

¹⁸F-florbetapir Positron Emission Tomography–determined Cerebral β -Amyloid Deposition and Neurocognitive Performance after Cardiac Surgery

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ABSTRACT

Background: Amyloid deposition is a potential contributor to postoperative cognitive dysfunction. The authors hypothesized that 6-week global cortical amyloid burden, determined by ¹⁸F-florbetapir positron emission tomography, would be greater in those patients manifesting cognitive dysfunction at 6 weeks postoperatively.

Methods: Amyloid deposition was evaluated in cardiac surgical patients at 6 weeks (n = 40) and 1 yr (n = 12); neurocognitive function was assessed at baseline (n = 40), 6 weeks (n = 37), 1 yr (n = 13), and 3 yr (n = 9). The association of 6-week amyloid deposition with cognitive dysfunction was assessed by multivariable regression, accounting for age, years of education, and baseline cognition. Differences between the surgical cohort with cognitive deficit and the Alzheimer's Disease Neuroimaging Initiative cohorts (normal and early/late mild cognitive impairment) was assessed, adjusting for age, education, and apolipoprotein E4 genotype.

Results: The authors found that 6-week abnormal global cortical amyloid deposition was not associated with cognitive dysfunction (13 of 37, 35%) at 6 weeks postoperatively (median standard uptake value ratio [interquartile range]: cognitive dysfunction 0.92 [0.89 to 1.07] vs. 0.98 [0.93 to 1.05]; *P* = 0.455). In *post hoc* analyses, global cortical amyloid was also not associated with cognitive dysfunction at 1 or 3 yr postoperatively. Amyloid deposition at 6 weeks in the surgical cohort was not different from that in normal Alzheimer's Disease Neuroimaging Initiative subjects, but increased over 1 yr in many areas at a rate greater than in controls.

Conclusions: In this study, postoperative cognitive dysfunction was not associated with 6-week cortical amyloid deposition. The relationship between cognitive dysfunction and regional amyloid burden and the rate of postoperative amyloid deposition merit further investigation. (**ANESTHESIOLOGY 2018; 128:728-44**)

Up to 50% of patients undergoing cardiac surgery may experience postoperative cognitive dysfunction at the time of hospital discharge.¹ While there appears to be an initial improvement in the months after surgery, cognitive dysfunction persists in up to 42% at 5 yr after surgery,¹ resulting in a diminished quality of life and loss of functional independence.²

The mechanisms underlying postoperative cognitive dysfunction remain elusive, although several contributing factors have been proposed: preoperative cognitive impairment, genetic predisposition, transcerebral platelet activation, cerebral microembolism or hypoperfusion during cardiopulmonary bypass (CPB), central nervous and systemic inflammatory responses to surgery, hemodilution, hyperglycemia, hyperthermia, and the unmasking of Alzheimer disease and acceleration of amyloid deposition associated with inhalational anesthetics (reviewed elsewhere³). Because cardiac surgery generally takes place in older adults, the possibility exists that cognitive dysfunction after cardiac surgery represents a form of mild cognitive impairment, which also affects older adults. Mild cognitive impairment has been suggested to be a transitional phase between normal aging and dementia and a precursor to Alzheimer disease.⁴ Both mild cognitive

What We Already Know about This Topic

- Cardiac surgery and anesthesia are associated with long-term cognitive deficits
- β -Amyloid deposition is associated with Alzheimer disease
- Anesthesia in animals has been associated with increases in brain β -amyloid
- It is unclear whether cardiac surgery and anesthesia are associated with changes in β -amyloid in humans

What This Article Tells Us That Is New

- In this prospective clinical study involving 40 patients undergoing cardiopulmonary bypass, there were no differences in global β -amyloid deposition between patients with or without cognitive impairment 6 weeks after cardiac surgery
- On secondary analysis, β -amyloid deposition in the hippocampus was increased 6 weeks after cardiac surgery in patients with postoperative cognitive deficits when compared to those without cognitive deficits, although these changes were not significant after adjustment
- A larger prospective study will be needed to determine whether surgery and anesthesia increase global or hippocampal β -amyloid

impairment and Alzheimer disease involve the accumulation of β -amyloid in the central nervous system. Laboratory studies have shown that inhalational anesthetics increase

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β -amyloid generation⁵ and promote β -amyloid oligomerization in cultured cells.⁶ Thus, anesthesia itself may influence β -amyloid processing and play a role in the evolution of cognitive dysfunction in the aging, in common with mild cognitive impairment/Alzheimer disease. However, human studies have provided conflicting results about whether cerebrospinal fluid (CSF) β -amyloid levels rise, fall, or remain unchanged after anesthesia and surgery.^{7,8} Thus, we attempted to directly measure amyloid deposition in the brain after surgery using the positron emission tomography tracer ¹⁸F-florbetapir.

Positron emission tomography agents have shown great promise in mapping fibrillar amyloid deposition in the brain. ¹⁸F-florbetapir [(E)-4-(2-(6-(2-(2-(¹⁸F-fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methylbenzamine] is a novel imaging agent that binds with high affinity (Kd 3.1 nM \pm 0.7) to β -amyloid peptide fibrils in brain amyloid plaques.^{9,10} In a multicenter study, ¹⁸F-florbetapir was shown to have the highest cortical retention in Alzheimer subjects, the lowest in cognitively normal subjects, and intermediate retention in those with mild cognitive impairment.¹¹ ¹⁸F-florbetapir has been used in an increasing number of investigations of Alzheimer disease and has demonstrated comparable, or better, sensitivity and specificity for diagnosing Alzheimer disease compared to clinical criteria.¹² Furthermore, ¹⁸F-florbetapir imaging is the modality used in the longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI)—a multicenter investigation of subjects with normal cognition, varying degrees of mild cognitive impairment, and Alzheimer disease.¹³

In this study, we utilized ¹⁸F-florbetapir imaging to assess the relationship between global cortical and regional amyloid deposition and cognitive dysfunction in patients at 6 weeks after cardiac surgery with CPB. We also conducted follow-up cognitive testing and imaging at 1 and 3 yr post-surgery for *post hoc* analyses. We hypothesized that 6-week ¹⁸F-florbetapir cortical amyloid burden would be greater in those patients manifesting postoperative cognitive dysfunction at 6 weeks, and that the amyloid deposition pattern in patients with cognitive dysfunction would be similar to that seen in individuals from the Alzheimer's Disease Neuroimaging Initiative cohort with mild cognitive impairment.

