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Cortical β-amyloid levels and neurocognitive performance after cardiac surgery

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ABSTRACT

Introduction: Neurological and neurocognitive dysfunction occurs frequently in the large number of increasingly elderly patients undergoing cardiac surgery every year. Perioperative cognitive deficits have been shown to persist after discharge and up to several years after surgery. More importantly, perioperative cognitive decline is predictive of long-term cognitive dysfunction, reduced quality of life and increased mortality. The proposed mechanisms to explain the cognitive decline associated with cardiac surgery include the neurotoxic accumulation of β-amyloid. This study will be the first to provide molecular imaging to assess the relationship between neocortical β-amyloid deposition and postoperative cognitive dysfunction.

Methods and analysis: 40 patients providing informed consent for participation in this Institutional Review Board-approved study and undergoing cardiac (coronary artery bypass graft (CABG), valve or CABG +valve) surgery with cardiopulmonary bypass will be enrolled based on defined inclusion and exclusion criteria. At 6 weeks after surgery, participants will undergo ^{18}F-florbetapir positron emission tomography imaging to assess neocortical β-amyloid burden along with a standard neurocognitive battery and blood testing for apolipoprotein E ε-4 genotype.

Results: The results will be compared to those of 40 elderly controls and 40 elderly patients with mild cognitive impairment who have previously completed ^{18}F-florbetapir imaging.

Ethics and dissemination: This study has been approved by the Duke University Institutional Review Board. The results will provide novel mechanistic insights into postoperative cognitive dysfunction that will inform future studies into potential treatments or preventative therapies of long-term cognitive decline after cardiac surgery.

ARTICLE SUMMARY

Strengths and limitations of this study

- This will be the first study to compare regional patterns of β-amyloid deposition in cardiac surgical patients with a group of elderly controls and mild cognitive impairment (MCI) participants, thus corroborating (or refuting) the similarities between postoperative cognitive dysfunction and MCI.
- ^{18}F-florbetapir is a novel tracer with high affinity for β-amyloid fibrils and a longer half-life.
- The analyses depend on the observational nature of the study and the use of existing controls.

INTRODUCTION

As our population ages, the manifestations of systemic atherosclerosis (stroke and cognitive impairment) extend the burden on our healthcare delivery system. The consequences of atherosclerosis are particularly relevant during cardiac surgery, where perioperative neurological events can have a dramatically detrimental effect on the duration and quality of survival. Little is more devastating to a patient or the patient's family than to have a successful operation that prolongs life but is complicated by cognitive impairment that results in a diminished quality of life and loss of functional independence. Because this does occur in a significant number of cardiac surgical patients, it is important to discover how this unfortunate consequence of surgery can be prevented or treated.

In patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), postoperative cognitive dysfunction (POCD) is evident in 53% at discharge and remains present in 36% of patients at 6 weeks after surgery.[1] Importantly, cognitive impairment may persist in 42% of patients up to 5 years after surgery.[1] Moreover, perioperative neurocognitive decline predicts long-term cognitive dysfunction, with dysfunction resulting in reduced quality of life.[2 3] The observed pattern of initial improvement in cognition followed by late deterioration was also reported by Stygall *et al*[4] who likewise concluded that a patient's vulnerability to short-term neurocognitive deterioration in the days after surgery and the ability to recover over a few weeks from the operative cerebral insult were predictors of the change in cognition 5 years after surgery. Zimpfer *et al*[5] objectively measured neurocognitive function by means of cognitive P300 evoked potentials and similarly noted that a deficit at the 4-month follow-up was predictive for cognitive deficit at the 3-year follow-up. Selnes *et al*[6] have recently reported that while late cognitive decline does occur in coronary artery bypass graft (CABG) patients, the degree of this decline is similar to that of patients with coronary artery disease who have not had surgical intervention. Although the 'non-surgical' control group in this study included patients who had undergone percutaneous coronary intervention or other surgical procedures under general anaesthesia, thus introducing the potential for additional neurocognitive injury in the control group, their results do suggest that the late cognitive decline after CABG is not specific to the use of CPB.

