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RESEARCH REPORT

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An exploratory research report on brain mineralization in postoperative delirium and cognitive decline

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Abstract

Delirium is a severe postoperative complication associated with poor overall and especially neurocognitive prognosis. Altered brain mineralization is found in neurodegenerative disorders but has not been studied in postoperative delirium and postoperative cognitive decline. We hypothesized that mineralization-

Abbreviations: AD, Alzheimer's dementia; BCAN, Berlin Center for Advanced Neuroimaging; CAM(-ICU), Confusion assessment method (for the intensive care unit); CI, confidence interval; CSF, cerebrospinal fluid; DARTEL, diffeomorphic anatomical registration through exponentiated lie algebra; df, degrees of freedom; DSM, The Diagnostic and Statistical Manual of Mental Disorders; 'g', global cognitive component; GPT, grooved pegboard test; ISPOCD, International Study of Post-Operative Cognitive Dysfunction; MPRAGE, magnetization prepared rapid acquisition gradient echo; MRI, magnetic resonance imaging; MMSE, mini-mental status examination; NuDesc, nursing delirium screening scale; OR, odds ratio; PAL, paired associate learning test; (p)BFCS, (posterior) basal forebrain cholinergic system; PCA, principal component analysis; PD, Parkinson's disease; POD, postoperative delirium; POCD, postoperative cognitive dysfunction; ROI, region of interest; SRT, simple reaction task; SWI, susceptibility-weighted imaging; TE, echo time; TMT-B, trail-making test, part B; TR, repetition time; VRM, verbal recognition memory.

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related hypointensity in susceptibility-weighted magnetic resonance imaging (SWI) is associated with postoperative delirium and cognitive decline. In an exploratory, hypothesis-generating study, we analysed a subsample of cognitively healthy patients ≥65 years who underwent SWI before ($N = 65$) and 3 months after surgery ($N = 33$). We measured relative SWI intensities in the basal ganglia, hippocampus and posterior basal forebrain cholinergic system (pBFCS). A post hoc analysis of two pBFCS subregions (Ch4, Ch4p) was conducted. Patients were screened for delirium until the seventh postoperative day. Cognitive testing was performed before and 3 months after surgery. Fourteen patients developed delirium. After adjustment for age, sex, preoperative cognition and region volume, only pBFCS hypointensity was associated with delirium (regression coefficient [90% CI]: $B = -15.3$ [−31.6; −0.8]). After adjustments for surgery duration, age, sex and region volume, perioperative change in relative SWI intensities of the pBFCS was associated with cognitive decline 3 months after surgery at a trend level ($B = 6.8$ [−0.9; 14.1]), which was probably driven by a stronger association in subregion Ch4p ($B = 9.3$ [2.3; 16.2]). Brain mineralization, particularly in the cerebral cholinergic system, could be a pathomechanism in postoperative delirium and cognitive decline. Evidence from our studies is limited because of the small sample and a SWI dataset unfit for iron quantification, and the analyses presented here should be considered exploratory.

KEYWORDS
anaesthesia, basal nucleus of Meynert, cholinergic system, delirium, magnetic resonance imaging, postoperative cognitive dysfunction, surgery, susceptibility weighted imaging

1 | INTRODUCTION

Delirium is a common but severe complication after surgery and anaesthesia marked by acute disturbances in attention, awareness, cognition, psychomotor behaviour and emotion. Especially older patients are at high risk for delirium (Androsova et al., 2015) and in particular postoperative delirium (POD) will gain further relevance as life expectancy is increasing in Western societies, and the need for surgical interventions is higher among the older (Fowler et al., 2019; Nielsen et al., 2021). This challenges healthcare systems since POD is associated with poor neurocognitive outcome, hospitalization, treatment costs, re-institutionalization and mortality (Abelha et al., 2013; Drews et al., 2015; Hshieh et al., 2017; Inouye et al., 2016; Koebrugge et al., 2009; Peter et al., 2016; Robinson et al., 2009; Rudolph et al., 2008).

Various interrelated pathomechanisms have been proposed to be involved in POD, for example, neuroinflammation and immune dysregulation, cholinergic dysfunction, disturbed network connectivity, oxidative stress and neurodegenerative changes (Androsova et al., 2015; Glumac et al., 2017; Maldonado, 2013). Pre-existing neurodegenerative diseases are a risk factor for POD (Dasgupta & Dumbrell, 2006), and vice versa, as cognitive decline is a common long-term sequela of POD in cognitively healthy individuals (Robinson et al., 2009; Teipel et al., 2018), but potentially shared pathomechanisms are yet to be investigated. For example, both volumetric magnetic resonance imaging (MRI) studies investigating Alzheimer-like atrophy patterns and positron emission tomography studies targeting amyloid have suggested neurodegenerative changes in POD and postoperative cognitive dysfunction (POCD) (Racine et al., 2017, 2020; Rolandi et al., 2018).

Cerebral mineralization, such as iron deposition and calcifications, has been suggested as a common feature in aging (Burgetova et al., 2021) and several neurodegenerative and neuroinflammatory diseases, such as Alzheimer's disease (AD) (Damulina et al., 2020), Parkinson's disease (PD) (Biondetti et al., 2021) and multiple sclerosis (Chawla et al., 2016, 2018; Hametner et al., 2013). For example, iron has been found to be associated with tau deposits of amyloid plaques in AD (Madsen et al., 2020; Spotorno et al., 2020; Wu et al., 2023). α-Synuclein as the main constituent of abnormal aggregates in PD and Lewy body dementia (LBD) has been shown to mediate potentially neurotoxic calcium influx as well as iron-dependent cell membrane oxidation (Angelova et al., 2020), and vice

versa, iron accelerates the fibril formation of α-synuclein (Bharathi et al., 2007). Iron may also mediate detrimental effects of neuroinflammation and neuroimmune dysregulation in POD and POCD (Forsberg et al., 2017; Glumac et al., 2017; Katsumi et al., 2020). For multiple sclerosis, it has been suggested that iron is released from the damaged myelin sheath and subsequently accumulates in microglia (Hametner et al., 2013). Furthermore, both iron and calcium deposition have been observed in animal models of traumatic brain injury and status epilepticus (Aggarwal et al., 2018; Schweser et al., 2019).

Although oxidative stress has been proposed as a pathomechanism in POD, which may be caused by free iron (Angelova et al., 2020; Maldonado, 2013), only few data have been published with regard to metals in the pathogenesis of delirium: A study conducted in 19 patients eventually reported altered plasma iron levels in patients with delirium tremens, but overall results were inconclusive (Hemmingsen & Kramp, 1980). A recent analysis of the UK biobank data suggested an association of homozygosity of haemochromatosis-related p.C282Y and cerebral MRI measures indicative of iron deposition as well as incident delirium (Atkins et al., 2021). A retrospective epidemiological study and one small randomized controlled trial suggested that brain-penetrating calcium channel blockers may reduce the risk for incident delirium (Colbourne & Harrison, 2022; Li et al., 2017). Hence, there are little to no studies investigating the role of iron deposits, tissue calcification and brain mineralization in POD.

