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Presurgical Thalamus Volume in Postoperative Delirium: a longitudinal observational cohort study in older patients.

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Marinus Fislage: This author helped with the research design, data collection, thalamus volume analyses, data analyses, data interpretation and wrote the manuscript.

Insa Feinkohl: This author helped with the preparation of cognitive data and the critical revision of the manuscript.

Tobias Pischon: This author helped with the study design and supervision of the project.

Claudia D. Spies: This author helped with the study design and supervision of the project.

Friedrich Borchers: This author helped with data collection and the revision of the manuscript.

Georg Winterer: This author helped with the research and study design, supervision of the project and the critical revision of the manuscript.

Norman Zacharias: This author helped with research design, supervision of the project, conception of the manuscript and the critical revision of the manuscript.

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Abstract

Background Previous studies suggest a role of the thalamus in cognitive function, while others implicate it as a central effect site of anesthetics. Yet, its role in postoperative neurocognition in the aging brain remains uncertain. We used presurgical thalamic volume as a functional indicator and determined its association with postoperative delirium (POD).

Methods For this study 301, older adults (aged ≥65) without dementia and scheduled for surgery were enrolled. Before surgery, participants underwent magnetic resonance imaging (MRI). Thalamus volume was segmented using Freesurfer (Version 5.3.). Participants were screened for POD twice a day until discharge or for a maximum of seven days. POD was defined as a positive screening on ≥1 of four validated instruments: Richmond Agitation Sedation Scale (RASS), Nursing Delirium Screening Scale (Nu-DESC), Confusion Assessment Method (CAM) and Confusion Assessment Method for the Intensive Care Unit score (CAM-ICU). A logistic regression associated thalamus volume with POD with adjustment for age, global brain atrophy and physical status according to the American Society of Anesthesiologists classification (ASA).

Results In this cohort 44 participants (14.6%) were diagnosed with POD. Independently of age, global brain atrophy and physical status score a higher preoperative thalamus volume was associated with a reduced odds of POD (Odds ratio per 1cm³ increment, 0.73 [95% CI 0.58-0.92] p = 0.008).

Conclusions A larger thalamus volume was associated with reduced odds of POD. Thus, the thalamus marks a region of interest in POD in the aging brain. These findings may help to understand the neuronal basis of POD.

Key Points Summary

Question: Is the presurgical thalamus volume associated with postoperative delirium?

Findings: Associations of thalamus volume with postoperative delirium were observed.

Meaning: The thalamus was identified as region of interest for further investigations in postoperative delirium.

Glossary of Terms

BioCog - 'Biomarker Development for Postoperative Cognitive Impairment in the Elderly' study

BPF – Brain Parenchymal Fraction

CAM - Confusion Assessment Method

CAM-ICU - Confusion Assessment Method for the Intensive Care Unit

DSM-V - 5th edition of the Statistical Manual of Mental Disorders

Nu-DESC – Nursing Delirium Screening Scale

IBM - International Business Machines Corporation

MP RAGE - Magnetization-Prepared Rapid Gradient Echo

MRI – Magnet Resonance Imaging

POD - Postoperative Delirium

RASS - Richmond Agitation Sedation Scale

SAGES – 'Successful Aging after Elective Surgery' study

SPSS - Statistical Product and Service Solutions

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

Introduction

The thalamus has been portrayed as a consciousness switch during anesthesia.[1] This may be related to the decreased metabolism and the reduction of regional cerebral blood flow caused by anesthetics.[2] [3] Also thalamocortical disconnection was reported in positron emission tomography during general anesthesia.[4] The loss of consciousness by suppression of thalamic activity appears to be desirable during anesthesia. Conversely, the disintegration of essential cognitive functions maintained by the thalamus can be observed during episodes of delirium. Consciousness and alertness, for instance, are known to be profoundly regulated by thalamic circuits and its rhythmogenic activity.[5] The same applies for sleep and wakefulness.[6]