A number of hypothetical mechanisms have been suggested to explain the cognitive decline associated with cardiac surgery, and these include but are not limited to the occurrence of cerebral emboli associated with surgery, influence of existent cardiovascular risk factors, effect of anaesthesia or CPB management and unmasking of Alzheimer disease (AD). Because cardiac surgery generally takes place in the aged, the possibility exists that the cognitive impairment seen in almost a third of the surgical patients is a form of mild cognitive impairment (MCI). A large proportion of MCI is understood to be a precursor to AD, and both are believed to originate from the same pathophysiology—the neurotoxical accumulation of β-amyloid (Aβ) in the central nervous system. Laboratory studies have shown that inhalational anaesthetics increase Aβ generation[7] as well as promote oligomerisation in cell cultures.[8] Thus, anaesthesia may also influence Aβ processing and play a role in the evolution of cognitive dysfunction in the clinical setting, in common with MCI/AD.

Positron emission tomography (PET) agents to map fibrillar amyloid in the brain offer great promise in studies aimed at correlating clinical and pathological findings. ^{18}F-florbetapir [(E)-4-(2-(6-(2-(2-(2-^{18}F-fluoroethoxy) ethoxy)ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine] is a novel PET imaging agent that binds with high affinity (Kd 3.1 nM+0.7) to the Aβ peptide fibrils that constitute amyloid plaques.[9–13] In vitro autoradiography studies show that when applied at tracer concentrations, ^{18}F-florbetapir labels Aβ plaques in sections from patients with pathologically confirmed AD.[11] In a phase 1 trial of ^{18}F-florbetapir in 16 cognitively normal volunteers and 16 patients with AD, patients with AD showed selective retention of tracer in cortical areas expected to be high in amyloid deposition, whereas cognitively normal controls showed rapid washout from these areas, with only minimal cortical tracer retention.[14] AD as well as cognitively normal volunteers also showed rapid washout in the cerebellum, which is usually devoid of plaques.

We have presented results of the first large multicentre cross-sectional study of ^{18}F-florbetapir PET with findings generally consistent with those of prior ^{11}C-Pittsburgh compound B (PIB) studies showing that participants with MCI were heterogeneous with regard to brain Aβ load.[15] Very little is known, however, about the sequence of events that lead to disruption of memory networks, either prior to, or as a result of Aβ pathology in at-risk candidates. Our study aims to bridge the links between in vivo brain amyloid pathology and neurocognitive impairment following cardiac surgery. The results of our study will be unique in that we will define the role of amyloid burden in POCD using molecular imaging markers that reveal the earliest neuronal changes and thus generate new mechanistic insights.

METHODS AND ANALYSIS

Study aims and hypotheses

Our primary aim is to determine the relationship between global neocortical Aβ deposition and postoperative cognitive dysfunction in patients undergoing cardiac surgery with CPB. Utilising the novel ^{18}F-florbetapir PET imaging agent, we will assess the amyloid burden at 6 weeks after surgery in 40 patients who have undergone cardiac surgery with CPB. We will compare global neocortical amyloid burden in patients with and without POCD, as assessed by a standard neurocognitive battery. We hypothesise that ^{18}F-florbetapir PET amyloid burden will be greater in patients with POCD.

We will also assess the regional pattern of amyloid deposition in patients with POCD by measuring ^{18}F-florbetapir PET uptake values in predefined anatomically relevant cortical regions relative to cerebellar grey matter. The regional uptake patterns will further be compared to those of a previously imaged group of 40 MCI candidates and 40 elderly controls. We hypothesise that the amyloid deposition patterns in patients with POCD will be similar to those in candidates with MCI.

Finally, we will correlate the apolipoprotein E ε-4 (APOE4) genotype and the amyloid burden in the 40 patients undergoing cardiac surgery. Our hypothesis is that the overall amyloid burden will be greater in patients with APOE4.

Study design

Forty informed and consenting patients for cardiac surgery with CPB (CABG, valve or CABG+valve) will be prospectively enrolled over a 2-year period. In addition, a group of 40 elderly controls (age: 69.5+11.1; education: 15.2+2.1; Mini-Mental State Examination (MMSE): 29.6+0.5, 44% male) and 40 participants with MCI (age: 71.5+10.0; education: 14.9+2.3; MMSE: 27.3+1.8, 45% male) who have already been enrolled and imaged with PET will be used to compare regional patterns of amyloid deposition (figures 1 and 2).