Susceptibility-weighted imaging (SWI) has previously been used to study increased iron deposition and calcification in aging (Harder et al., 2008) and conditions such as Parkinson's disease (Meijer et al., 2015; Schneider et al., 2016). In a previous work, we studied cerebral microbleeds in POD using SWI (Lachmann et al., 2019). Although the work did not find evidence for an association of microhaemorrhages with a predisposition for POD, it is unknown if iron deposits or calcification from other sources with distinct distribution patterns, for example, metal-binding protein aggregates or accumulation in microglia, could contribute to POD development. Here, we use the same cohort to study iron deposition and brain calcification in three regions of interest (ROI): the basal ganglia, the hippocampus and the posterior basal forebrain cholinergic system (pBFCS).

Physiological (Haacke et al., 2005), age-related (Acosta-Cabronero et al., 2016; Betts et al., 2016; Burgetova et al., 2021) and neurodegenerative iron deposition is most prominent and well documented in the basal ganglia and subcortical grey matter (Damulina et al., 2020; Fu et al., 2021; Meijer et al., 2015; Schneider et al., 2016). Less consistently, hippocampal iron deposition has been reported in aging (Acosta-Cabronero et al., 2016) and AD (Kim et al., 2017; Small et al., 2000; Zhu et al., 2009). In light of previous research suggesting cholinergic deficiency in delirium (Androsova et al., 2015; Hshieh et al., 2008; Muller et al., 2019), and disruption of both structural and functional connectivity of the pBFCS (Cavallari et al., 2016; Choi et al., 2012; Oh et al., 2019), we included this region as an ROI as well.

In this exploratory and hypothesis-generating study, we analysed cerebral iron deposition and calcification measured by relative SWI hypointensities in the basal ganglia, hippocampus and pBFCS in a surgical cohort. We hypothesized that preoperative hypointensity would be found in patients with a predisposition for POD and cognitive decline after surgery. We further describe associations between aggravation of hypointensities with poor cognitive outcome at follow-up 3 months after surgery and anaesthesia.

2 | MATERIALS AND METHODS

2.1 | Study design

We analysed data from a small subproject of the BioCog (Biomarker Development for Postoperative Cognitive Impairment in the Elderly, www.biocog.eu) study. The BioCog project is a cohort study aiming at identification of risk factors for POD and POCD, which has been conducted at the Charité-Universitätsmedizin Berlin, Germany, and the University Medical Centre Utrecht, Netherlands.

Patients aged ≥65 years presenting for elective surgery with an expected duration of ≥60 min were screened at the outpatient clinic of the Department of Anaesthesiology and Intensive Care Medicine of the Charité-Universitätsmedizin and included after obtaining written informed consent. Patients were excluded in case of positive screening for pre-existing major neurocognitive disorder defined as a Mini-Mental Status Examination (MMSE) score of ≤23 points (Anthony et al., 1982), any condition interfering with the neurocognitive assessment (severe hearing or visual impairment, neurological or psychiatric disease), unavailability for follow-up assessment (e.g., due to homelessness), participation in another interventional study during hospital stay, accommodation in an institution due to official or judicial order and missing informed consent.

Before surgery, patients underwent an extensive clinical interview and comprehensive cognitive assessment and blood sampling. Eligible patients were additionally scheduled for MRI. After surgery, patients were prospectively screened for POD for up to 7 days until discharge. Three months after surgery, patients were invited for a follow-up assessment including cognitive testing, MRI and blood sampling. As part of the subproject, an additional SWI sequence was added to the MRI protocol to

study the association of microbleeds with POD and POCD. Methods and procedures have already been described extensively in previous publications (Heinrich et al., 2020; Lachmann et al., 2019; Lammers-Lietz et al., 2022; Lammers et al., 2018; Winterer et al., 2018).

Since BioCog was an observational study, the choice of anaesthesia was left to the discretion of the anaesthesiologist in charge who performed all procedures in accordance with the standard operating procedures of the Department of Anesthesiology and Intensive Care Medicine at the Charité-Universitätsmedizin Berlin. A German version of the standard operating procedures has been published (Spies, 2013).

All study procedures were conducted in line with the declaration of Helsinki with approval by the local medical ethics committees of the study centres in Berlin, Germany (EA2/092/14) and Utrecht, Netherlands (14-469). All participants gave written informed consent prior to inclusion in the study. The study is registered at clinicaltrials.gov under NCT02265263.

2.2 | Screening for POD

Delirium assessment was conducted independently from the routine hospital procedures by the study team twice daily starting on the day of surgery. POD was diagnosed in accordance with criteria in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or a positive screening result on the Nursing Delirium Screening Scale (NuDesc, ≥2 points), either Confusion Assessment Method (CAM) score or CAM for the Intensive Care Unit (CAM-ICU) or written evidence for delirium found by patient chart review. The use of screening tools (NuDesc, CAM[-ICU]) in addition to clinical appraisal of DSM criteria by the study physician was implemented since it has been found that even experienced intensivists tend to overlook delirium (van Eijk et al., 2009). However, chart review was used since POD symptoms fluctuate and delirious patients may have been missed because of undersampling.

2.3 | Assessment of cognitive function

Since the incidence of POCD in the sample presented here was very low (Lachmann et al., 2019), we decided to analyse the association of SWI hypointensities with a continuously scaled parameter for global cognitive function. Therefore, we calculated the global cognitive component 'g' to assess cognitive decline after surgery as described in previous publications (Feinkohl et al., 2019; Feinkohl, Janke, et al., 2020; Lammers et al., 2018). This is a deviation from the pre-defined cognitive endpoint after 3 months of the BioCog study, which was a binary definition of POCD according to the ISPOCD study criteria (Moller et al., 1998; Spies et al., 2021).

At baseline assessment before surgery, all participants underwent a comprehensive computerized neuropsychological test battery (CANTAB, Cambridge Cognition Ltd., UK) and additional tests (Trail-Making Test, TMT-B, and the Grooved Pegboard Test, GPT). The CANTAB test battery comprised the Simple Reaction Task (SRT), Paired Associate Learning test (PAL), Verbal Recognition Memory (VRM) and the Simple Span test (SSP). The tests have been described elsewhere in detail (Lammers et al., 2018). Testing was performed by trained staff based on a standard operating procedure, which was consented to with two neuropsychologists.

2.3.1 | Calculation of the global component 'g'

We calculated 'g' as the first component of a principal component analysis (PCA) of multiple cognitive tests (Feinkohl et al., 2019; Feinkohl, Janke, et al., 2020; Lammers et al., 2018).

Since the derivation of 'g' requires a complete neuropsychological assessment, we applied multiple imputations using chained equations to replace missing data in patients who began but did not complete the assessment. Missing cognitive data at baseline were imputed from available data at baseline, and missing postoperative cognitive data were imputed from available postoperative data. Results are based on 1000 imputations using predictive mean modelling. As described previously, PCA of performance in TMT-B, GPT, SRT, PAL and VRM immediate free recall was used to derive 'g' from the first principal component. TMT-B, GPT and SRT were log-transformed and reversed, and all variables were centred to the mean and normalized prior to PCA.

