from the full CAM instrument to quantify the intensity of delirium features (Inouye et al., 2014a). CAM-S demonstrates strong psychometric properties and strong associations with important clinical outcomes (Inouye et al., 2014a). When interrater reliability for CAM-S long form in the SAGES data was evaluated in 73 pairs, the overall agreement was 97% and intraclass correlation coefficient was 0.88 (Inouye et al., 2014a). Scores on the CAM-S long form range from 0 to 19, with higher scores indicating more severe delirium. CAM-S was evaluated for each patient by assessing the peak CAM-S value, the highest single CAM-S rating observed during hospitalization (Vasunilashorn et al., 2016).

2.3.3. **Cognitive function**

Cognitive abilities were assessed at baseline using a standardized neuropsychological battery including 11 tests covering cognitive domains of attention, memory, language, and executive functioning. Baseline cognitive function was assessed in two ways. First, an age-adjusted neuropsychological test battery composite measure, General Cognitive Performance (GCP), was calculated as described in previously (Inouye et al., 2016; Jones et al., 2010). GCP is a continuous measure calibrated on a T-score metric (mean of 50; standard deviation [SD] of 10) to a nationally representative sample of adults aged ≥70 years (Gross et al., 2014; Langa et al., 2005). For all participants who scored 1.5 SDs below population means on two or more neuropsychological tests (one of which tested memory), or who scored > 2 SDs below the population mean on a measure of memory were identified for review by a consensus panel of seven experienced clinical experts. Patients were assigned as having amnestic MCI (aMCI) using National Institute of Aging/Alzheimer’s Association (NIA-AA) criteria (Albert et al., 2011), following review of demographic data, neuropsychological testing results, Informant Questionnaire on Cognitive
Decline in the Elderly (IQCODE) short-form (Jorm, 1994), activities of daily living (ADL) scores, and instrumental activities of daily living (IADL) scores.

2.4. Covariate data

Participant age and sex were obtained by interview. Vascular comorbidity was defined as presence or absence of at least one of the following pathological conditions: confirmed or history of myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes (with or without end organ damage), cerebrovascular disease (carotid stenosis, history of stroke or transient ischemic attack), or hemiplegia.

2.5. Statistical Models

Differences between the delirious and non-delirious groups were analyzed using t-test and chi-square tests for continuous and dichotomous variables, respectively. For the main hypotheses, covariate-adjusted associations were estimated using multiple regression models. Type-I error probability ($\alpha$) was set at 0.05. All analyses were performed in Stata MP 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Covariates for all models included age at surgery, sex, and presence of a vascular comorbidity. Covariates were selected to adjust for important baseline influences while avoiding over-controlling for variables that might be intermediaries between delirium and AD (Schisterman et al., 2009). Multiple logistic regression was used to assess the association between the AD signature and delirium incidence, and multiple linear regression was used to assess associations between the AD signature and CAM-S peak. The AD signature was scaled by a factor of 10 so that the resultant odds ratio (OR) and regression coefficient (b) indicate, respectively, the odds of developing delirium or the change in CAM-S peak score associated with a 0.10 mm (slightly less than 1.5 SD) increase in AD signature cortical thickness. Because it is possible that subtle cognitive changes due to preclinical AD—rather than delirium—could increase scores on the CAM-S (e.g. mild memory impairment), latter analyses were restricted to those 32 individuals exhibiting incident delirium. We
examined two measures of multicollinearity, variance inflation factor (VIF) and tolerance, which were
deemed acceptable if VIF was less than 10 and tolerance was greater than 0.1.

2.5.1. Additional Sensitivity and Exploratory Analyses

Further analyses were performed to establish the robustness or to facilitate interpretation of
statistically significant associations as follows. First, analyses of CAM-S peak were replicated using the
CAM-S summed score (sum of all CAM-S ratings across all hospital days), which increases not only with
severity of delirium, but also with longer duration of delirium (Vasunilashorn et al., 2016). Second,
because CAM-S is positively skewed, the primary linear regression model was replicated using Poisson
regression. Third, to investigate whether a particular ROI was driving the effect for the association
between the AD signature and delirium, separate regression models for each of the 9 ROIs (average of left
and right) that comprise the AD signature were performed. Last, the association of AD signature with
delirium outcomes was examined after accounting for a strong predictor of delirium, preoperative
cognitive function measured by the GCP score (Jones et al., 2016). Similarly, because it is expected that
the AD signature would be more extreme in aMCI compared to the earliest stages of preclinical AD,
another analysis controlling for aMCI status at baseline was conducted to investigate whether observed
relationships were driven by extreme phenotypes (i.e. aMCI).