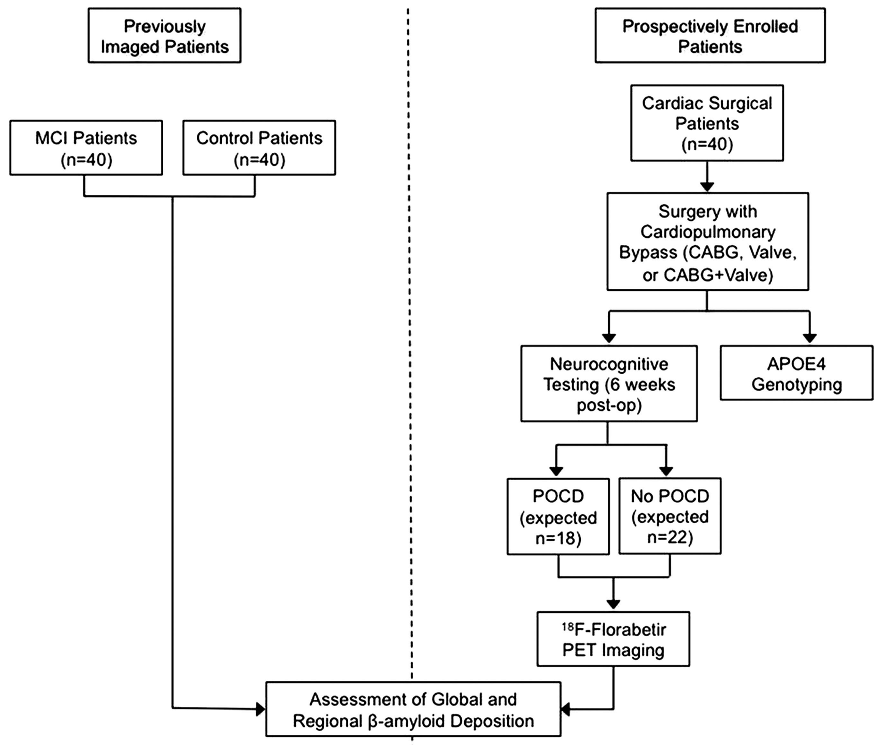

Figure 1 Flow diagram of study design.

Eligibility criteria

All participants entered into the study will be patients of the Duke University Health System. Institutional Review Board (IRB) approval has been obtained, and all patients will sign a written informed consent form. Patients are eligible for enrolment in this trial if they are >60 years of age and are scheduled for CABG, valve or CABG+valve surgery with the use of CPB as part of their required surgical treatment. Enrolment is open to genders, aged >60, as well as all minority groups, and we expect our enrolment to match regional and local trends for gender and ethnicity in cardiac surgery and medical management of coronary disease.

Exclusion criteria

Patients with a history of symptomatic cerebrovascular disease (eg, prior stroke) with residual deficit, alcoholism (>2 drinks/day), psychiatric illness (any clinical diagnoses requiring therapy), drug abuse (any illicit drug use in the past 3 months), hepatic insufficiency (aspartate transaminase, alanine transaminase >1.5 times the upper limit of normal), severe pulmonary insufficiency (requiring home oxygen therapy) or renal failure (serum creatine >2.0 mg/dL) will be excluded. Pregnant or premenopausal women and patients who are unable to read and thus unable to complete the cognitive testing or who score <24 on a baseline MMSE or >27 on

Figure 2 Study measures.

Event	Baseline (Pre-Op)	Day of Surgery	Daily During Hospital Stay	6 Weeks Post-Op
History	x	x	x	x
Physical Exam	x	x	x	x
Demographic data	x	x	x	x
Outcome data		x	x	x
Neurologic Exam	x			x
^{18}F-Florbetapir PET Scan				x
Neurocognitive Testing	x			x
Blood sampling for APOE		x		
Quality of Life	x			x

the baseline Centre for Epidemiological Studies Depression (CES-D) Scale will also be also excluded. Patients who have received any antiamyloid therapies or had any radiopharmaceutical imaging or treatment procedure within 7 days prior to the study session will be ineligible.

Procedure

Patient data

All of the data for this study will be collected according to protocol and recorded on paper forms developed to insure the consistency and accuracy of collection. Detailed demographic and outcome data will be collected daily until hospital discharge and at all follow-up visits. All surgical patients will undergo non-pulsatile hypothermic (30–32°C) CPB with a membrane oxygenator and an arterial line filter. The pump will be primed with crystalloid and serial haematocrit levels will be maintained at >21%. Perfusion will be maintained at pump flow rates of 2–2.4 $L/min^{-1}\ m^2$ throughout CPB to maintain mean arterial pressure at 50–80 mm Hg. Arterial blood gases will be measured every 15–30 min to maintain arterial carbon dioxide partial pressures of 35–40 mm Hg, unadjusted for temperature (α-stat) and oxygen partial pressures of 150–250 mm Hg. Anaesthesia will be induced and maintained with midazolam, fentanyl, propofol and isoflurane or sevoflurane.