To calculate postoperative 'g', postoperative cognitive test parameters underwent the same transformations using centring and normalization parameters from preoperative data. We applied the rotation matrix derived from PCA of preoperative data to the postoperative cognitive data to calculate postoperative 'g'.

2.4 | Neuroimaging

2.4.1 | MRI acquisition

As a subproject of the BioCog study, a SWI sequence was added to the MRI protocol of the ongoing study.

All patients underwent a standardized MRI protocol including a 3D susceptibility weighted gradient echo sequence (SWI: voxel size: $0.7 \times 0.6 \times 1.2$ mm^3, field of view: 230×180 mm^2 in 120 transversal slices, TR = 28 ms, TE = 20 ms, 15° flip angle) designed to detect cerebral microbleeds, and a 3D T1 magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE in 192 sagittal slices, FOV = 256×256 mm^2, 1 mm^3 isotropic voxels, TR = 2500 ms, TE = 4.77 ms, 7° flip angle, parallel imaging with generalized autocalibrating partially parallel acquisitions using 24 reference lines, acceleration factor $R = 2$). Of note, phase images from SWI were not saved, and hence, superior approaches to measure iron deposition (e.g., quantitative susceptibility mapping) were not performed. Data were acquired on one single 3T Magnetom Trio RIM MR scanner (Siemens) equipped with a 32-channel head coil at the Berlin Center for Advanced Neuroimaging (BCAN).

2.4.2 | Rationale of SWI-derived biomarkers

Hypointensities in SWI may originate from various sources of dia- and paramagnetic substances, such as blood products (e.g., haemosiderin) as posthaemorrhagic remnants, iron or calcium content and intravenous deoxyhaemoglobin (Haller et al., 2021). Given that highly specific neuroimaging approaches for the detection of cerebral iron deposition are available, few studies have used SWI to assess hypointensity as a surrogate parameter for iron and calcifications. Apart from semi-quantitative rating methods, previous studies applied various intensity-derived metrics to measure brain mineralization in SWI: Harder and Schneider reported intensity per area as atrophy-adjusted parameters of mineralization (Harder et al., 2008; Schneider et al., 2016), whereas Gupta and Meijer used CSF-normalized measures of intensity to adjust for inconsistencies in a reference standard (Gupta et al., 2010; Meijer et al., 2015).

In this study, we applied a similar normalization procedure as the groups of Gupta and Meijer (Gupta et al., 2010; Meijer et al., 2015), that is, relative intensity in the regions of interest compared with mean intensity of the whole brain white matter, as this parameter best-reflected patterns of age-associated iron deposition (see Supporting Information (A), especially Figure S1). To address concerns of confounding by regional atrophy posed in the works by Harder and Schneider, ROI volumes were included as covariates in the analyses.

2.4.3 | Analysis of susceptibility-weighted images

Mean SWI intensities in each ROI (basal ganglia, hippocampus and pBFCS) were calculated following creation of binarized ROI maps from MPRAGE images using standard atlases coregistered to each patient scan. SPM12 (The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK, RRID: SCR_007037, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in a MATLAB environment (The Mathworks. Inc. Natick. MA, RRID: SCR_001622), the log_roi_batch extension by Adrian Imfeld (http://www.aimfeld.ch/neurotools/neurotools.html) and FSLeyes (FMRIB, Analysis Group, Oxford, UK, RRID: SCR_002823, https://fsl.fmrib.ox.ac.uk/) were used for all MRI processing steps.

FSLeyes was used to create binary masks from the Harvard-Oxford subcortical (basal ganglia) and cortical probabilistic atlases. For the basal ganglia mask, we combined the 50% probability masks of the caudate nucleus, pallidum, putamen and nucleus accumbens. For the hippocampus, 50% probability masks of the cornu ammonis, dentate gyrus, entorhinal cortex and subiculum were combined. The binary atlas of the BFCS had been described and provided by Laszlo Zaborszky and was already used in previous works (Lammers et al., 2018; Zaborszky et al., 2008). The pBFCS here refers to the combined regions of Ch4 and Ch4p.

SWI were coregistered to MPRAGE images of each patient. Grey and white matter as well as cerebrospinal fluid were parcellated from MPRAGE scans using the SPM12 segmentation routine and transformed to DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) space. The segmented patient data were mapped onto a common template using the DARTEL flow fields implemented in SPM12, as described earlier (Heinrich et al., 2020; Lammers et al., 2018).

Atlas reference regions (MNI152 for hippocampus and basal ganglia, Colin27 for the pBFCS) were coregistered to a template. Using the SPM12 Deformations tool, a composition of the resulting DARTEL flow fields was applied to the binary ROI masks of the basal ganglia, the hippocampus and the pBFCS, resulting in individually labelled anatomical patient MRI data. Labelling of the white matter for normalization was achieved by binarizing the white matter probability maps generated by SPM at a threshold of 0.6. Mean signal intensity and volume of the ROI were derived using the log_roi_batch extension for SPM.

Finally, relative SWI intensities were calculated as the ratio of mean ROI SWI intensity and the mean white matter SWI intensity.

2.5 | Statistical analysis

2.5.1 | Preoperative neuroimaging

We analysed the association of relative SWI intensities in the basal ganglia, hippocampus and pBFCS and POD using generalized linear models with logit link function and assuming binomial error distribution (logistic regression). Analyses were conducted twice, with the first model including relative SWI intensity and duration of surgery as independent variables (reduced models), and the second model additionally including the patient characteristics age, sex, baseline MMSE and ROI volume as independent variables (extended models).

To study associations of relative SWI hypointensities in the three ROIs with postoperative cognitive decline after 3 months, we used a general linear model treating postoperative global cognitive function 'g' as the dependent variable and including preoperative 'g', preoperative relative SWI intensity and surgery duration as independent variables (reduced models). Preoperative 'g' was included in the model with the intention to assess associations between preoperative hypointensities and postoperative cognitive decline rather than absolute postoperative cognitive function. We repeated the analysis with adjustment for age, sex and ROI volume (extended models).

2.5.2 | Postoperative neuroimaging

Postoperative cognitive decline was analysed in a general linear model treating the global cognitive component 'g' as the dependent variable. The reduced model included perioperative change in relative SWI intensities, preoperative 'g' and surgery duration as independent variables. The extended models additionally included age, sex and postoperative ROI volume. The perioperative change in relative SWI intensity was calculated as the residual of postoperative relative SWI intensity after regression on preoperative relative SWI intensity.

Since the number of patients who experienced POD with postoperative SWI data was too low for a reliable analysis, these analyses are only available as Supporting Information (section D, including Tables S3–S6).

2.5.3 | Post hoc analysis of pBFCS subregions

In a post hoc analysis, we studied the associations of two subregions in the pBFCS (Ch4 and Ch4p) with POD and postoperative cognitive function. Based on our observations, post hoc analyses were restricted to associations of relative preoperative hypointensity of Ch4 and Ch4p with POD as well as associations of perioperative changes in relative hypointensity of Ch4 and Ch4p with postoperative cognitive functions. Reduced and extended models included the same additional variables as described above.