3. RESULTS

3.1. Sample Characteristics

Participants’ demographic, cognitive, and clinical characteristics are described in Table 1. Thirty-
two participants (22%) developed delirium. Nine participants (6%) had aMCI at baseline prior to surgery.
The delirium group had greater rates of aMCI at baseline (16% compared to 4%) and, similarly, had
lower GCP scores by about 4 points on average. As expected, the delirium group had significantly higher
scores on CAM-S peak and CAM-S sum (8 and 20 points higher on average, respectively).
Table 1. Sample characteristics of SAGES neuroimaging sub-cohort

<table>
<thead>
<tr>
<th>Sample characteristic</th>
<th>SAGES MRI (N=145)</th>
<th>No Delirium (N=113)</th>
<th>Delirium (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean±SD)</td>
<td>76 ± 4.5</td>
<td>76±4.6</td>
<td>77±4.3</td>
</tr>
<tr>
<td>Female sex (n, %)</td>
<td>87, 60%</td>
<td>65, 58%</td>
<td>22, 69%</td>
</tr>
<tr>
<td>Non-white race (n, %)</td>
<td>12, 8%</td>
<td>10, 9%</td>
<td>2, 6%</td>
</tr>
<tr>
<td>Education (years, mean±SD)</td>
<td>15 ± 2.8</td>
<td>15±2.8</td>
<td>14±2.7</td>
</tr>
<tr>
<td>GCP score (mean±SD)</td>
<td>59 ± 7.1</td>
<td>60±6.7</td>
<td>55±7.4</td>
</tr>
<tr>
<td>aMCI diagnosis at baseline (n, %)</td>
<td>9, 6%</td>
<td>4, 4%</td>
<td>5, 16%</td>
</tr>
<tr>
<td>Vascular comorbidity (n, %)*</td>
<td>57, 39%</td>
<td>44, 39%</td>
<td>13, 41%</td>
</tr>
<tr>
<td>Charlson comorbidity index (mean±SD)</td>
<td>0.9±1.0</td>
<td>0.8±1.0</td>
<td>1.0±1.2</td>
</tr>
<tr>
<td>Surgery type (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedic</td>
<td>119, 82%</td>
<td>91, 81%</td>
<td>28, 88%</td>
</tr>
<tr>
<td>Vascular</td>
<td>8, 6%</td>
<td>7, 6%</td>
<td>1, 3%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18, 12%</td>
<td>15, 13%</td>
<td>3, 9%</td>
</tr>
<tr>
<td>CAM-S peak</td>
<td>4±3.2</td>
<td>2±1.6</td>
<td>8±3.8</td>
</tr>
<tr>
<td>CAM-S sum</td>
<td>8±10.5</td>
<td>5±3.9</td>
<td>20±16.3</td>
</tr>
<tr>
<td>AD signature (mm, mean±SD)</td>
<td>2.42±0.131</td>
<td>2.42±0.126</td>
<td>2.44±0.146</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>2.23±0.223</td>
<td>2.22±0.221</td>
<td>2.28±0.229</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>2.27±0.156</td>
<td>2.27±0.154</td>
<td>2.27±0.163</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>2.49±0.287</td>
<td>2.49±0.287</td>
<td>2.50±0.290</td>
</tr>
<tr>
<td>Medial temporal</td>
<td>2.58±0.343</td>
<td>2.57±0.336</td>
<td>2.62±0.367</td>
</tr>
<tr>
<td>Precuneus</td>
<td>2.43±0.191</td>
<td>2.42±0.186</td>
<td>2.46±0.210</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>2.66±0.213</td>
<td>2.66±0.209</td>
<td>2.67±0.231</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>2.45±0.200</td>
<td>2.45±0.196</td>
<td>2.45±0.217</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>1.94±0.168</td>
<td>1.92±0.169</td>
<td>2.00±0.149</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>2.76±0.244</td>
<td>2.77±0.227</td>
<td>2.72±0.298</td>
</tr>
</tbody>
</table>

SAGES=Successful Aging after Elective Surgery. MRI=magnetic resonance imaging; GCP=General Cognitive Performance; aMCI=amnestic Mild Cognitive Impairment; CAM-S= Confusion Assessment Method Severity score (peak=largest single CAM-S rating observed during hospitalization [possible range 0-19]; sum=summed value of CAM-S across all hospitalization days); AD signature=average cortical thickness (mm) in 9 bilateral cortical regions of interest.