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*Members of the Alzheimer's Disease Neuroimaging Initiative (ADNI) Study Group are listed in appendix 1. Data used in preparation of this article were obtained from the ADNI database (<https://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ANDI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf and in appendix 1.

†Members of the Neurologic Outcomes Research Group (NORG) are listed in appendix 2.

Materials and Methods

Study Population

Following approval by the Duke University Health Systems Institutional Review Board (Durham, North Carolina) and informed consent, 40 patients age 60 yr or older and undergoing cardiac surgery (coronary artery bypass grafting [CABG], CABG + valve, or valve only) with CPB were prospectively enrolled between July 2011 and November 2013. Patients were excluded if they had a history of symptomatic cerebrovascular disease (*e.g.*, previous stroke) with residual deficits, alcoholism (more than two drinks/day), psychiatric illness (any clinical diagnoses requiring therapy), drug abuse (any illicit drug use in the preceding 3 months before surgery), hepatic insufficiency (liver function tests greater than 1.5 times the upper limit of normal), severe pulmonary insufficiency (requiring home oxygen), or renal failure (serum creatinine greater than 2.0 mg/dl). Pregnant or premenopausal women and patients who were unable to read and thus complete the cognitive testing or who scored lower than 24 on a baseline Mini Mental State examination or higher than 27 on the baseline Center for Epidemiological Studies Depression scale were similarly excluded. Patients who received any anti-amyloid therapies or had any radiopharmaceutical imaging in the 7 days before the surgery were also excluded.

Elderly control patients and patients with early mild cognitive impairment and late mild cognitive impairment (early *vs.* late defined by specific cutoffs on the Logical Memory II subscale of the Wechsler Memory Scale–Revised, as defined by ADNI-2),¹⁴ who had been previously enrolled and imaged with ¹⁸F-florbetapir positron emission tomography through the ADNI (<https://adni.loni.usc.edu>)^{15,16} were utilized to compare regional patterns of amyloid deposition to our surgical cohort. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, M.D. The primary goal of the ADNI has been to assess whether serial magnetic resonance imaging, positron emission tomography, biologic markers, and clinical and neuropsychologic assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer disease. ¹⁸F-florbetapir imaging was included in the ADNI-GO and ADNI-2 protocols. All participants gave written informed consent that was approved by the institutional review board of each participating institution.

Surgical Patient Management

Anesthesia was induced with propofol, midazolam, fentanyl, and neuromuscular blocking agents, and isoflurane was used for maintenance. All patients underwent nonpulsatile, hypothermic (30° to 32°C) CPB with a membrane oxygenator and arterial line filter by a pump primed with crystalloid. Serial hematocrit levels were maintained at 0.21 or greater. Before initiating CPB, heparinization (300 to 400 U/kg) was performed to a target activated coagulation time greater than 480 s. Perfusion was maintained at flow rates of 2 to 2.4 l · min⁻¹ · m⁻² throughout CPB to maintain a mean arterial

pressure of 50 to 80 mmHg. Arterial blood gases were measured every 15 to 30 min to maintain the P_{aCO_2} at 35 to 40 mmHg, unadjusted for temperature (α -stat) and the P_{aO_2} at 150 to 250 mmHg.

Neuroimaging

Cardiac surgical study participants underwent ^{18}F -florbetapir positron emission tomography/computerized tomography imaging at the Duke Positron Emission Tomography Center (Durham, North Carolina) at 6 weeks after surgery. Given funding constraints, imaging was performed at 6 weeks after surgery, since amyloid burden is not expected to change significantly over a 6-week period.¹⁷ At approximately the midpoint of the study, imaging was added at the 1-yr postoperative time point to provide pilot data on the change in amyloid burden over this time interval. A 10 mCi (370 MBq) dose of ^{18}F -florbetapir (Avid Radiopharmaceuticals, USA) was assayed with a dose calibrator and administered *via* bolus injection through a peripheral vein. Once 50 min had elapsed after ^{18}F -florbetapir injection, patients underwent 10 min of continuous brain positron emission tomography imaging. A low-dose computerized tomography scan was also performed for attenuation-correction of the positron emission tomography images. Positron emission tomography images were immediately reconstructed after the scan, and if any motion was detected, another 10-min continuous scan was performed.

For quantitative evaluation, ^{18}F -florbetapir images were spatially normalized to the stereotactic Montreal Neurologic Institute brain atlas space.¹⁸ A standard uptake value ratio was calculated using an average of six target regions (medial orbital frontal, anterior cingulate, parietal, posterior cingulate, precuneus, and lateral temporal) with respect to the whole cerebellum as a reference region. ^{18}F -florbetapir signal was also measured in the hippocampus, pons, centrum, putamen, and caudate, and the standard uptake value ratio for each region was calculated with respect to the cerebellum. Amyloid burden, as previously described,¹⁹ was identified based on standard uptake value ratio values (greater than or equal to 1.10 is β -amyloid-positive [abnormal amyloid deposition] and less than 1.10 is β -amyloid-negative).