According to the 5th edition of the Statistical Manual of Mental Disorders the acute impairment of attention and cognition sets an important diagnostic criterion in delirium.[7] There is a growing amount of literature that elucidates the thalamic impact on cognition. A variety of cognitive domains appears to rely on the thalamus. Impaired executive function, attention and working memory was observed after thalamic infarction.[8] Recent studies have demonstrated that the mediodorsal thalamus governs representation within the prefrontal cortex by recruiting inhibitory cortical neurons.[9] Attention and decision-making appear to rely on thalamic nuclei, especially the pulvinar and the mediodorsal thalamus. [10] [11]

For the perioperative setting, 136 older adults (>70 years) received diffusion tensor imaging prior to surgery in the ‘Successful Aging after Elective Surgery’ (SAGES) study. In this cohort 19 patients (21%) were classified as delirious. The SAGES study group reported an association of a lower fractional anisotropy in the thalamus with an increased incidence of postoperative delirium (POD).[12] Furthermore, mean diffusivity

and fractional anisotropy in the thalamus were correlated with delirium severity. The authors hypothesized that their findings might be a sign for structural dysconnectivity of the thalamus and the prefrontal cortex. In another study, Shiori et al. also observed an association between thalamic fractional anisotropy and the risk for POD in 116 patients scheduled for cardiac surgery.[13]

Here, we report on an exploratory secondary analysis run within the framework of a perioperative observational cohort study with older surgical patients. In prospective analyses, we aimed to elucidate the association of the thalamus volume with the risk of developing POD during the hospital stay. Older patients are particularly prone to developing POD.[14] Analogously, brain and thalamic atrophy proceeds with aging. [15] [16] A diminished cellular reserve might increase the vulnerability against stressors related to surgery. We hypothesize that smaller, potentially atrophic, thalamus volumes predispose older patients to an increased POD risk.

Material and Methods

Study Setting and Study Population

Data for this exploratory analysis were derived from the multicentric prospective observational cohort study 'Biomarker Development for Postoperative Cognitive Impairment in the Elderly' (BioCog; www.biocog.eu;). The study was approved by the local ethics committees and registered on clinicaltrials.gov prior to enrolment (NCT02265263). Study objectives and protocol have been described previously.[17] This manuscript adheres to the applicable 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines. We analyzed data obtained at one of the two study centers of BioCog, the university hospital Charité – Universitatsmedizin Berlin, Germany. Consequently, the final analysis set consisted of data from 301 patients. [see FIGURE1]

According to the inclusion criteria, female, or male patients older or at the age of 65 were recruited. (https://clinicaltrials.gov/ct2/show/NCT02265263) We were aiming to recruit participants, who were scheduled for major surgery. Hence, the estimated total duration of the planned elective surgical intervention was at least 60 minutes. A preoperative minimum score of 23 at the Mini Mental State Examination was required to ensure a non-demented cognitive status preoperatively. Severe deafness and blindness led to exclusion. Furthermore, eligibility for magnet resonance imaging was compulsory for this subsample analysis. Informed and written consent was obtained at inclusion. For patient's characteristics see TABLE1.

Assessment of Postoperative Delirium

The postoperative delirium (POD) assessment was administered once preoperatively and twice a day after surgery, once in the morning and in the evening. The tests were carried out until discharge or for a maximum of seven days after surgery. Study physicians, study nurses or study assistants, who were working under supervision of a study physician, undertook the POD assessment. They received training in the format of blended learning. This was followed by courses, which were designed as on-site evaluation. Interrater reliability was not determined.

The assessment consisted of the following validated tests[18]: Richmond Agitation Sedation Scale (RASS), Nursing Delirium Screening Scale (Nu-DESC), Confusion Assessment Method (CAM) and Confusion Assessment Method for the Intensive Care Unit score (CAM-ICU). Applied tests correspond with the 5th edition of the Statistical Manual of Mental Disorders (DSM-V). For validation purposes, the patient chart review was screened. The objective was to ensure that the study assessment aligned with routinely made observations by the ward staff.

POD was defined before data acquisition according to DSM-V criteria. Patients were considered delirious in case of i.) ≥ 2 cumulative points on the Nu-DESC ii.) and/or a positive CAM score iii.) and/or a positive CAM-ICU score.