*Vascular comorbidity is a dichotomous variable defined as presence or absence of at least one of the following pathological conditions: confirmed or history of myocardial infarction, congestive heart failure, peripheral vascular disease, diabetes (with or without end organ damage), cerebrovascular disease (carotid stenosis, history of stroke or transient ischaemic attack), or hemiplegia.
3.2. AD Signature and Delirium Incidence

AD signature cortical thickness did not predict incidence of delirium (OR=1.16, 95% C.I. [0.85, 1.6]; Table 2 and Figure 2).

Table 2. Association between the AD signature and delirium incidence (CAM-S)

<table>
<thead>
<tr>
<th>Model covariates</th>
<th>Odds Ratio (SE)</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.03 (0.05)</td>
<td>0.95, 1.13</td>
<td>0.40</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.57 (0.69)</td>
<td>0.67, 3.70</td>
<td>0.30</td>
</tr>
<tr>
<td>Vascular comorbidity present</td>
<td>1.19 (0.50)</td>
<td>0.52, 2.70</td>
<td>0.68</td>
</tr>
<tr>
<td>AD signature (mm)</td>
<td>1.16 (0.19)</td>
<td>0.85, 1.59</td>
<td>0.36</td>
</tr>
</tbody>
</table>

C.I.=Confidence Interval; AD signature=average cortical thickness (mm) in 9 bilateral cortical regions of interest; CAM-S= Confusion Assessment Method.

3.3. AD Signature and Delirium Severity

Among those who developed delirium, thinner cortex in the AD signature was associated with greater delirium severity, measured by CAM-S peak (b=-1.2, 95% C.I. [-2.2, -0.2]; Table 3A, Figure 3).

Table 3. Association between the AD signature and delirium severity (CAM-S peak or CAM-S sum) in the delirium group only (N=32)

<table>
<thead>
<tr>
<th>Model covariates</th>
<th>Regression Coefficient (SE)</th>
<th>95% C.I.</th>
<th>p-value</th>
<th>R²</th>
<th>R² change*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) CAM-S Peak</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.03 (0.2)</td>
<td>-0.36, 0.30</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Sex</td>
<td>0.42 (1.4)</td>
<td>-2.48, 3.32</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular comorbidity present</td>
<td>0.19 (1.4)</td>
<td>-2.58, 2.96</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AD signature</strong></td>
<td>-1.2 (0.5)</td>
<td>-2.20, -0.18</td>
<td>0.02</td>
<td>0.21</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>B) CAM-S Sum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.03 (0.7)</td>
<td>-1.32, 1.37</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Sex</td>
<td>-2.3 (5.8)</td>
<td>-14.15, 9.47</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular comorbidity present</td>
<td>1.2 (5.5)</td>
<td>-10.07, 12.48</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AD signature</strong></td>
<td>-5.8 (2.0)</td>
<td>-9.60, -1.73</td>
<td>0.007</td>
<td>0.31</td>
<td>0.22</td>
</tr>
</tbody>
</table>

On average, a 1/10 mm reduction in AD signature cortical thickness is associated with an increase of 1.2 points on the CAM-S peak score and an increase of 5.8 points on the CAM-S summed score.

C.I.=Confidence Interval; AD signature=average cortical thickness (mm) in 9 bilateral cortical regions of interest; CAM-S= Confusion Assessment Method Severity score (peak=largest single CAM-S rating observed during hospitalization [possible range 0-19]; sum=summed value of CAM-S across all hospitalization days). *R² change refers to the change in R² after the AD signature was added to the covariates-only model (only age, sex, and vascular comorbidity as independent variables).
3.4. Additional Sensitivity and Exploratory Analyses

The AD signature was significantly associated with CAM-S sum (Table 3B). Results from the Poisson regression were consistent with the primary model using linear regression (CAM-S peak incidence rate ratio=0.87, 95% C.I. [0.78, 0.97]).