Neurocognitive Testing

Neurocognitive testing was performed at baseline (preoperatively) and at 6 weeks. *Post hoc*, 1-yr, and 3-yr follow-up points were added to provide pilot data on the relationship between baseline amyloid burden and long-term neurocognitive function. In accordance with the consensus statement on assessment of neurobehavioral outcomes after cardiac surgery,²⁰ the following tests were included in the assessment battery: (1) Hopkins Verbal Learning Test,²¹ (2) Randt Short Story Memory Test,²² (3) Modified Visual Reproduction Test from the Wechsler Memory Scale,²³ (4) Digit Span and Digit Symbol and Vocabulary subtests from the Wechsler Adult Intelligence Scale-Revised,²³ and (5) Trail Making Test, Parts A and B.²⁴

Blood Sample and Apolipoprotein E Genotyping

One 10-ml sample of peripheral blood was obtained from each patient and stored at 4°C. Genomic DNA were extracted for each sample and stored at the Duke Molecular Physiology Institute (Durham, North Carolina) at -20°C. Genotyping for apolipoprotein E was performed at the Molecular Genetics Core at the Duke Molecular Physiology Institute following previously described protocols.²⁵

Statistical Analyses

To characterize cognitive function over time while minimizing potential redundancy in the cognitive measures, a factor analysis with oblique rotation (a linear transformation of the data, which allows for correlated factors) was performed on the 14 cognitive test scores from baseline. Scoring coefficients (weights) of each test on each factor were determined using the rotated factor solution from the factor analysis conducted on 508 eligible cardiac patients in our ongoing prospective post-CABG cognitive testing database. Factors of each subject in our cohort were computed for all time points using the same scoring coefficients, so that the cognitive domain structure remained consistent and comparable over time. Factor analysis suggested a five-factor solution, which accounts for 80% of the variability in the original test scores, and represents five cognitive domains: (1) structured verbal memory (*i.e.*, the ability to recall from a list); (2) unstructured verbal memory (*i.e.*, the ability to remember from a narrative); (3) visual memory; (4) executive function; and (5) attention and concentration. Two outcome measures were calculated to represent postoperative cognitive dysfunction: (1) continuous outcome—the change in cognitive score calculated by subtracting the baseline cognitive index (the five-domain mean) from the follow-up cognitive index (a change score of 0 indicates no change from baseline, while a negative score indicates cognitive decline, and a positive score indicates cognitive improvement); and (2) binary outcome (cognitive deficit), defined as a decline of greater than 1 SD in at least one domain.

The relationship between 6-week global cortical amyloid burden (standard uptake value ratio 1.1 or greater) and cognition at 6 weeks after surgery was prespecified as the primary outcome. Secondary outcomes included the relationship between regional amyloid burden and cognition at 6 weeks postoperatively, and the relationship between global amyloid burden and cognition at 1 yr. We used the chi-square test, Fisher exact test, or Wilcoxon rank sum test, as appropriate, to examine differences between patients with and without cognitive deficit. We then computed Pearson's correlation coefficients of amyloid burden with age, years of education, baseline cognitive score, 6-week cognitive score, and change in cognitive score. Finally, multivariable regression was used to test the association of cognitive deficit and mean 6-week cognitive score change with abnormal amyloid deposition (standard uptake value ratio 1.1 or greater), accounting for age, years of education, and baseline cognition. Subject demographics and

amyloid burden in our surgical cohort was compared to age- and sex-matched normal, early mild cognitive impairment, and late mild cognitive impairment subsets in the ADNI database using the two-sample *t* test, Wilcoxon rank sum test, chi-square test, or Fisher exact test, as appropriate.

Apolipoprotein E4 genotype was categorized by the presence (homozygous or heterozygous) or absence of the apolipoprotein E-ε4 allele. The association of apolipoprotein E4 status with amyloid burden at 6 weeks was assessed using the two-sample *t* test, Wilcoxon rank sum test, chi-square test, or Fisher exact test, as appropriate. An analysis of covariance model was then used to test differences among four cognitive categories: cognitive deficit at 6 weeks in our surgical cohort and normal, early mild cognitive impairment, and late mild cognitive impairment in the ADNI cohort (adjusting for age, years of education, and apolipoprotein E4 genotype).

In the absence of any published data on amyloid deposition in surgical patients, we relied upon preliminary data from a study conducted by a coinvestigator (P.M.D.) evaluating amyloid deposition in healthy, mild cognitive impairment, and Alzheimer disease subjects, where the estimated mean and SD of the healthy and mild cognitive impairment groups were used for power calculation. Based on these data, we assessed the statistical power for detecting the correlation between cognitive score changes and amyloid burden. Under a linear regression model with the SD of amyloid burden at 0.25 from preliminary data, we estimated that 40 patients in the cardiac surgical group would provide 80% power to detect a correlation between cognitive score changes and amyloid burden at an R-square of 0.171.

All analyses were performed with SAS version 9.4 (SAS Institute Inc., USA). $P < 0.05$ was considered significant. *Post hoc* analyses of regional amyloid deposition were adjusted for multiple comparisons by computing a false discovery rate.

Results

Neurocognitive Outcomes

Of the 40 patients initially enrolled, 37 had complete baseline and 6-week cognitive and neuroimaging data; at 1 yr after surgery, 28 patients had complete baseline and 1-yr cognitive data and 12 had neuroimaging; and at 3 yr after surgery, 18 patients completed cognitive testing. The mean (SD) cognitive change score (from baseline) was 0.10 (0.29) at 6 weeks, 0.13 (0.31) at 1 yr after surgery, and 0.08 (0.51) at 3 yr after surgery. Cognitive deficit, defined as a 1 or greater SD decline in at least one cognitive domain, was present in 35% (13 of 37) of the cardiac surgical patients at 6 weeks after surgery, 57% (16 of 28) at 1 yr, and 44% (8 of 18) at 3 yr. Interestingly, several patients without deficit at 6 weeks went on to develop deficit at 1 yr postoperatively, while others recovered (Supplemental Digital Content 1, <http://links.lww.com/ALN/B616>, and Supplemental Digital Content 2, <http://links.lww.com/ALN/B617>). Table 1 lists the demographic and surgical characteristics of the enrolled patients.

Global Cortical Amyloid Deposition and Postoperative Cognitive Dysfunction at 6 Weeks and 1 Yr.

Representative images from our study cohort of normal (A) and abnormal (B) amyloid deposition as measured by ^{18}F -florbetapir imaging are shown in figure 1. Global cortical amyloid deposition was measured as standard uptake value ratio 1.03 (0.17) in the 40 patients imaged at 6 weeks and 1.04 (0.20) in the 12 patients imaged at 1 yr. Cortical amyloid deposition was considered abnormal (standard uptake value ratio greater than or equal to 1.1) in seven patients (17.5%) imaged at 6 weeks and in two patients (16.7%) imaged at 1 yr. The cognitive change score at 6 weeks and 1 yr after surgery in patients with and without 6-week abnormal global cortical amyloid deposition was 0.108 (0.186) *versus* 0.095 (0.311), $P = 0.92$; and 0.193 (0.266) *versus* -0.121 (0.325), $P = 0.62$, respectively.