We report effect sizes as regression coefficients with confidence intervals and model degrees of freedom (df). For linear regression models, we calculated adjusted R^2 for the whole model and partial R^2 for the SWI intensity measures. Additionally, we report odds ratios (OR) for logistic regression that have been normalized to a change in relative intensity by 0.1 (denoted as $OR_{0.1}$) for interpretability, which approximately corresponds to a change by two standard deviations.

Since we had prior assumptions about the direction of the association and calculate 90% confidence intervals and one-sided *p*-values. We expected lower (or a decrease in, respectively) relative SWI intensities to be associated with POD and lower postoperative cognitive function 'g'. Since the available dataset was too small for a confirmatory study, we refrain from stating 'significance' for our results. *P*-values have been reported for orientation but have not been adjusted for multiple testing. To emphasize the uncertainty of the results, we address the impact of Bonferroni-correction for multiple testing in a concluding remark in the results section. Statistical analysis was conducted in R version 4.2.1 (Funny-Looking Kid, RRID: SCR_001905) with additional use of the car, factoextra, questionr, sensemakr and mice packages for analyses as well as ggplot2, jpeg, magick and cowplot for creation of figures.

3 | RESULTS

3.1 | Sample

A total of 933 patients were enrolled in the whole BioCog study between 2014/11 and 2017/04. The SWI subproject was initiated 2016/04. Sixty-five patients with preoperative SWI data were included in the analysis; 14/65 (22%) of the patients experienced POD and 40/65 (62%) returned for neuropsychological testing after 3 months. Overall POD rates were comparable with other analyses that used data from the BioCog cohort (i.e., 20% [Heinrich et al., 2021] and 25% [Lammers-Lietz et al., 2022]) as well as other studies conducted in our centre (i.e., 16% [Spies et al., 2021] and 31% [van Norden et al., 2021]).

Of all 14 patients with POD, at least two out of four assessment tools (DSM criteria, CAM[-ICU], NuDesc and chart review) were positive in 11/14 patients. Only three patients were identified by only one out of four assessment tools (two by CAM[-ICU] alone, one by NuDesc alone). DSM criteria were fulfilled in 11/14 (79%) delirious

patients, and CAM(-ICU) and NuDesc were positive in 10/14 (71%) and 12/14 (86%) of delirious patients. Chart review was positive in only 7/14 (50%) of POD cases (see also Table S7 in the Supporting Information, section E).

Since SWI was added to the MRI protocol during enrolment of patients, some patients underwent SWI at the follow-up session, but not before surgery. Postoperative SWI data were available for 54 patients in total, of whom only 34 patients had pre- and postoperative SWI. Among these, 3/34 (9%) experienced POD and 33/34 (97%) had two neuropsychological assessments before and 3 months after surgery. Tables 1 and 2 describe the preoperative ($N = 65$) and longitudinal ($N = 33$) samples. Patient flow charts are given in the Supporting Information (section C, Figure S2).

3.2 | Associations of preoperative relative SWI hypointensities with POD

Figure 1 displays relative SWI intensity for all three regions of interest in all patients separated by POD in

TABLE 1 Demographic and clinical characteristics of the study sample with preoperative SWI data ($N = 65$).

		N	%
Women		35	54
ISCED	**Level 1–2**	5	9
	Level 3–4	27	47
	Level 5–6	25	44
Intrathoracic, -abdominal or -pelvic surgery[a]		21	32
ASA physical status	**I**	1	2
	II	41	63
	III	23	35
(Pre-)frailty		28	44
Hazardous alcohol consumption (AUDIT)		4	6
Anaesthesia	**Regional**	2	3
	General + regional	23	35
ICU admission		11	17
Postoperative pain[b]		27	44
Postoperative complication		31	48
POD		14	22
90-d survival		2	3
	Median	**Interquartile range**	**Min.–max. range**
Age (y)	72	68–75	65–87
CCI (p)	1	0–2	0–5
Baseline MMSE (p)	29	28–30	24–30
Baseline 'g'	0.33	−0.88-1.53	−2.45–4.15
Postoperative 'g'	0.58	−0.49-1.66	−3.96–3.60
Surgery duration (min)	105	70–197	3–495
Days in hospital	7	5–10	2–67

Abbreviations: ASA, American Society of Anesthesiologists; AUDIT, Alcohol Use Disorder Identification Test; CCI, Charlson Comorbidity Index; d, days; ISCED, International Standard Classification of Education; Max., Maximum; min, minutes; Min., Minimum; MMSE, Mini-mental Status Examination; p, points; y, years.

[a]Most commonly performed intrathoracic, -abdominal or -pelvic procedures were pancreatic surgery ($N = 5$); urological surgery including robot-assisted prostatectomy, nephrectomy or cystectomy ($N = 5$); and hepatectomy ($N = 4$). $N = 4$ patients underwent other major abdominal or gynaecological surgery usually requiring laparotomia. $N = 2$ had thoracoscopic surgery and $N = 1$ underwent hernia repair. Peripheral surgery included arthroplasty ($N = 20$, usually hip or knee); minor urological or gynaecological surgery (e.g., transurethral resection of the prostate and surgery of the mammae, $N = 8$); various procedures of the face, head, neck and upper airway including thyreoid surgery ($N = 8$); and spinal surgery ($N = 6$). $N = 2$ patients underwent other peripheral procedures.

[b]Positive screening from a compound assessment including the Non-visual Rating Scale (NRS), Behavioral Pain Scale (BPS and BPS-NI) and Critical Pain Observation Tool (CPOT) during the first seven postoperative days.

TABLE 2 Demographic and clinical characteristics of the study sample with longitudinal SWI and neuropsychological data ($N = 33$).

		N	%
Women		17	52
ISCED	**Level 1–2**	2	7
	Level 3–4	13	43
	Level 5–6	15	50
Intrathoracic, -abdominal or -pelvic surgery		5	15
ASA physical status	**I**	1	3
	II	21	64
	III	11	33
(Pre-)frailty		13	41
Hazardous alcohol consumption (AUDIT)		1	3
Anaesthesia	**Regional**	1	3
	General + regional	11	33
ICU admission		1	3
Postoperative pain		12	61
Postoperative complication		14	42
POD		3	10
	Median	**Interquartile range**	**Min.–max. range**
Age (y)	72	67–75	65–86
CCI (p)	0	0–2	0–5
Baseline MMSE (p)	28	28–30	25–30
Baseline 'g'	0.02	−0.90–1.15	−2.45–4.15
Postoperative 'g'	0.64	−0.53–1.52	−3.96–3.42
Surgery duration (min)	138	107–182	56–404
Days in hospital	7	4–8	2–12

Abbreviations: see Table 1.