Neuroimaging

Participants will undergo ^{18}F-florbetapir PET/CT imaging at the Duke PET Centre. During the scanning, each participant is kept quiet and exposed only to ambient room sound in a dimmed room with eyes open and ears unplugged. Their safety is monitored by a physician/nurse. A 10 mCi (370 MBq) dose of ^{18}F-florbetapir is assayed with a dose calibrator and administered as a bolus injection through a peripheral vein. Ten minutes of continuous brain PET imaging will begin 50 min post-injection. A low-dose CT scan will be acquired for attenuation–correction of the PET images. The PET images will be reconstructed immediately after the 10 min scan, and if any motion is detected, another 10 min continuous scan will be acquired. For quantitative evaluation, standard uptake values (SUV) will be calculated for cortical target areas (frontal cortex, temporal cortex, parietal cortex, precuneus) and the cerebellum. SUV ratios (SUVR) for cortical target areas relative to the cerebellum will also be calculated, and a global mean SUVR will be calculated from the average across all cortical target areas (figure 3). PET images will also be visually examined by an experienced nuclear medicine physician (blinded to the subject diagnosis) and will be reported as either Aβ-positive (AD-like) or Aβ-negative (not AD-like). Tracer for this study is provided free of cost from Avid Radiopharmaceuticals, and the PET scan is being carried out under a standardised Investigational New Drug protocol set by the manufacturer.

The ^{18}F-florbetapir PET has been studied previously in eight patients with probable AD (mean age 70) and nine controls (mean age 44) studied up to 4 weeks apart. Regional SUVR test–retest variability measured by absolute differences ((test–retest)/test) ranged from 4.6% to 5.9% (mean 5.1%) in AD and 1.6–4.0% (mean 2.2%) in controls. Regional SUVR test–retest correlation coefficients ranged from 0.98 to 1.00 for patients with AD and from 0.94 to 0.99 for controls. Thus, ^{18}F-florbetapir SUVR values have high test–retest reliability in each of the seven cortical brain regions evaluated, indicating that the images are reliable markers of ligand retention. There was excellent separation between AD and controls and excellent reliability even with scan times as short as 5 min.

Neurocognitive testing

Cognitive testing will occur at the baseline (preoperatively) and 6 weeks after surgery. In accordance with the consensus statement on assessment of neurobehavioral outcomes after cardiac surgery,[16] the following tests will be included in the assessment battery:

1. Hopkins Verbal Learning Test[17]: assesses multiple cognitive parameters associated with learning and memory.
2. Randt Short Story Memory Test[18]: assesses discourse memory (immediate and delayed) and oral language comprehension.
3. Modified Visual Reproduction Test from the Wechsler Memory Scale[19]: measures short-term and long-term figural memory.
4. Selected subtests from the WAIS-R[19]:
   A. Digit Span: test of short-term auditory memory and attention.
   B. Digit Symbol: measures psychomotor processing speed and attention.
   C. Vocabulary: serves as a measure of verbal intelligence.
5. Trail Making Test, Parts A and B[20]: test of processing speed and attention.
6. Grooved Pegboard[21]: timed test of motor speed and coordination.

Blood sampling

One 10 mL sample of peripheral blood will be obtained from each patient and stored at 4°C prior to processing. Genomic DNA for analysis will be obtained from this sample and banked with the Duke Center for Human Genetics at −20°C for APOE genotyping as previously described.[22]

Sample size calculation

The 40 patients in the cardiac surgery group will provide 86% power to detect an association with amyloid SUVR having an R^2 of 0.20 (r=0.447) and 80% power to detect an R^2 as small as 0.171. We expect about 44%, or 18 of the 40 cardiac surgery participants, to have POCD. This expectation is based on the incidence of POCD