Imaging

All magnet resonance images were acquired using a 3 Tesla magnet resonance imaging-scanner (Siemens Trio Magnetom) at the Berlin Center for Advanced Neuroimaging. A T1-weighted 3D magnetization-prepared rapid gradient echo (MP RAGE) sequence was conducted using a 32-channel head coil (TR=2500ms, echo

time=4.77ms, flip angle=7°, 192 sagittal slices, field of view =256x256mm², voxel size=1x1x1mm³). As a matter of routine, images were neuroradiologically examined to detect potential intracranial pathologies.

In the course of the reconstruction process,[19] subcortical volumes were automatically segmented using Freesurfer (5.3.) on Linux CentOS6 (x86). The automated Freesurfer processing pipeline includes an adjustment of T1 weighted images using motion correction and averaging.[20] After non-brain tissue was removed, a Talairach transformation was performed, and subcortical structures were tagged.[21] Segmentation results were specified in cubic millimeter.

Automated segmentation of subcortical structures was described to be as accurate as manual labelling. This was reported to especially apply when quantifying the thalamus.[22] Nonetheless, a manual review of the accuracy was required after reconstruction. To ensure reproducibility, a manual correction of the labels was not performed.

Finally, the Freesurfer variables ‘LeftThalamusProper’ and ‘RightThalamusProper’, were added up to determine the total thalamus volume. Moreover, we used the Freesurfer variable ‘EstimatedTotalIntraCranialVol’ as measure for intracranial volume and ‘BrainVolNotVent’ as measure for brain parenchymal volume. (https://surfer.nmr.mgh.harvard.edu/fswiki/MorphometryStats). We calculated the brain parenchymal fraction (BPF) as ratio of brain parenchymal volume and intracranial volume.[23]

Statistical Analysis

There was no statistical plan for this specific analysis defined before data collection. The sample size for this secondary analysis was based on general estimates for any neuroimaging marker, which was examined within the BioCog study [see Suppl.]. Ultimately, we adapted our sample size according to higher dropout and lower incidence rates for the imaging sample. Please note that due to the novel scope effect size estimates were based on general assumptions, instead of observed effect sizes described.

To simplify the interpretation and visualization of the data, we adjusted the scaling of MRI volumetric data from cubic millimeters to cubic centimeters. Multivariable logistic regression analysis was performed. Thalamus volume was used as the predictor variable of interest. Covariates were selected based on the expected dependence structure as suggested by the literature. This includes variables, which might have a confounding effect on both - thalamus volume and postoperative delirium. For instance, higher age was described to increase the risk for POD and to decrease thalamus volume.[24] The American Society of Anesthesiologists Physical Status classification score (ASA) was used to classify morbidity and individual risk for POD. We chose the brain parenchymal fraction (BPF), the ratio between brain size and intracranial volume, as predictor variable to account for brain atrophy.[25] BPF recurs to the presumption that brain size and intracranial volume must be considered both, when directing at overall brain atrophy. It represents the ratio of the brain parenchyma within the skull.

A special emphasize was placed on multicollinearity, which was assessed by checking the variance inflating factor (VIF) for each variable.

Statistical significance was defined as $p < 0.05$. The statistical analysis was executed using IBM SPSS Statistics for Windows (Version 28.0.)

For graphs and figures Graphpad Prism (Version 9.1. GraphPad Software, Inc.) was used. Color schemes are intended to be colorblind safe. For visualization purposes, an unpaired, two-tailed t-test was deployed.

Results

Of the 301 participants, 44 (14.6%) were diagnosed with POD. The mean thalamus size of the non-delirious participants was 13.03cm³ [95%CI 12.84 - 13.22], whereas the mean of the delirious group was 12.31cm³ [95%CI 11.91 – 12.72]. Mean differences was 0.72cm³ as determined by an unpaired two-tailed t-test (T(299)= 2.86; p = 0.004) [see Figure 2 and 3]. Furthermore, characteristics across groups are shown in Table 2.