The individual ROIs comprising the AD signature were associated with a similar pattern observed for the entire AD signature: thinner cortex in the ROIs was associated with greater delirium severity (Table 4). However, only the superior frontal gyrus demonstrated a statistically significant effect (Figure 4).

Table 4. Association between the individual ROIs comprising the AD signature and CAM-S peak in the delirium group only (N=32)

<table>
<thead>
<tr>
<th>AD signature ROI</th>
<th>Regression Coefficient (SE)</th>
<th>95% C.I.</th>
<th>T</th>
<th>p-value</th>
<th>R²</th>
<th>R² change*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angular gyrus</td>
<td>-0.6 (0.3)</td>
<td>-1.3, 0.11</td>
<td>-1.7</td>
<td>0.09</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>-0.5 (0.5)</td>
<td>-1.4, 0.5</td>
<td>-1.1</td>
<td>0.30</td>
<td>0.07</td>
<td>0.04</td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>-0.3 (0.3)</td>
<td>-0.8, 0.2</td>
<td>-1.2</td>
<td>0.23</td>
<td>0.09</td>
<td>0.05</td>
</tr>
<tr>
<td>Medial temporal</td>
<td>-0.3 (0.2)</td>
<td>-0.7, 0.14</td>
<td>-1.3</td>
<td>0.19</td>
<td>0.10</td>
<td>0.06</td>
</tr>
<tr>
<td>Precuneus</td>
<td>-0.4 (0.3)</td>
<td>-1.2, 0.3</td>
<td>-1.3</td>
<td>0.21</td>
<td>0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>-0.6 (0.3)</td>
<td>-1.2, -0.41</td>
<td>-2.2</td>
<td>0.04</td>
<td>0.18</td>
<td>0.15</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>-0.5 (0.3)</td>
<td>-1.2, 0.2</td>
<td>-1.6</td>
<td>0.12</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>-0.8 (0.5)</td>
<td>-1.8, 0.3</td>
<td>-1.5</td>
<td>0.14</td>
<td>0.11</td>
<td>0.08</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>-0.1 (0.3)</td>
<td>-6.2, 4.1</td>
<td>-0.42</td>
<td>0.68</td>
<td>0.04</td>
<td>0.01</td>
</tr>
</tbody>
</table>

On average, a 1/10 mm reduction in the cortical thickness of the individual ROIs comprising the AD signature is associated with an increase of 0.1 to 0.8 points on the CAM-S peak score. AD=Alzheimer’s disease; ROI=Region of Interest; SD=standard deviation; SE=standard error; C.I.=Confidence Interval. *R² change refers to the change in R² after the AD signature was added to the covariates-only model (only age, sex, and vascular comorbidity as independent variables), and vascular comorbidity as independent variables).

After controlling for preoperative cognitive function (measured by GCP), one of the strongest predictors of delirium, the AD signature was still significantly associated with delirium severity as measured by the CAM-S peak (b=-1.04, 95% C.I. [1.95, -0.14]). As expected, GCP was a significant predictor of delirium severity (b=-0.26, 95% C.I. [-0.45, -0.08]). When GCP or the AD signature were added to the baseline model (covariates of age, sex, and vascular comorbidity), GCP explained an additional 24% variance (R² change=0.24) and the AD signature explained an additional 17% variance.
(R² change=0.17). GCP and the AD signature were only mildly correlated in the SAGES MRI total sample (Pearson’s correlation 0.12, p=.14) and were moderately (albeit not statistically significantly) correlated in the delirium subsample (Pearson’s correlation 0.29, p=.11). After controlling for aMCI, the AD signature was still significantly associated with CAM-S peak (b=-1.17, 95% C.I. [-2.21, -0.12]).