$N = 65$ patients. Adjusted for duration of surgery, relative SWI hypointensities in the basal ganglia and the pBFCS, but not in the hippocampus, were associated with increased risk for POD. After additional adjustment for age, sex, baseline MMSE and ROI volume, the association persisted for the pBFCS, but neither for basal ganglia nor the hippocampus. See Figure 1 for details on the statistical results.

3.3 | Associations of preoperative relative SWI hypointensities with postoperative decline in global cognitive performance 'g'

In $N = 40$ patients with preoperative SWI data and longitudinal neuropsychological testing, neither relative hypointensities in the basal ganglia ($B = 3.64$ [−1.71; 9.00], $R^2 = 0.74$, partial $R^2 = 0.035$, $p = 0.13$), nor hippocampus ($B = 0.86$ [−5.97; 7.70], $R^2 = 0.73$, partial $R^2 = 0.001$, $p = 0.42$), nor pBFCS ($B = -0.71$ [−5.81; 4.40], $p = 0.59$, $R^2 = 0.73$, partial $R^2 = 0.002$) were associated with postoperative 'g' after adjustment for surgery duration and preoperative 'g' ($df = 3/36$ for all reduced models). Results were not substantially changed after adjustment for age, sex and ROI volume (basal ganglia: $B = 2.94$ [−2.65; 8.52], $R^2 = 0.75$, partial $R^2 = 0.023$, $p = 0.45$; hippocampus: $B = -1.71$ [−8.94; 5.52], $R^2 = 0.73$, partial $R^2 = 0.005$, $p = 0.65$; posterior BFCS: $B = -0.61$ [−5.67; 4.44], $p = 0.58$, $R^2 = 0.74$, partial $R^2 = 0.001$; $df = 6/33$ for all extended models).

3.4 | Associations of perioperative changes in relative SWI hypointensities with postoperative decline in global cognitive performance 'g'

pBFCS intensity changes in $N = 33$ patients with pre- and postoperative SWI data and neurocognitive testing at

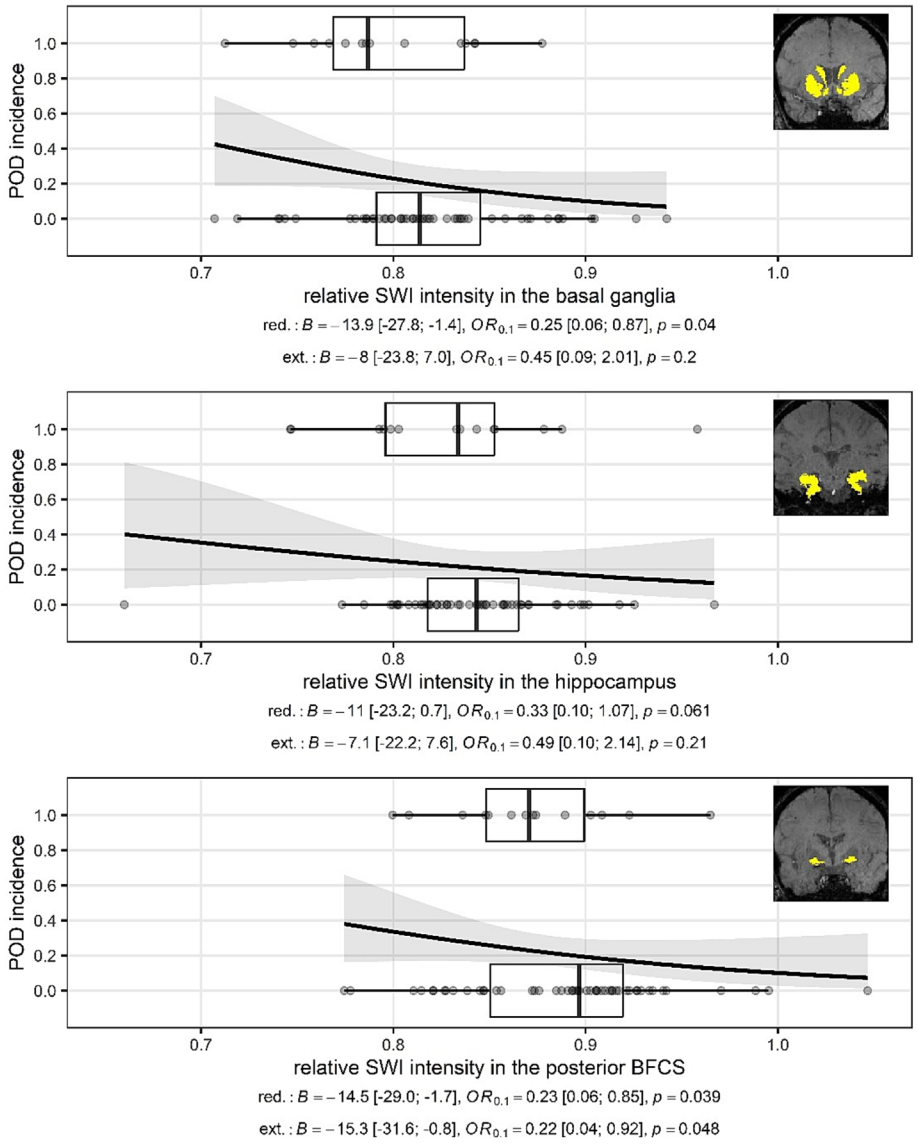

FIGURE 1 The association of relative SWI intensity (x-axis) in three regions of interest (ROI) with POD (y = axis) in $N = 65$ patients as dot plots. Horizontal boxplots summarize the distribution of SWI relative intensity values for patients who experienced POD (top in each plot, POD incidence = 1) and those who did not (bottom in each plot, POD incidence = 0). The line shows the conditional POD incidence for each relative SWI intensity value with 90% CI (shaded area) based on a simple logistic regression. Lower values for the relative SWI intensity indicate that the ROI appears darker in the MRI, suggesting higher mineralization. Intensities must be interpreted with reference to the mean intensity of the white matter, that is, a value of 1 means equal signal intensity of the ROI and white matter, whereas values <1 indicate a hypointense appearance of the ROI compared with the white matter. Inlays display the regions of interest. The pBFCS here refers to the combined regions of Ch4 and Ch4p in Zaborzsky's modification of Mesulam's nomenclature of the cholinergic system (Zaborszky et al., 2008). Details of the statistical models (regression coefficients B, odds ratios for 0.1 change in relative SWI intensity with 90% confidence intervals, and one-sided *p*-value) are given in the plot captions. Degrees of freedom are 2/62 for all reduced, and 6/58 for all extended models. Abbreviations: B: logistic regression coefficient; BFCS: basal forebrain cholinergic system; ext.: extended model results; $OR_{0.1}$: odds ratio for 0.1 unit change in relative intensity; *p*: *p*-value; POD, postoperative delirium; SWI: susceptibility-weighted imaging; red.: reduced model results.

follow-up were positively associated with baseline-adjusted postoperative 'g' in the reduced model, and in the extended model on a trend level, that is, a further postoperative decrease of relative SWI intensity was associated with lower postoperative global cognitive function. Associations were neither observed in the hippocampus nor the basal ganglia (see Figure 2 for details on the statistical results).