In the logistic regression model POD was set as the dependent variable. Thalamus volume served as exposure variable of interest. Adjustment variables were age, BPF and the ASA classification. Covariates might have a possible effect on the onset of POD and the thalamus volume. Thalamus volume was significantly associated with reduced odds of POD (OR for each 1cm³ increment 0.73 [95% CI 0.58-0.92] p = 0.008). The odds for POD were reduced by 27% for each increase in 1cm³ thalamus volume. The adjustment variables, age, BPF and ASA classification were not significantly associated with POD [TABLE 3]. Multicollinearity was not present (VIF thalamus = 1.07; VIF age = 1.18; VIF BPF = 1.14; VIF ASA classification = 1.04).

Discussion

In this analysis of an observational cohort study of older patients, we found that a higher thalamic volume was associated with reduced odds of developing POD.

Preserving or even expanding autonomy in older people is regarded as important outcome of therapy, especially after surgery and anesthesia. Since delirium is known to be an independent risk factor not only for premature death, but also for the onset of dementia and institutionalization, patients at risk need to be identified.[2424]

The thalamus marks a central site for the effect of general anesthesia.[26] Anesthetics, except for ketamine, cause a reduction of thalamic blood flow and metabolism.[1] Albeit cortical function needs to be considered in anesthesia-induced unconsciousness and the thalamus as a single consciousness switch might be overstated[27], the observed decline in thalamic circulation and metabolism potentially causes cellular distress. By choosing a longitudinal study design, future investigations might detect POD-related morphological alterations in the thalamus of patients that underwent surgery. Furthermore, future studies may also consider investigating the consequences of adapting the choice of anesthetics or depth of anesthesia in respect of the anticipated burden for the thalamus.

While we have shown that thalamus volume correlates with POD, the role of specific thalamus compounds could not be identified. The thalamus consists of 50-60 nuclei, which differ in size and function. The overall size of the thalamus might be determined by the pulvinar and the mediodorsal thalamus, the largest and the second largest nuclei.[9] However, previous works have described an association between the fractional anisotropy in the anterior ventral nuclei and POD.[13] This may be a focus of future research.

We were able to transfer the results from diffusion tension imaging as observed in the SAGES cohort to a volumetric analysis. Diffusion tensor imaging and functional magnet resonance imaging use volumetric data as template. Alterations in diffusion tensor imaging like those observed in other frameworks might therefore act on the assumption, that the volumetric reserve was reduced in the first place.

This notion represents a link to the cognitive reserve theory.[28] It postulates that adults have a certain cognitive capacity, which enables them to cope with neurodegenerative alterations caused by age or disease. This concept can be expanded to brain size and volumetric measures in general as part of the 'brain reserve theory'.[29] In short: "Size matters."[30] In these terms, a volumetric reserve represents the surplus in volume that can buffer any possible reduction due to degenerative processes before a potential dysfunction becomes apparent. Regarding the thalamic volume, we might determine a possible protective effect of higher volumes against stressors like surgeries. Accordingly, thalamic atrophy represents the corresponding risk factor, due to a lack of potentially protective reserve of neurons.

Limitations

Depth of anesthesia was monitored by intraoperative electroencephalogram, but other parts of anesthesiologic management were not standardized. We were not able to account for potential confounders that arise from surgery type or the related anesthesiologic handling.

Interrater reliability for the POD assessment was not determined. This would have helped to detect variability in results between raters.

Due to the novel scope and the exploratory character of this study, the sample size was not predetermined.

Conclusion

A larger preoperative thalamic volume was associated with reduced odds of POD, and independently of age, ASA classification and overall brain atrophy. It might represent a neural correlate of POD risk. Thus, we identified the thalamus to be a region of interest in POD in older patients. This may help to further understand the etiology of POD. Moreover, these findings have the potential to build the basis for future studies focusing on risk stratification of older patients and eventually, on adapting anesthesiologic management aiming at reducing the burden for the already vulnerable, atrophic thalamus.

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FIGURE1 '**Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) diagram**

Note: The diagram shows the inclusion process and reasons for exclusion.