With regard to our primary outcome, 6-week global cortical amyloid deposition was not different in patients with and without cognitive deficit at 6 weeks (median standard uptake value ratio [interquartile range], 0.92 [0.89 to 1.07] *vs.* 0.98 [0.93 to 1.05], $P = 0.455$; table 2), nor was there a difference in the proportion of patients with and without postoperative cognitive dysfunction who had abnormal amyloid deposition (proportion difference, 0.106). Similar patterns were seen at 1 yr after surgery (median standard uptake value ratio [interquartile range], 0.96 [0.89 to 1.02] *vs.* 1.02 [0.97 to 1.06]). Abnormal 6-week amyloid deposition was seen in three patients with cognitive deficit and in three patients without deficit at 6 weeks postoperatively ($P = 0.644$; table 3). Similarly, one patient with cognitive deficit at 1 yr had abnormal global cortical amyloid deposition at 1 yr, while one patient without deficit had abnormal deposition. There were no significant correlations of global cortical amyloid deposition at 6 weeks with baseline, 6-week, 1-yr, or 3-yr cognitive scores or change scores. In multivariable regression analyses, we found no significant association between 6-week abnormal global cortical amyloid burden and cognitive change scores (β , 0.09; model R^2 , 0.12) or with the occurrence of postoperative cognitive dysfunction at 6 weeks (odds ratio, 0.47; 95% CI, 0.07 to 3.43; model R^2 , 0.09) when controlling for age, years of education, and baseline cognition. There were also no significant associations of 6-week amyloid burden with cognitive outcomes at 1 or 3 yr after surgery.

Regional Amyloid Deposition and Postoperative Cognitive Dysfunction.

In *post hoc* analyses we found that the frequency of abnormal amyloid deposition (standard uptake value ratio greater than or equal to 1.1) in the hippocampus was significantly different between patients with and without postoperative cognitive dysfunction at 6 weeks postoperatively, although this difference was no longer significant after adjustment for multiple comparisons ($P = 0.041$, false discovery rate = 0.429; table 3). Patients who had abnormal 6-week amyloid in the hippocampus showed significantly greater decline in the structured verbal memory domain

Table 1. Characteristics of the Cardiac Surgical Cohort

Variable	Baseline (n = 38)*	6 weeks (n = 40)†	1 yr (n = 12)‡	3 yr (n = 18)*
Age (yr)	69 (6)	69.4 (6)	71 (5)	71 (6)
Sex (% female)	9 (23%)	8 (22%)	2 (17%)	4 (22%)
Race (% white)	34 (85%)	32 (86%)	11 (92%)	15 (86%)
Weight (kg)	85 (17)	86 (18)	83 (17)	85 (16)
History of hypertension	33 (83%)	31 (84%)	9 (75%)	15 (84%)
Diabetes mellitus	22 (55%)	20 (54%)	4 (33%)	9 (54%)
Previous MI	13 (33%)	13 (35%)	3 (25%)	4 (35%)
Ejection fraction (%)	51 (9)	51 (9)	52 (8)	54 (4)
Years of education	14 (4)	14 (3)	16 (5)	15 (4)
Preoperative statins (%)	28 (80%)	27 (82%)	9 (90%)	14 (82%)
Preoperative platelet inhibitors (%)	30 (86%)	29 (88%)	7 (70%)	16 (88%)
Surgical procedure (%)				
CABG	24 (60%)	23 (62%)	8 (67%)	11 (62%)
CABG + valve	8 (20%)	7 (19%)	2 (17%)	3 (19%)
Valve only	8 (20%)	7 (19%)	2 (17%)	4 (19%)
No. of grafts (%)‡				
1	6 (19%)	6 (20%)	2 (20%)	3 (21%)
2	5 (16%)	4 (13%)	1 (10%)	2 (14%)
3	10 (31%)	10 (33%)	5 (50%)	5 (36%)
> 3	11 (34%)	10 (33%)	2 (20%)	4 (29%)
Cross-clamp time (min)	90 (34)	87 (33)	90 (30)	84 (34)
CPB time (min)	145 (49)	141 (44)	136 (35)	142 (46)
Baseline cognitive score	-0.17 (0.57)	-0.15 (0.56)	-0.19 (0.48)	-0.17 (0.64)
6-week cognitive score	-0.07 (0.61)	-0.05 (0.62)	-0.06 (0.64)	-0.09 (0.69)

Values are mean (SD) unless otherwise indicated.

*Number of patients with cognitive testing data at these time points. †Number of patients with imaging at these time points. ‡Patients undergoing CABG or CABG + valve procedures. Differences in demographics and comorbidities between baseline/6-week and the 1- and 3-yr time points are due to patient loss to follow-up.

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; MI = myocardial infarction.

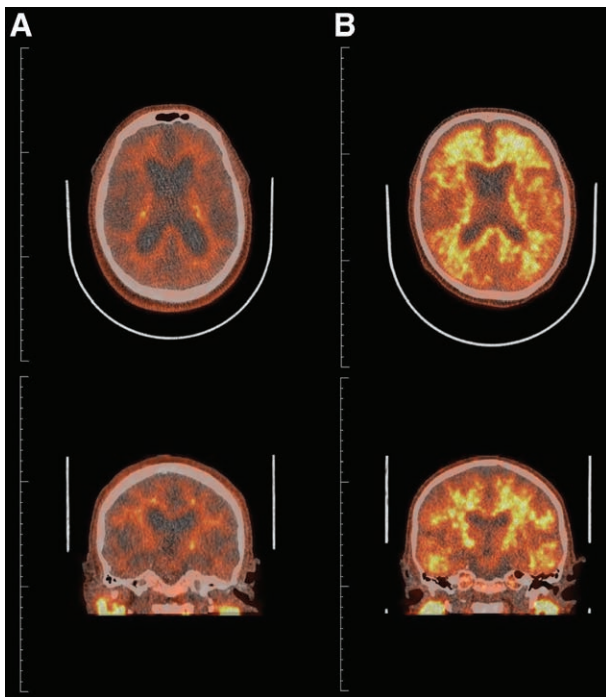


Fig. 1. Images of patients with normal (A) and abnormal (B) amyloid deposition by ^{18}F -florbetapir positron emission tomography imaging. The brighter orange to yellow colors indicate greater amyloid deposition.