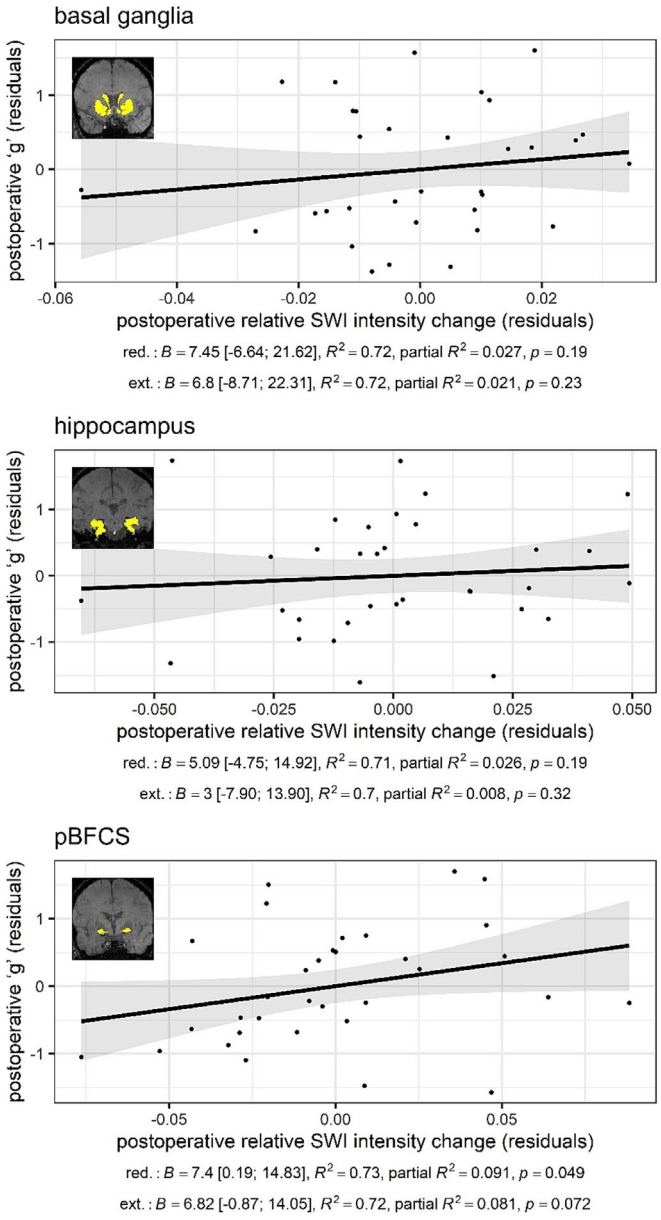

FIGURE 2 Associations of perioperative relative SWI intensity change in the three regions of interest with postoperative global cognitive function 'g' at follow-up 3 months after surgery in $N = 33$ patients. The graphs are partial regression plots of the extended models adjusted for preoperative 'g', surgery duration, age, sex and postoperative ROI volume. Inlays display the regions of interest. The captions give regression coefficients B with 90% confidence intervals, adjusted R^2 for the whole model and partial R^2 for the SWI intensity measure and p-values for the reduced and extended models. Degrees of freedom are 3/29 and 6/26 for reduced and extended models, respectively. Abbreviations: red.: reduced; ext.: extended.

3.5 | Post hoc analyses of pBFCS subregions

Relative preoperative SWI hypointensities in Ch4 were associated with POD in the reduced model and at a trend level in the extended model, but no association was observed for Ch4p. We observed associations of postoperative decrease in relative SWI intensities of Ch4p with postoperative 'g', which were independent of age, sex, preoperative 'g' and ROI volume, but not Ch4. Hence, postoperative longitudinal decline in cognition was associated with progressing postoperative hypointensities in region Ch4p. Results from the post hoc analysis including statistical details are displayed in Figure 3.

3.6 | Statement on multiple statistical tests

Because of the exploratory character of this study in a small sample providing insufficient statistical power for a confirmatory approach, we decided against setting a level of significance and adjustment of p-values for multiple statistical tests. However, it should be noted that rigorous adjustment for analysing three independent brain regions would lead to a Bonferroni-adjusted level of significance of $p < 0.05/3 \approx 0.017$. Hence, none of the results presented in the a priori analyses would have achieved significance in a confirmatory study with equal sample size.

4 | DISCUSSION

Here, we studied the association of SWI hypointensities in the basal ganglia, the hippocampus and the pBFCS with POD and postoperative cognitive decline.

We observed an association of preoperative hypointensity of the pBFCS and basal ganglia with POD, but only in the pBFCS, this association was found to be independent of confounders such as age, MMSE, sex and region volume. A post hoc analysis suggested that relative hypointensity in the rostral pBFCS, region Ch4, might be more relevant for POD than Ch4p. Ch4 has been described as the main source of cholinergic innervation to associative and sensory frontoparietal cortical areas (Mesulam et al., 1983). Although iron deposition in the BFCS has rarely been investigated, and existing studies did not report an association with neurodegenerative disease (Gu et al., 1998), diffusion tensor imaging studies reported brain tissue alterations in the BFCS as a predisposing factor for POD (Cavallari et al., 2016). In accordance, studies reported altered connectivity of the cholinergic system, especially region Ch4, in Lewy body dementia with hallucinations (Hepp et al., 2017; Mehraram et al., 2022).

In contrast, preoperative hypointensity was not associated with decline in global cognitive function 3 months