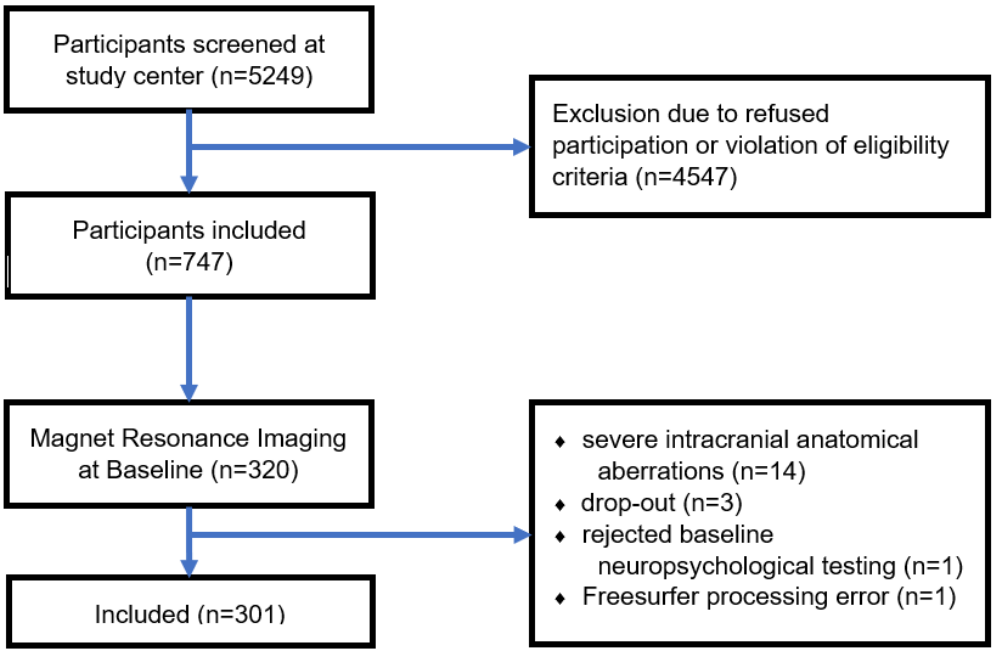

FIGURE 2 **Box plots of group difference in thalamus size – Postoperative Delirium (POD)**

Note: Thalamus volume in cm³ is drawn on the y-axis. The boxplot on the left shows the group of participants, who were not diagnosed with postoperative delirium (No Delirium)[n=257; mean thalamus size= 13.03cm², SD 1.57]. The boxplot on the right represents the postoperative delirium group (Delirium)[n=44; mean thalamus size= 12.31cm², SD 1.33]. The mean difference between both groups was -0.72cm³ [unpaired, two-tailed t-test: T(299)= 2.86; p = 0.004]. Colorblind safe selection of coloring was applied.