(median change score [interquartile range], -1.08 [-2.05 to -0.69] in patients with standard uptake value ratio greater than or equal to 1.1 *vs.* -0.075 [-0.82 to 0.46] for patients with standard uptake value ratio less than 1.1; $P = 0.019$). Total hippocampal standard uptake value ratio (continuous variable), although higher, was not statistically different between patients with and without deficit (table 2). The caudate standard uptake value ratio was also greater in patients who had a cognitive deficit at 6 weeks, but this difference was no longer significant after adjustment for multiple comparisons (median [interquartile range], deficit 0.96 [0.85 to 1.03] *vs.* no deficit 0.81 [0.70 to 0.94]; $P = 0.047$, false discovery rate = 0.561). Furthermore, the standard uptake value ratios in the caudate failed to meet the greater than or equal to 1.1 threshold for defining abnormal amyloid deposition.

Trajectory of Amyloid Deposition. While cognitive deficit and the cognitive change score were not associated with abnormal global cortical amyloid deposition in the smaller cohort of 12 patients with 1-yr neuroimaging, amyloid deposition increased in many brain regions over time. In these 12 patients, global cortical amyloid deposition increased significantly from 6 weeks to 1 yr (mean standard uptake value ratio change, 0.02 ± 0.02 ; $P = 0.011$). Statistically significant increases in standard value uptake ration from 6 weeks to 1 yr postoperatively were observed in the hippocampus, posterior cingulate, caudate, and occipital regions (fig. 2).

Table 2. Global Cortical and Regional SUVR Values in Patients with and without Cognitive Deficit at 6 Weeks

Brain Region	No Deficit (n = 24), SUVR (median [IQR])	Deficit (n = 13), SUVR (median [IQR])	P Value	FDR	Mean Difference (95% CI)
Global cortical	0.98 [0.93 to 1.05]	0.92 [0.89 to 1.07]	0.455	0.754	-0.06 [-0.23 to 0.10]
Posterior cingulate	0.98 [0.88 to 1.04]	0.87 [0.84 to 1.08]	0.514	0.754	-0.04 [-0.21 to 0.13]
Precuneus	1.09 [1.02 to 1.15]	0.99 [0.94 to 1.20]	0.417	0.754	-0.05 [-0.24 to 0.15]
Frontal medial orbital	0.89 [0.87 to 0.93]	0.88 [0.85 to 0.92]	0.691	0.754	-0.06 [-0.18 to 0.07]
Parietal	0.90 [0.82 to 1.03]	0.89 [0.81 to 1.09]	0.622	0.754	-0.09 [-0.26 to 0.09]
Temporal	1.07 [1.01 to 1.13]	1.06 [1.00 to 1.16]	0.787	0.787	-0.07 [-0.22 to 0.07]
Anterior cingulate	1.01 [0.95 to 1.10]	0.96 [0.93 to 1.07]	0.417	0.754	-0.08 [-0.29 to 0.12]
Hippocampus	1.05 [1.01 to 1.09]	1.10 [1.02 to 1.12]	0.417	0.754	0 [-0.06 to 0.06]
Centrum	1.67 [1.59 to 1.78]	1.62 [1.56 to 1.71]	0.301*	0.754	0.04 [-0.05 to 0.13]
Occipital	1.00 [0.86 to 1.04]	0.94 [0.90 to 1.08]	0.763*	0.754	-0.02 [-0.14 to 0.09]
Putamen	1.19 [1.15 to 1.30]	1.18 [1.13 to 1.24]	0.417	0.754	0.01 [-0.08 to 0.09]
Caudate	0.81 [0.70 to 0.94]	0.96 [0.85 to 1.03]	0.047	0.561	-0.12 [-0.25 to 0]

*P value determined by t test. All other P values determined by Wilcoxon rank sum test.
FDR = false discovery rate; IQR = interquartile range; SUVR = standard uptake value ratio relative to cerebellum.

Table 3. Frequency of Abnormal Global Cortical and Regional Amyloid Deposition at 6 Weeks in Patients with and without Cognitive Deficit

Brain Region	No Deficit (n = 24), SUVR ≥ 1.1 (%)	Deficit (n = 13), SUVR ≥ 1.1 (%)	P Value*†	FDR
Global cortical	3 (12.5)	3 (23.1)	0.644*	0.787
Posterior cingulate	3 (12.5)	3 (23.1)	0.644*	0.787
Precuneus	9 (37.5)	5 (38.5)	0.954†	1
Frontal medial orbital	0 (0)	2 (15.4)	0.117*	0.429
Parietal	2 (8.3)	2 (15.4)	0.602*	0.787
Temporal	7 (29.2)	6 (46.2)	0.302†	0.787
Anterior cingulate	5 (25.0)	6 (46.3)	0.108*	1
Hippocampus	5 (20.8)	7 (54.8)	0.041†	0.429
Occipital	3 (12.5)	3 (23.1)	0.644*	0.787
Putamen	23 (95.8)	10 (76.9)	0.115*	0.429
Caudate	2 (8.3)	0 (0)	0.532*	0.787

P value determined by *Fisher exact test or †chi-square test.
FDR = false discovery rate; SUVR = standard uptake value ratio relative to cerebellum.

Comparison to ADNI Cohort. Overall, our cardiac surgical cohort was more similar to the ADNI subjects with normal cognition than the age- and sex-matched early or late mild cognitive impairment cohorts, with regard to education and apolipoprotein E4 carrier status (Supplemental Digital Content 3, <http://links.lww.com/ALN/B618>) and global and regional amyloid deposition (Supplemental Digital Content 4, <http://links.lww.com/ALN/B619>, and Supplemental Digital Content 5, <http://links.lww.com/ALN/B620>).