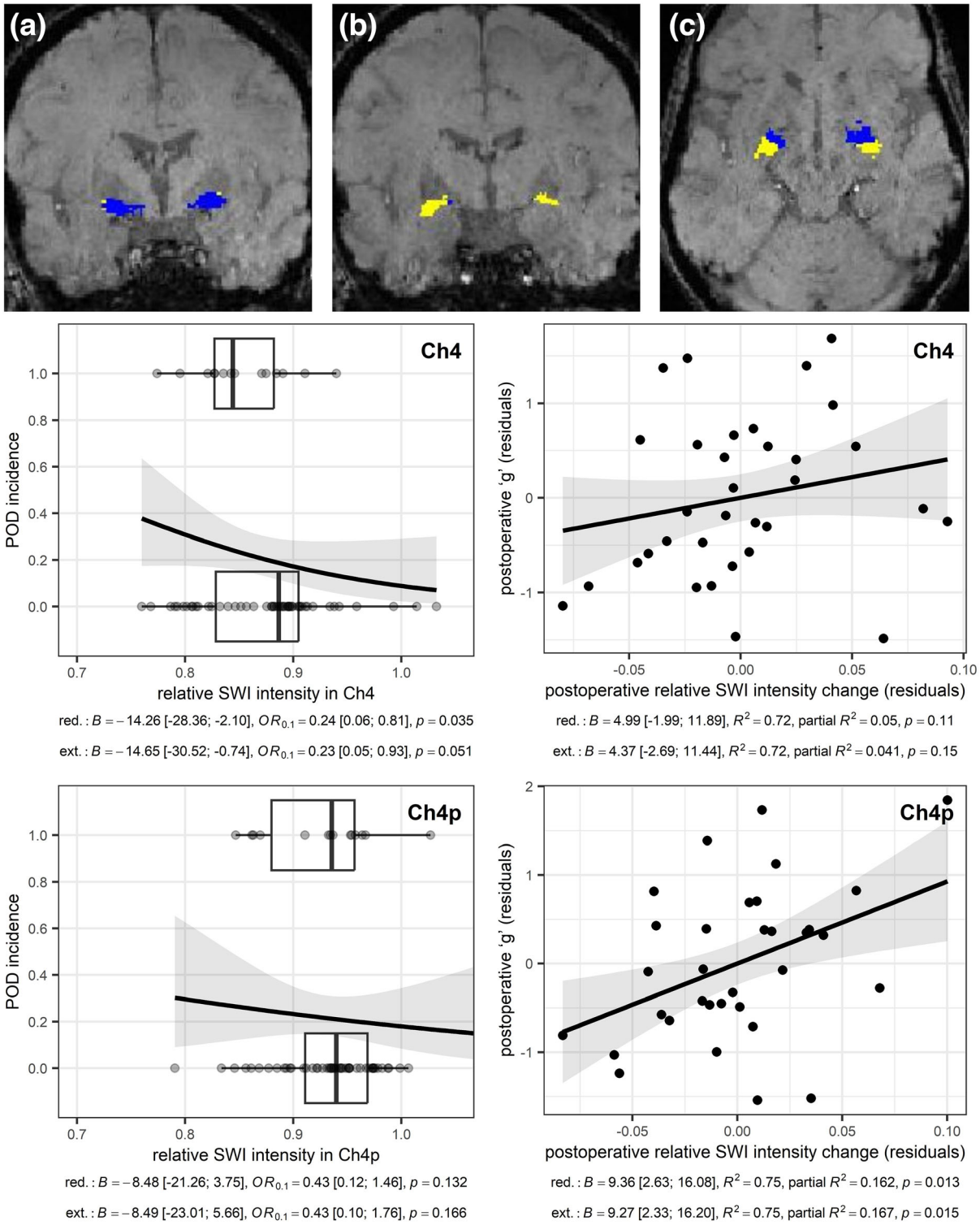

FIGURE 3 The two subregions of the pBFCS (top row) and the results of the post hoc analysis (middle and bottom row). In the top row, Ch4 (blue) and Ch4p (yellow) are depicted in coronal (a, b) and one axial slice (c). Associations of regions Ch4 (middle) and Ch4p (bottom) with POD (left, $N = 65$) and postoperative cognitive function (right, $N = 33$). Degrees of freedom are 2/62 and 6/58 for reduced and extended models of POD, respectively, as well as 3/29 and 6/26 for models of 'g'. For a detailed explanation of the figures, see also Figures 1 and 2.

after surgery. However, a postoperative decrease of pBFCS intensity was associated with postoperative decline in cognitive function in the reduced model and in the extended model at a trend level. In the post hoc analysis, we found that this association was driven by an association of cognitive decline and relative SWI

hypointensity in the most posterior part of the pBFCS (Ch4p), which was independent of age, sex and region volume in the extended model. Hence, SWI hypointensity as a surrogate parameter for neurodegeneration seems to contribute differentially to POD and postoperative cognitive decline. Although it seems to be a predisposing factor for POD, postoperative progress of mineral and iron deposition in the pBFCS may rather reflect ongoing neurodegenerative processes related to postoperative cognitive decline. The post hoc analysis revealed an association with SWI intensity changes in the Ch4p, which is assumed to provide cholinergic innervation of the temporal lobe, rather than the whole pBFCS (Mesulam et al., 1983). Previous imaging studies reported early atrophy of Ch4p in AD (Kilimann et al., 2017). Of note, cerebral iron accumulation has also been reported to be associated with both amyloid plaques and tau fibril aggregates in AD, and hence, our findings may point to common pathways in postoperative cognitive decline and AD (Collingwood et al., 2005; Spotorno et al., 2020).

Interestingly, we found no independent association of hypointensity in the basal ganglia or the hippocampus, although these regions are commonly reported to be vulnerable to mineralization and calcification in any of the extended models (Betts et al., 2016; Burgetova et al., 2021; Haacke et al., 2005). This might be due to methodological aspects, since the relative hypointensity measure was chosen based on this association with age, and hence, distinction between effects of age and hypointensity on postoperative neurocognitive disorders is difficult to make. On the other hand, the pBFCS may be a particularly vulnerable region for mineralization and calcification and may have a critical role for the pathogenesis of POD and postoperative cognitive decline: In fact, the Successful Aging after Elective Surgery study group reported white matter alterations in the BFCS as a risk factor for POD (Cavallari et al., 2016) and one anecdotal case report on donepezil-responsive delirium due to severe lesioning of the basal forebrain after surgical removal of a craniopharyngeoma exists (Kobayashi et al., 2004). Various studies reported increased sensitivity to anaesthetics in animals with BFCS lesions (Leung et al., 2014; Leung & Luo, 2021), and it has been shown that animals were more susceptible to inflammation-induced cognitive deterioration after lesioning the BFCS, suggesting a role in septic encephalopathy (Field et al., 2012). BFCS integrity was an essential mediator for the therapeutic effect of vagal nerve stimulation in a rat model of POCD, suggesting that cortical acetylcholine released from the BFCS may inhibit overshooting neuroinflammation after anaesthesia (Zhou et al., 2023).

The interpretation of hypointensity in SWI is difficult, as it may originate from cerebral bleeding, iron or calcium content and even intravenous deoxyhaemoglobin (Haller et al., 2021). Calcifications are common findings in cerebral imaging of otherwise healthy aging patients, although they may also originate from various diseases and may be associated with neuropsychiatric symptoms (Deng et al., 2015; Harrington et al., 1981; Saade et al., 2019). A recent review on neuroimaging findings in COVID-19 reported microhaemorrhages to be a common finding in COVID-19-associated encephalopathy (Ghaderi et al., 2023). Microbleeds in the pBFCS have not been assessed in this study; however, in the previous analysis of microbleeds conducted in the same sample, there was no significant association of microbleeds with POD or POCD, suggesting that posthaemorrhagic remnants and the associated increase in neurovascular risk are not the major mediator in the association of SWI hypointensities with POD or postoperative cognitive decline. Furthermore, the prevalence of deep microbleeds possibly affecting our regions of interest was very low in the investigated sample (four out of 65 patients) (Lachmann et al., 2019).

This is the first pilot study on brain mineralization in postoperative neurocognitive disorders. Since this is a post hoc analysis of an available dataset, the study has certain methodological shortcomings. First, SWI was added to the MRI protocol of an ongoing study without prior statistical planning. Hence, the statistical power is low, and all results need to be considered exploratory, warranting larger validation studies. Hence, no statistical inference can be derived from *p*-values reported here. In fact, Bonferroni-adjustment for multiple tests would have led to rigorous rejection of all findings with *p*-values of ≤ 0.05. Hence, evaluating statistical significance could lead to high probability of false-positive results, further substantiating the need for a confirmatory study. However, our study provides effect size estimates as well as a priori hypotheses for ROI to evaluate in future studies.