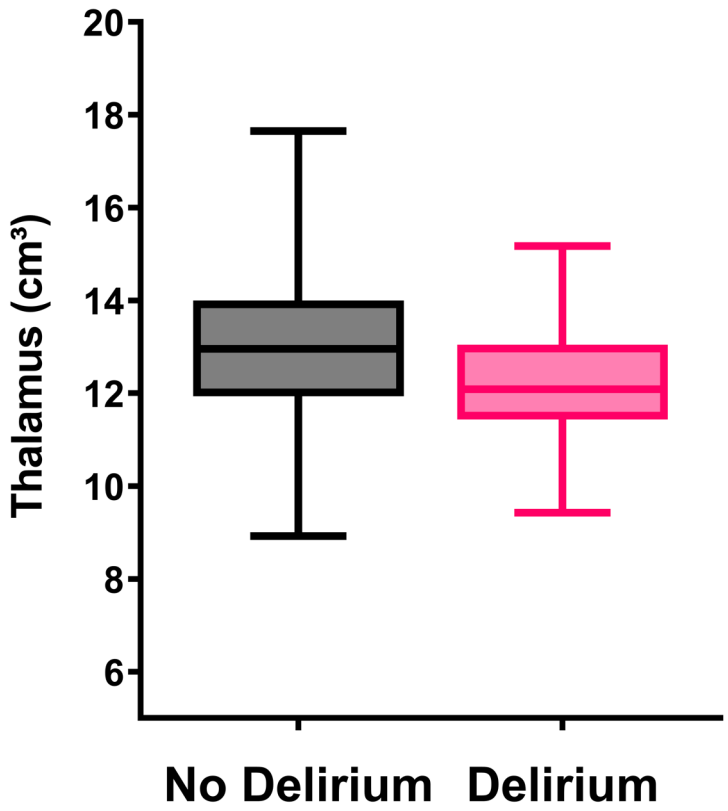

FIGURE 3 **Mean and confidence intervals – Postoperative Delirium (POD)**

Note: Thalamus volume in cm³ is drawn on the y-axis. The dot on the left shows the mean thalamus size of participants, who were not diagnosed with postoperative delirium. The attached error bars display the 95% confidence interval (No Delirium)[n=257; mean thalamus size= 13.03cm², 95%CI 12.84 - 13.22]. The red dot represents the postoperative delirium group (Delirium)[n=44; mean thalamus size= 12.31cm², 95%CI 11.91 – 12.72]. The mean difference between both groups was -0.72cm³ [unpaired, two-tailed t-test: T(299)= 2.86; p = 0.004]. Colorblind safe selection of coloring was applied.

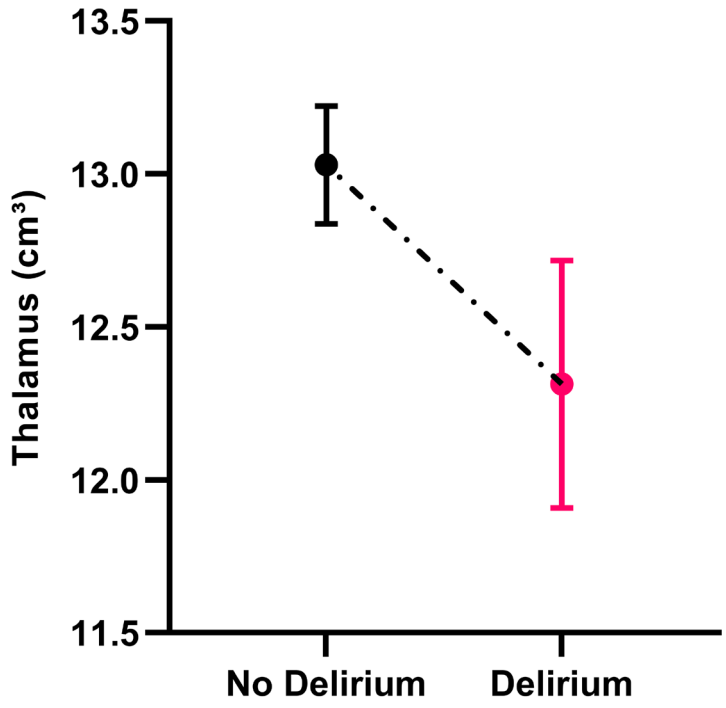

TABLE 1 **Characteristics of patients**

Variable	**N**	**Mean (SD)**	**Range**
Age	301	72.4 (4.9)	65 – 87
Female Sex	131	43.5%	
Body Mass Index (BMI)	300	26.9 (4.4)	14.7 – 44.3
Mini-Mental State Examination (MMSE)	301	Median 29 (IQR 2) [25^{th}/75^{th} 28/30]	24 - 30
Brain Volume [cm^3]	301	979.2 (101.7)	705.8 – 1222.3
Thalamus Volume [cm^3]	301	12.9 (1.6)	8.9 – 17.6
Duration of anesthesia [min]	295	183.9 (116.3)	30.0 – 600.0
Type of anesthesia	300		
1. General	230	76.4%	
2. Regional	14	4.7%	
3. Combined	56	18.6%	
Type of surgery	301		
1. Musculoskeletal	85	28.2%	
2. Gastrointestinal	51	16.9%	
3. Cardiovascular or thoracic	17	5.6%	
4. Genitourinary	66	21.9%	
5. Otorhinolaryngology	23	7.6%	
6. Oral and maxillofacial	16	5.3%	
7. Ophthalmology	22	7.3%	
8. Neurosurgery	6	2.0%	
9. Other	15	5.0%	
ASA score	301		
1. ASA I	7	2.3%	
2. ASA II	204	67.8%	