Abnormal Amyloid Deposition and Cognitive Deficit in Apolipoprotein E4 Carriers. Apolipoprotein E genotype was available for 37 patients in our cohort. Eight patients were found to be apolipoprotein E4 carriers (seven heterozygous, one homozygous), and 29 were noncarriers. Of the eight apolipoprotein E4 carriers, seven had complete 6-week cognitive testing data; of the 29 noncarriers, 27 had complete 6-week cognitive testing data. Of the seven apolipoprotein E4 carriers with complete 6-week cognitive testing, four (57%) demonstrated cognitive deficit at 6 weeks. This was not statistically different from the deficit rate in the

non-apolipoprotein E4 carriers (7 of 27, 26%; $P = 0.178$). Apolipoprotein E4 genotype was, however, significantly associated with worse baseline cognitive score (mean [SD], $-0.631 [0.382]$ vs. $0.001 [0.555]$ in noncarriers; $P = 0.005$), but there was no difference at 6 weeks or in the change score from baseline to 6 weeks between apolipoprotein E4 carriers and noncarriers. Global and regional standard uptake value ratios in apolipoprotein E4 carriers versus noncarriers are shown in Supplemental Digital Content 6 (<http://links.lww.com/ALN/B621>). An analysis of covariance model, incorporating the ADNI cohort, revealed a significant association of global cortical amyloid deposition at 6 weeks with apolipoprotein E4 genotype ($P < 0.001$) and age ($P = 0.001$), and that the surgical cohort with cognitive deficit at 6 weeks had smaller global cortical amyloid deposition at 6 weeks than the late mild cognitive impairment subjects ($P = 0.001$) in the ADNI cohort, but not the normal ($P = 0.68$) or early mild cognitive impairment patients ($P = 0.07$).

When evaluating regional standard uptake value ratio greater than or equal to 1.1 in apolipoprotein E4 carriers,

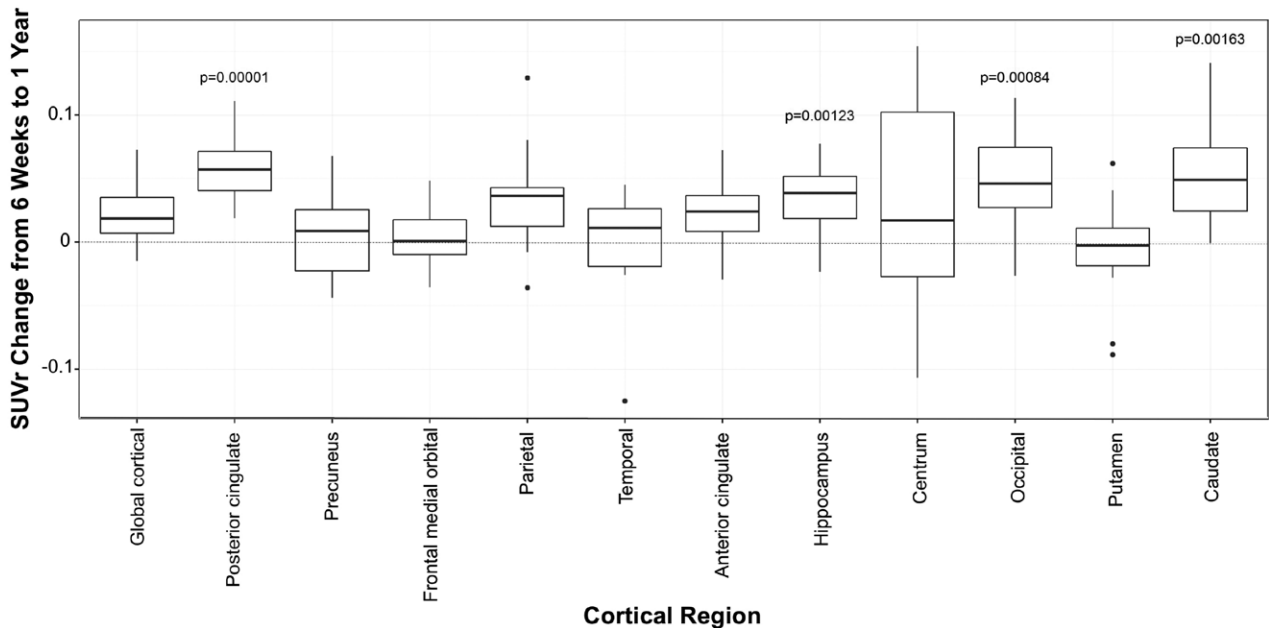


Fig. 2. Box plots showing median (interquartile range) change in standard uptake value ratio relative to cerebellum (SUVr) in each imaged brain region from 6 weeks to 1 yr postoperatively. Positive values represent increase in SUVr, while negative values represent decrease in SUVr. N = 12.

only the parietal region was different between the carriers and noncarriers before adjustment for multiple comparisons (38% [3 of 8] in carriers *vs.* 3% [1 of 29] in noncarriers; $P = 0.02$; false discovery rate = 0.282).

Discussion

We did not find an association between 6-week global cortical amyloid burden and cognitive dysfunction at 6 weeks after cardiac surgery. Cognitive dysfunction after cardiac surgery remains a significant problem without a clear etiology. Given that cardiac surgery predominantly takes place in the aged, the possibility exists that the cognitive decline seen in some patients is similar to mild cognitive impairment, which in many will eventually progress to Alzheimer disease. Both diseases are believed to involve the accumulation of β -amyloid and τ proteins in the brain. While the role of β -amyloid oligomers in the pathogenesis of Alzheimer disease remains controversial,²⁶ there is evidence that β -amyloid can lead to synaptic dysfunction and memory deficits in animals.²⁷ CPB is known to disrupt the blood-brain barrier,²⁸ and blood-brain barrier dysfunction is associated with increased entry of amyloid into the brain.²⁹ Alzheimer-type neurodegeneration is accelerated by neuroinflammation,³⁰ raising the possibility that perioperative inflammation could stimulate/accelerate β -amyloid-mediated neurologic degeneration, which could contribute to postoperative cognitive dysfunction. Finally, cardiac surgical patients share many of the risk factors for Alzheimer disease,³¹ and there is a known intersection between Alzheimer and cardiovascular/cerebrovascular disease.³² While there is no evidence that cardiovascular disease severity directly affects amyloid burden,³³ it is plausible

that some component of postoperative cognitive dysfunction may be related to cardiovascular risk factors that accelerate the progression toward Alzheimer-type cognitive decline.