Age is a relevant cofounder in our study, especially since the normalization procedure was chosen based on the correlation of normalized SWI intensities with age. Of note, relative hypointensity of basal ganglia was no longer associated with POD after adjustment for additional variables including age. Hence, results from the reduced models may be confounded by age, whereas additional inclusion of age in the extended models may result in overcorrection of the model leading to false-negative results.

To obtain generalizable results, the BioCog did not in- or exclude patients based on surgical procedures. However, almost one third of the patients in the sample underwent joint arthroplasty (see Table 1), and hence, our small subsample may neither reflect the complete population of surgical patients nor a homogeneous

population undergoing a certain surgical procedure. In addition, it is known that anaesthetics affect POD risk (Koch et al., 2023). At the study centre where the study was conducted, anaesthesiologists follow standard operating procedures (Spies, 2013), but deviation from these protocols is expected to be common. The dataset analysed here does not provide extensive data on anaesthetic medication. Thus, adjustment of models for procedure-related precipitating factors is limited to duration of surgery, whereas the choice of anaesthetic medication is not included in our analyses.

Delirium diagnosis by an experienced psychiatrist is the preferred gold standard for clinical and scientific purposes. In this study, delirium was diagnosed by anaesthesiologists based on a structured prospective assessment. Especially differentiation between delirium and dementia is a critical question, which may better be referred to a psychiatrist than an anaesthesiologist. However, since only patients with a minimum MMSE of 24 points were eligible for inclusion, POD assessment by an anaesthesiologic team was feasible in the context of this study. However, the use of screening tools and chart review was implemented in addition to clinical appraisal of DSM criteria to achieve adequate sensitivity for POD. In fact, only 50% of POD patients in this subsample had been identified by chart review, substantiating our assumption that delirium is often overlooked in clinical routine (van Eijk et al., 2009). On the other hand, the use of multiple POD assessments including screening tools may bear the risk of low specificity and a high rate of false-positive findings. In this sample, only three patients were identified by only one assessment, whereas in the majority of 11 patients, POD diagnosis was confirmed by at least two independent assessment tools. Whereas CAM (-ICU) evaluates DSM criteria in an operationalized procedure (Ely et al., 2001; Inouye et al., 1990) and is hence sufficient to confirm delirium diagnosis in our sample, the NuDesc may be considered a screening tool (Gaudreau et al., 2005; Luetz et al., 2010). In accordance with these assumptions, the number of delirious patients detected by NuDesc was slightly higher than the number of patients by either DSM or CAM(-ICU). In 13 out of 14 POD patients, diagnosis was made at least by CAM (-ICU) or appraisal of DSM criteria by study staff. Hence, in the majority of cases, POD has been ascertained, whereas one case may be considered as 'probable delirium' (see also Table S7 in section E of the Supporting Information).

Furthermore, the MRI protocol was designed for microbleeds assessments rather than measurement of iron or calcium deposition, whereas advanced neuroimaging methods such as quantitative susceptibility mapping, R2* relaxometry and biophysical modelling approaches have been developed to quantify cerebral iron deposition (Drori et al., 2022; Haacke et al., 2005). Hence, our results are somewhat indiscriminate to the aetiology of hypointensities, as outlined above, and additional studies with MRI protocols designed to measure brain tissue composition are needed (Chawla et al., 2016, 2018; Cooper et al., 2020; Wieland et al., 2021). Results from these studies could then justify trials, that is, on iron chelation therapy in the perioperative setting, as preliminary studies suggest efficacy in several neurodegenerative diseases, including Parkinson's disease and Alzheimer's dementia (Nunez & Chana-Cuevas, 2018).

5 | CONCLUSION

We present the first although highly exploratory and hypothesis-generating study on brain tissue mineralization in postoperative neurocognitive disorders. Our results suggest that brain mineralization, particularly in the cholinergic system, could be a possible contributor to POD and postoperative cognitive decline. Whereas preoperative relative SWI hypointensities seem to be related to patients predisposed to POD, tissue changes leading to lasting cognitive decline in surgical patients seem to occur in the postoperative period. Although warranting further studies, our results imply that there could be a prognostic benefit in added treatment options, that is, chelation therapy or calcium channel blockade, for patients with or at risk for postoperative neurocognitive disorders.

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CONFLICT OF INTEREST STATEMENT

Florian Lammers-Lietz, MD, received personal fees from PI Health Solutions GmbH during the conduct of the study. Claudia Paarmann-Chien, PhD, received research

funding from Novartis and Alexion, unrelated to this study, and is a Standing Committee on Science Member for the Canadian Institutes of Health Research (CIHR). Claudia Spies, MD, PhD, received grants from the European Commission during the conduct of the study. During the past 36 months, Prof. Spies received grants from Deutsche Forschungsgemeinschaft, Deutsches Zentrum für Luft- und Raumfahrt e.V., Einstein Stiftung Berlin, Federal Joint Committee (GBA Innovationsfond), inner university grants, Projektträger im DLR, Stifterverband, Federal Ministry for Economic Affairs and Climate Action, payments by the Georg Thieme Verlag, sponsoring from Dr F. Köhler Chemie GmbH, Sintetica GmbH, Federal Joint Committee (GBA Innovationsfond), Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V., Stifterverband für die deutsche Wissenschaft, Philipps Electronics Nederland BV, Federal Ministry of Education and Research, Robert-Koch-Institut and the European Commission. Prof. Spies is involved in patents 15753 627.7 (issued), PCT/EP 2015/067731 (issued), 3 174 588 (issued), 10 2014 215 211.9, 10 2018 114 364.8, 10 2018 110 275.5, 50 2015 010 534.8, 50 2015 010 347.7, 10 2014 215 212.7. She participates in or is a member of the Association of the Scientific Medical Societies in Germany (AWMF), Deutsche Forschungsgemeinschaft and the German National Academy of Sciences (Leopoldina) without receiving payments. Georg Winterer, MD, PhD: grants from the European Commission during the conduct of the study. CEO of Pharma-Image Biomarker Solutions GmbH Berlin (Germany) and President of its subsidiary Pharmaimage Biomarkers Incl. (Cambridge, MA, USA) and PI Health Solutions GmbH Berlin (Germany). Grants from the Deutsche Forschungsgemeinschaft/German Research Society and from the German Ministry of Health. Friedrich Borchers, MD; Stefan Hetzer, PhD; Insa Feinkohl, PhD; Cicek Kanar, BSc; Frank Konietschke, PhD; Gunnar Lachmann, MD, PhD; Laszlo Zaborszky, PhD; Norman Zacharias, PhD; and Friedemann Paul, MD, PhD, declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16282.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study. Data from the BioCog study are not publicly available due to constraints imposed in the consent forms. An anonymized version is available from the authors on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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