4. DISCUSSION

With the maturation of imaging and fluid biomarkers, the study of AD has undergone a critical paradigm shift by including the preclinical phase. This has important implications for the study of delirium. While dementia is a known risk factor for delirium, a greater understanding of why and how dementia incurs this risk, and when risk begins, is needed. We found that in a sample of patients without dementia that a well-validated biomarker of AD-related neurodegeneration—the AD signature of cortical atrophy—did not predict who would develop postoperative delirium, but did predict delirium severity among those who developed delirium. This suggests that preclinical AD serves as a vulnerability factor that increases severity once delirium is incited by noxious precipitants. These results provide support for the use of preclinical AD biomarkers, like the AD signature, in delirium research and suggest that one contributor to delirium severity is pre-existing neurodegeneration from preclinical AD.

Prior studies have found that MCI is associated with greater risk of delirium incidence and severity (Kazmierski et al., 2014; Oldham et al., 2015). Our study showed that the AD signature was not associated with delirium incidence but was associated with delirium severity even after controlling for aMCI, suggesting that a relationship between AD and delirium begins prior to MCI. That the association of delirium severity and the AD signature persisted even after accounting for one of the strongest predictors of delirium, baseline cognitive performance, suggests this is a relatively robust effect and that the AD signature is not just a surrogate measure of cognitive performance. This supports the notion that a relationship between delirium and AD begins in the preclinical stage of AD, and that the association is at least in part related to AD-related cortical atrophy.
When the AD signature was broken down into regional subcomponents, the superior frontal gyrus showed the strongest effect. Similarly, Gunther et al. (2012) found that volume loss in this region was associated with longer duration of delirium. The AD signature accounted for more variance than the superior frontal gyrus alone (17% compared to 15%) suggesting that while atrophy in this frontal lobe region contributes the greatest vulnerability to delirium severity of the 9 ROIs, the AD signature is still a better predictor of delirium severity.

Neuroimaging studies of delirium have been mixed and investigations of underlying brain vulnerabilities are ongoing (Cavallari et al., 2016; Cavallari et al., 2015; Gunther et al., 2012; Root et al., 2013; Shioiri et al., 2016). This literature is likely mixed in part because of the heterogeneous nature of delirium and the variety of imaging analysis methods used. For instance, previous work from our group has shown that diffusion imaging biomarkers are associated with delirium incidence and severity (Cavallari et al., 2016) but brain volumes are not (Cavallari et al., 2015). In this study we examined an MRI measure that is relatively specific for AD-related neurodegeneration. Unlike other neuroimaging measures, such as voxel-based morphometry techniques, cortical thickness used in the AD signature has adequate resolution for interpretation at the individual subject level and is highly reliable within scanner systems and across manufacturers and field strengths (Dickerson et al., 2008). These features make it a reliable measure of atrophy, which could translate to potential clinical applications in individual patients, and may also explain why cortical thickness, but not brain volumes, were associated with delirium severity in this cohort. Moreover, the temporal dynamics of biomarker changes during the course of AD are still being investigated; it is possible that white matter degeneration, cortical thinning, and volumetric atrophy occur in a progressive manner and/or that different degrees of abnormality are needed to detect an association with delirium outcomes. Processes unrelated to AD might contribute to white matter abnormalities or other changes in brain structure and function, thus explaining some of the variability in the observed associations between different neuroimaging biomarkers and delirium. Future work is needed to better understand how AD pathology may interact with co-occurring pathology and to identify specific types of neurological stressors that together may contribute to delirium incidence and/or severity.
Indeed, a combination of biomarkers will likely be most effective in predicting delirium incidence and severity, and its long-term sequelae.

Delirium affects as many as 50% of hospitalized seniors and is preventable in 30-40% of cases through targeted interventions that are feasible and cost-effective (Inouye et al., 2014b). Biomarkers for delirium severity could help to identify individuals at greatest risk of developing severe cases of delirium in order to enroll them in established therapeutic preventive interventions. This study suggests that biomarkers sensitive to preclinical AD pathology could be beneficial in this effort. It will be important to conduct future studies to determine whether delirium interventions are equally effective (or perhaps more effective) in individuals harboring MCI or preclinical AD.