To investigate the relationship between postoperative cognitive dysfunction and β -amyloid protein deposition in patients undergoing cardiac surgery, we utilized the novel positron emission tomography tracer, ¹⁸F-florbetapir, which binds with high affinity to β -amyloid fibrils and has been shown to differentiate cerebral β -amyloid deposition between both cognitively normal and deficient subjects.³⁴ With regard to our primary outcome, we did not find a significant association between 6-week global cortical amyloid burden and cognitive dysfunction at 6 weeks. Six-week amyloid burden was also not associated with cognitive dysfunction at 1 or 3 yr postoperatively, although our sample size at these time points was very small.

In *post hoc* analyses of regional amyloid deposition, we found an increased proportion of patients with cognitive dysfunction at 6 weeks with abnormal 6-week amyloid deposition in the hippocampus, which was associated with a verbal memory deficit. While these results were not significant after adjustment for multiple comparisons, the unadjusted findings may point to regions that deserve closer scrutiny in future studies. The hippocampus is an intriguing region because it plays an important role in the acquisition and storage of episodic memories³⁵—those related to unique personal experiences—and has been linked with postsurgical cognitive changes in animals.³⁶ Hippocampal synapse loss occurs early in Alzheimer and, to a greater extent than in other brain regions, in advanced Alzheimer. Furthermore, hippocampal damage correlates better with cognitive impairment in

Alzheimer disease than the presence/quantity of β -amyloid plaques or neurofibrillary tangles.³⁷ Finally, Badgaiya *et al.* previously showed significant decreases in memory-related regional cerebral blood flow within the hippocampus and parahippocampus after cardiac surgery,³⁸ which may indicate regions of the brain that are more vulnerable to ischemic blood-brain barrier dysfunction and consequent cerebral deposition of circulating amyloid after cardiac surgery.²⁹

We also observed that amyloid deposition significantly increased from 6 weeks to 1 yr after surgery in many regions of the brain and that this rate of increase was greater than that reported elsewhere. In a study by Palmqvist *et al.*,³⁹ the mean global standard uptake value ratio change/year in nondemented subjects with normal positron emission tomography scans was 0.0024 (95% CI, 0.0010 to 0.0039), while that for subjects with abnormal CSF and scan results was 0.011 (95% CI, 0.0083 to 0.013). Similarly, in the longitudinal ADNI cohort, the mean standard uptake value ratio change in 154 control subjects with a normal baseline scan was 0.0027 (0.0100), but was 0.0160 (0.0161) in 61 controls with abnormal baseline scans (Susan Landau, Ph.D., Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, California; email communication, October 2017). In comparison, the mean (SD) global cortical standard uptake value ratio change in our surgical patients was 0.02 (0.02), nearly tenfold than seen in scan-negative nonsurgical patients, and just slightly higher than that in scan-positive nonsurgical patients. When we removed patients with abnormal 6-week amyloid deposition (N = 2) from our analyses, the rate of change in our surgical cohort remained higher at 0.014 (0.018). Percent standard uptake value ratio change, which discounts variation in reference regions, may be more informative; in the Palmqvist *et al.* study,³⁹ the percent global standard uptake value ratio change/year was 0.35% (95% CI, 0.14 to 0.56%), compared to $1.9 \pm 2.0\%$ in our surgical cohort. However, our study sample is limited, and changes over the course of a year are small.

This trajectory of amyloid at 1 yr after surgery raises the question of how surgery and/or anesthesia may impact cerebral amyloid deposition and longer-term cognitive outcomes. Several *in vitro* and animal studies have established a link between anesthetic agents and enhanced β -amyloid formation, aggregation, and β -amyloid-induced cytotoxicity.^{5,6} Human studies have demonstrated that low preoperative ratios of β -amyloid/ τ proteins in the CSF are associated with postoperative delirium and cognitive decline, although this is thought to predict a predisposition to cognitive dysfunction due to preclinical Alzheimer disease, rather than a direct anesthetic effect.⁴⁰ Surgery may also have an independent effect on the risk of Alzheimer development in the postoperative setting.⁴¹ Tang *et al.*⁷ and Berger *et al.*⁸ both demonstrated a CSF change in the ratio of β -amyloid/ τ proteins in patients undergoing surgery consistent with that seen in Alzheimer and correlated with perioperative neuro-inflammatory mediator release. The association of perioperative inflammatory changes and Alzheimer-like cognitive

decline may be particularly relevant in the highly inflammatory milieu of cardiac surgery. Cardiac surgery with CPB has been shown to produce an intense cerebral inflammatory response in conjunction with Alzheimer-like changes in CSF β amyloid.⁴² Vascular dysfunction and inflammation, both hallmarks of cardiac surgery, have also been associated with amyloid deposition.⁴³ Thus, one concern has been whether cardiac surgery itself could increase the rate of amyloid deposition as a consequence of blood-brain barrier disruption.²⁸

Our finding that some patients experienced cognitive decline over time, while others improved also merits further study and correlation with observed changes in the trajectory of global and regional cortical amyloid deposition. Cognitive improvement over time after surgery is certainly a recognized phenomenon and can be seen either globally or in select cognitive domains.⁴⁴ However, no mechanistic explanation has yet been uncovered as to why some patients improve while others continue to decline/recover more slowly.