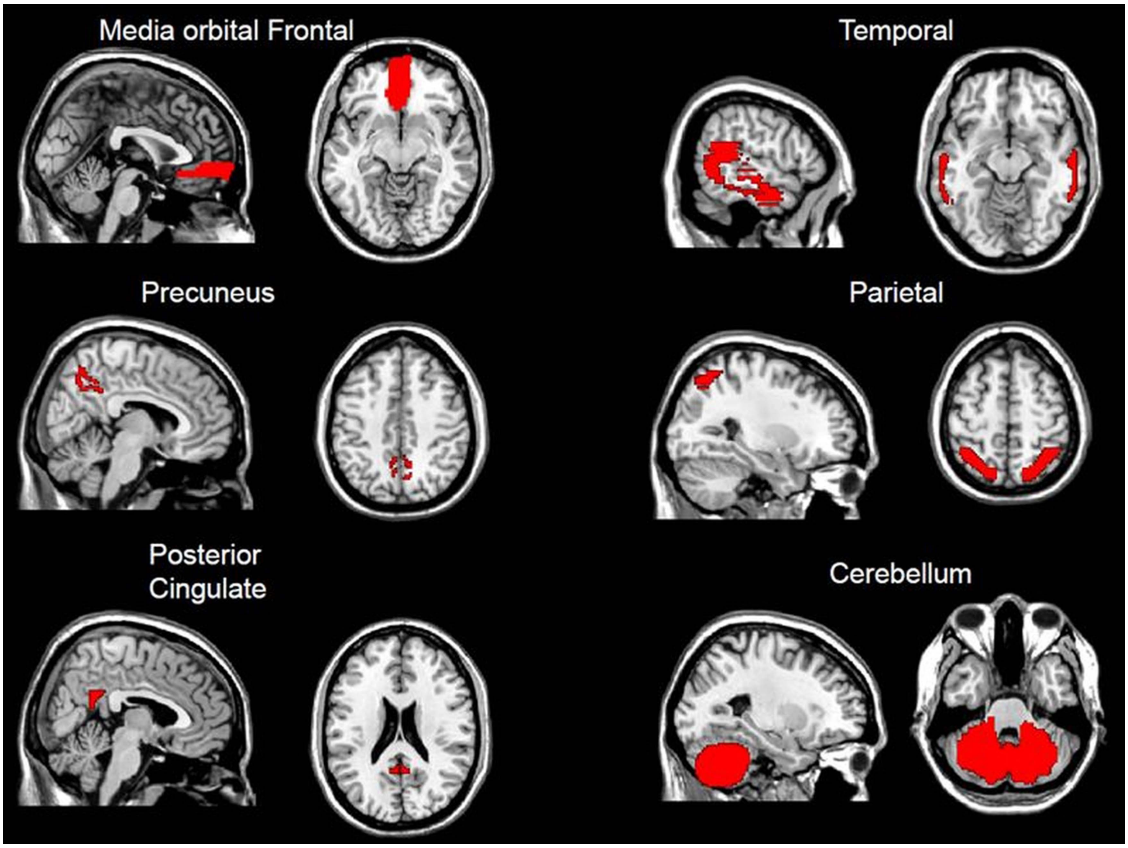

Figure 3 MRI overlay with the regions of interest that are used to measure regional positron emission tomography standard uptake values ratios.

observed in our existing database of 654 cardiac surgery patients like those to be enrolled. We expect the amyloid SUVR in these participants to be similar to the MCI group and greater than the normal controls.

On the basis of mean amyloid SUVR observed in the already-enrolled elderly controls and patients with MCI and a common SD of 0.30, the three-group comparison will have 96% power to detect an overall group effect between group means of 1.0, 1.24 and 1.30. In Bonferroni-adjusted post hoc pairwise group comparisons, the MCI against elderly controls comparison will have 85% power, and the surgery POCD against elderly controls comparison will have 86% power, for the group means stated above. If the MCI and POCD group means differ by as much as 0.22, we will have 80% power to detect it with adjusted α.