3. ASA III	90	29.9%	
Length of Stay [days]	301	8.1 (9.5)	1 – 84

Note: The table shows characteristics of participants. For categorial variables percentages are given instead of mean and standard deviation (SD) in brackets. (ASA ≙ 'American Society of Anesthesiologists Physical Status' Classification; IQR ≙ Interquartile Range $25^{th}/75^{th}$ ≙ 25^{th} and 75^{th} percentile)

TABLE 2 **Comparison of groups (No Delirium vs. Delirium)**

Variable	**No Delirium** **N = 257**	**Delirium** **N = 44**
Age [years] – mean (SD)	72.27 (5.01)	73.36 (4.31)
Female Sex	106 (41.2%)	25 (56.8%)
Body Mass Index (BMI) – median (IQR)	26.57 (5.3) N= 256	26.72 (5.43)
Mini-Mental State Examination (MMSE) [points] – median (IQR)	29 (2)	28.5 (3)
Brain Volume [cm³] – mean (SD)	983.69 (101.79)	952.63 (98.06)
Thalamus Volume [cm³] – mean (SD)	13.03 (1.57)	12.31 (1.33)
Duration of anesthesia [min] – mean (SD)	163.76 (96.96) N= 251	298.95 (147.99)
Type of anesthesia 1. General 2. Regional 3. Combined	 203 (79%) 14 (5.4%) 40 (15.6%)	 27 (61.4%) 1 (2.3%) 16 (36.4%)
Type of surgery 1. Musculoskeletal 2. Gastrointestinal 3. Cardiovascular or thoracic 4. Genitourinary 5. Otorhinolaryngology 6. Oral and maxillofacial 7. Ophthalmology 8. Neurosurgery	 75 (29.2%) 37 (14.4%) 14 (5.4%) 54 (21.0%) 23 (8.9%) 15 (5.8%) 21 (8.2%) 6 (2.3%)	 10 (22.7%) 14 (31.8%) 3 (6.8%) 12 (27.3%) 0 1 (2.3%) 1 (2.3%) 0

9. Other	12 (4.7%)	3 (6.8%)
ASA score 1. ASA I 2. ASA II 3. ASA III	 5 (1.9%) 176 (68.5%) 76 (29.6%)	 2 (4.5%) 28 (63.6%) 14 (31.8%)
Length of Stay [days] – median (IQR)	5 (5)	13 (20.75)

Note: The table shows different characteristics in the group without delirium (No Delirium) in comparison to the group with postoperative delirium (Delirium). For categorial variables amount and percentages within the specific group are given. (ASA ≙ 'American Society of Anesthesiologists Physical Status' Classification; IQR ≙ Interquartile Range 25th/75th ≙ 25th and 75th percentile)

TABLE 3 **Multivariable logistic regression: Postoperative Delirium (POD)**

Dependent variable: **Postoperative Delirium**	Estimated Beta	Standard Error	Sig.	Odds Ratio	95% Confidence Interval (Odds Ratio) Lower	Upper
Thalamus Volume [cm³]	-0.316	0.120	0.008	0.729	0.577	0.922
Age [year]	0.035	0.035	0.312	1.036	0.967	1.109
BPF	1.460	1.912	0.445	4.306	0.101	182.665
ASA classification	-0.189	0.343	0.582	0.828	0.423	1.622
Constant	-0.996	3.977	0.802	0.369		

(n total = 301; POD = 44)

Note: BPF ≙ Brain Parenchymal Fraction; ASA ≙ American Society of Anesthesiologists

Sample Size Calculation

For neuroimaging markers, the BioCog Consortium was initially aiming for effect sizes (Hedges g) of 0.5-1.5. Initially an incidence of 20-30%for postoperative delirium and a 10% drop-out rate expected. Accordingly, an effect size of 0.5 to yield 80% power (α=5%, two-sided) roughly required a sample size of N ~ 200 for any single neuroimaging biomarker.