It is important to interpret our findings in the context of our sample size limitations. Without any previous studies on amyloid burden in surgical patients, our initial sample size estimation was based on the hypothesis that patients with postoperative cognitive dysfunction would have amyloid deposition to individuals with mild cognitive impairment. For our primary outcome, comparison of the binary variables of abnormal amyloid deposition and postoperative cognitive dysfunction demonstrated a proportion difference of 0.106; we are only powered to detect a proportion difference of 0.5, thus we cannot conclusively exclude an association between 6-week abnormal amyloid deposition and a clinically meaningful decline in cognitive function after cardiac surgery. Furthermore, we estimate that we have 80% power to detect a mean standard uptake value ratio difference of 0.16 between patients with and without postoperative cognitive at 6 weeks postoperatively; thus, our detected standard uptake value ratio difference of 0.06 falls below this threshold. Based on these data, we estimate that 117 patients would be needed to achieve 80% power in a future study (Supplemental Digital Content 7, <http://links.lww.com/ALN/B622>).

The lack of baseline imaging and longer-term (more than 3 yr) follow-up are further limitations of our study. While the existing literature indicates a longer time course for change in amyloid,¹⁷ we cannot say with certainty that surgery does not produce changes in amyloid deposition in the immediate postoperative period. Future studies should include a baseline assessment of brain amyloid before surgery as well as longer duration of follow-up. Based on the existing literature in mild cognitive impairment subjects, the time course of clinically significant β -amyloid deposition needed to produce cognitive decline may be significantly longer.^{45,46} Finally, we are limited by the relatively younger and male-dominated nature of our surgical cohort. Older age has been shown to increase the risk for postoperative cognitive dysfunction⁴⁷ and Alzheimer disease, and multiple studies have indicated that females have a higher prevalence

and incidence of Alzheimer disease⁴⁸ and mild cognitive impairment progression over time than men.⁴⁹ Future studies should include an older surgical group that more closely matches the ADNI mild cognitive impairment cohort.

In conclusion, this study employed amyloid imaging using ¹⁸F-florbetapir to investigate 6-week and evolving brain amyloid burden in patients undergoing cardiac surgery with CPB. We observed that postoperative cognitive dysfunction was not associated with 6-week global cortical amyloid deposition, but the rate of amyloid deposition after surgery was greater than what has been reported in normal elderly subjects. The findings from this study support further investigation of: (1) the relationship between hippocampal amyloid deposition and early postoperative cognitive dysfunction; and (2) the significance of amyloid deposition increases within 1 yr of cardiac surgery.

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Competing Interests

Dr. Doraiswamy has received research grants (through Duke University) from Avid (Philadelphia, Pennsylvania),

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Appendix 1. Members of the Alzheimer's Disease Neuroimaging Initiative (ADNI)

I. ADNI I, GO, and II

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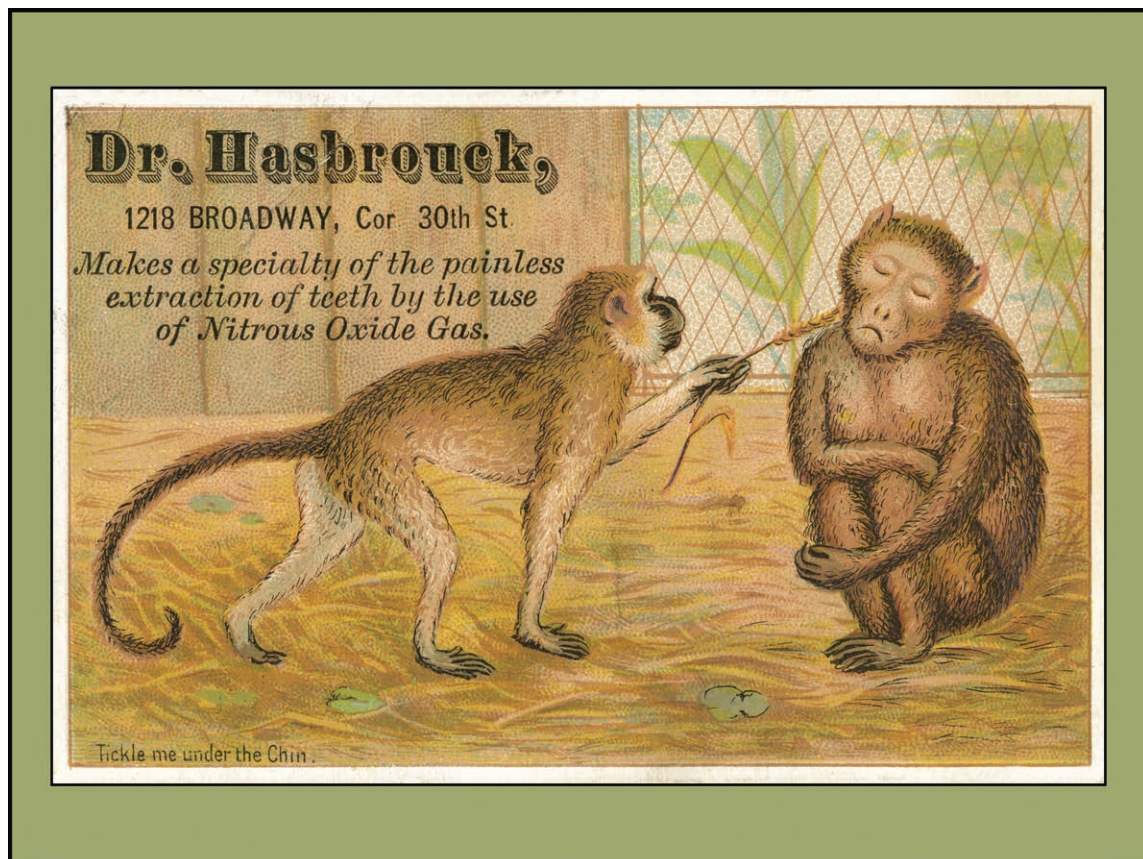
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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Monkeying Outside Central Park Zoo: Hasbrouck Advertises His Nitrous Oxide



At the Arsenal building near the southeast corner of Central Park, New York's Central Park Zoo was less than a two-mile walk north of the dental offices of Dr. Ferdinand Hasbrouck. Perhaps monkeys at the zoo inspired Hasbrouck to advertise with this trade card titled, "Tickle me under the Chin." Having earned his dental doctorate in Philadelphia, Hasbrouck delighted in poking fun at Manhattan's Colton Dental Association, many of whose dentists lacked academic training in either dentistry or anesthetics. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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