Statistical analysis

Amyloid burden will be quantified as SUVR (standard uptake value in cortex relative to cerebellum), a unitless ratio. Standard descriptive statistics for the elderly controls, MCI and surgery groups will be provided, including 95% confidence limits for the mean and comparative plots including histograms and box plots. Cognitive function will be assessed at the preoperative screening visit and 6 weeks postoperatively with a well-validated battery of neurocognitive tests. Because this battery assesses multiple functions and returns many scores, we will use factor analysis to combine the scores based on their intercorrelations into a set of independent, continuous and standardised summary scores representing function in separate domains of cognitive function. Based on our extensive experience with the test battery, we expect to obtain factor scores for four separate domains.[1 23–25] The separate factor scores of each testing time will be averaged to obtain an overall score for each test period, and postoperative change in cognitive function will then be quantified as the difference between the preoperative and postoperative overall scores. Analysis using this continuous measure of change can most powerfully identify a correlation between amyloid SUVR and cognitive function. In addition, for descriptive purposes, we will define a binary indicator of POCD as a decline in performance on any of the domain scores equal to or greater than one SD of the baseline domain score. We will investigate the association between amyloid SUVR and cognitive change first with Pearson (linear) and Spearman (rank) tests of correlation and then with linear regression models with cognitive change as the dependent variable. If the distributions of either measure are non-normal, we will investigate transformations to make them more nearly normal. We will include as covariables in the models those characteristics that are found to influence cognitive change, including baseline cognitive score, age and years of education, as well as other characteristics associated with SUVR. We will also investigate non-linear fits in the models. Finally, we will describe the distribution of amyloid SUVR in patients with and without POCD as defined above and conduct a secondary logistic regression analysis similar to the regression above using POCD as the binary outcome.

Amyloid deposition will be assessed and described for the 40 cardiac surgery candidates in the same manner as performed for the MCI and elderly control candidates.[26] The amyloid deposition SUVR will then be compared among three groups: the 40 elderly controls, the 40 patients with MCI and those patients from the cardiac surgery group classified as having POCD. Thorough comparisons of the relevant group characteristics will be conducted with χ^2 and Wilcoxon tests. Normality of the SUVR measure will be investigated and corrected with transformation if necessary. A general linear ANOVA model will be used to test group differences and account for other important covariables including age and two-way interactions.

ApoE4 will be categorised as the presence or absence of the APOE-ε4 allele, either singly or in both alleles. This binary indicator will be tested for association with amyloid SUVR as a predictor in a multivariable general linear ANOVA model, which will also account for other important covariables such as age.

ETHICS AND DISSEMINATION PLANS

This study protocol is approved by the Duke University IRB (Pro00028580). It is unlikely that any of the participants enrolled in the study will directly benefit from participation. However, the risk to participation is minimal. Participation in the research study will not significantly alter the routine anaesthetic or surgical management techniques as currently practiced at Duke University Medical Center.

The results of this study will be submitted for publication in a peer reviewed journal and presented at national and international meetings.

DISCUSSION

One of the principal limitations of this study is that it is an observational study using existing controls. However, the data will be collected and the values will be determined in exactly the same way for all patients and by the same experienced investigators. Group comparisons and covariate adjustments will also be conducted to ensure that estimates are as accurate as possible in this exploratory study.

While there are more publications on the use of ^{11}C-PIB in PET imaging of brain amyloid, this compound has only recently completed an FDA quality phase 3 study. We chose ^{18}F-florbetapir because: (1) it is the only tracer that has completed phase 2 and phase 3 studies; (2) it has safety data from a large multicenter phase 2 trial performed in the USA; (3) it has undergone a successful multicentre phase 3 study with PET-autopsy correlation in terminally ill participants who received a PET while alive and an autopsy on death a few months later with results suggesting that baseline amyloid in MCI candidates predicts greater cognitive and functional decline[27] and (4) it has been used in a multicentre NIA-sponsored trial (ADNI-GO) of AD and MCI and several phase 3 industry trials of antiamyloid therapies, suggesting that our data will be easily comparable to those obtained from these other studies.

This study will be the first to utilise PET imaging to analyse the role of amyloid burden in POCD following cardiac surgery with CPB. It extends our previous work on this unfortunate consequence of surgery by incorporating a sensitive molecular imaging technique that can be employed in living patients. By comparing the regional patterns of Aβ deposition in cardiac surgical patients with those seen in a group of elderly controls and MCI participants, we will be able to begin to corroborate or refute the similarities between POCD and MCI. The results of this study will provide novel mechanistic insight into the potential aetiology of POCD, and in the future other forms of long-term cognitive decline, thereby suggesting targets for treatment and/or prevention.

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Competing interests PMD has received research grants and advisory/speaking fees from several pharmaceutical and imaging companies, including Avid Radiopharmaceuticals. He owns shares in Sonexa, Clarimedix and Adverse Events Inc. whose products are not discussed here. TZW serves on the advisory board for Eli Lilly and Company. OGJ served as a trainer for the Amyvid Reader Training Programme for Eli Lilly and Company.

Patient consent Obtained.

Ethics approval Duke Institutional Review Board.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement No additional data are available.

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