4.1. Limitations

The primary limitation of this study is sample size. However, we performed sensitivity and exploratory analyses to test the robustness of our results and showed that, despite a small sample size, the association between the AD signature and delirium severity in those who experienced delirium remained when using another measure of delirium severity (CAM-S sum), using nonlinear regression models, and after controlling for baseline cognitive performance or aMCI. In this sample, the presence of aMCI was small (n=9), potentially contributing to the lack of association with delirium incidence; future studies using the AD signature in patients with MCI and delirium is an important extension of this work. A second limitation is that the sample was well-educated and mostly white, so may not be generalizable to more socioeconomic and racially diverse groups. Greater than average cognitive reserve, which can occur in all persons regardless of whether or not they have preclinical AD, may further explain why an association was not observed with delirium incidence. A third limitation of this study was that protein biomarkers of AD-specific pathology (e.g. CSF Aβ and tau) were not available. While the AD signature is a well-established and robust imaging biomarker of neurodegeneration in AD, it may be that other AD biomarkers (e.g., CSF or PET measures of tau or Aβ) need to be measured to obtain a complete perspective on the relationship between delirium and preclinical AD. CSF or PET was not collected as
part of the SAGES study so this was not possible to examine directly. However, the AD signature is strongly correlated with CSF AD biomarkers (Dickerson et al., 2012, 2013), so it is likely the effects of underlying pathology were at least partly accounted for in the present analyses.

4.2. Conclusions

Biomarkers for severity of delirium are important to advance the field. Given that considerable evidence suggests that delirium and AD dementia are related, it is possible that AD biomarkers, even in the absence of dementia, may also be useful biomarkers for predicting greater severity of delirium. This study suggests that cortical atrophy related to AD increases brain vulnerability (decreased reserve/resilience) in the face of delirium, resulting in increased delirium severity. Greater delirium severity may be evidence of underlying brain pathology related to AD. Future studies with larger sample sizes are needed to confirm the present results and to correlate these results with other preclinical AD biomarkers.
5. **ACKNOWLEDGMENTS**

The authors gratefully acknowledge the contributions of the patients, family members, nurses, physicians, staff members, and members of the Executive Committee who participated in the Successful Aging after Elective Surgery (SAGES) Study.

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6. **DISCLOSURES**

DCA receives post-market institutional royalties for MRI inventions unrelated to the techniques used in this report. All other authors report no conflicts of interest.
7. REFERENCES


thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex 19(3), 497-510.


8. FIGURE LEGENDS

**Figure 1.** Brain regions comprising the AD signature: (A, yellow) medial temporal cortex, (B, light blue) inferior temporal gyrus, (C, red) temporal pole, (D, purple) angular gyrus, (E, green) superior frontal gyrus, (F, orange) superior parietal lobule, (G, chartreuse) supramarginal gyrus, (H, aqua) precuneus, (I, dark blue) inferior frontal sulcus.

**Figure 2.** Probability of developing postoperative delirium as a fractional polynomial function of the AD signature (solid black line) with 95% confidence bands (grey shaded area). Black dots are the raw AD signature values for those with (top) and without (bottom) delirium. C-statistic=.61. AD signature=average cortical thickness (mm) in 9 bilateral cortical regions of interest.

**Figure 3.** Partial regression plot of AD signature by delirium severity measured by CAM-S peak (for the delirium group only, N=32). The Y-axis represents residuals from regressing CAM-S peak against all the independent variables (age, sex, vascular comorbidity) except the AD signature. The X-axis represents the residuals from regressing the AD signature against all other independent variables (age, sex, and vascular comorbidity). 95% confidence intervals are displayed in gray. Scatter plots of raw values are also available in the supplementary material (Supplementary Figure A.1).

**Figure 4.** Scatter plot of cortical thickness of the superior frontal gyrus (mm) by peak CAM-S scores in individuals who developed delirium (N=32). 95% confidence intervals are displayed in gray.
Figure A.1. Scatter plot of the AD signature raw values by CAM-S peak with 95% confidence intervals (gray shaded region).
Model LR Chi-square(df)=6.2(2), $P=.066$; c-statistic=.61.
Figure 3

A scatter plot showing the relationship between Peak CAM-S Scores (Residuals) and AD Signature, mm (Residuals). The plot includes a trend line and confidence interval shaded area.

Y-axis: Peak CAM-S Scores (Residuals)
X-axis: AD Signature, mm (Residuals)
Figure 4

A scatter plot showing the relationship between Peak CAM-S Scores and Superior Frontal Gyrus Cortical Thickness (mm). The plot includes a trend line and a shaded area indicating the confidence interval.