NEUROIMAGING OF FRAILTY, DELIRIUM AND POSTOPERATIVE COGNITIVE DYSFUNCTION

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Neuroimaging of frailty, delirium and postoperative cognitive dysfunction

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For consistency some terms and graphical presentation of Tables and Figures have been standardized throughout this thesis. Therefore, there may be some differences with the articles that have been published.

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Neuroimaging of frailty, delirium and postoperative cognitive dysfunction

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(met een samenvatting in het Nederlands)

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CHAPTER 1

General introduction

Advances in technology and healthcare have increased life expectancy and the quality of life of older individuals over the past decades[1]. Especially in western countries, older patients take up an increasing share of the healthcare system[1]. Despite the fact that this has benefited many, some are vulnerable for adverse outcomes, which has been defined as frailty[2]. Frailty has therefore become an important issue in weighing risks and benefits of scheduled healthcare interventions such as surgery. Besides frailty, other issues that have been raised include adverse neurocognitive outcomes after surgery. Despite the careful preoperative screening, many older patients develop these adverse outcomes, ranging from a single delirious episode to long-term cognitive dysfunction[3,4].

FRAILTY

Frailty is an age-associated biological syndrome of decreased reserve that leads to an increased vulnerability to physiological stressors, affecting around 10% of community-dwelling older individuals[1,2]. Frail individuals are vulnerable for a disproportionate physiological response to what may seem as small stressors to non-frail individuals, such as a minor disease or routine interventions. Frail patients that are scheduled for major surgery are therefore at higher risk for developing postoperative adverse outcomes (e.g. delirium) compared to their non-frail counterparts[5].

DELIRIUM

Delirium is a common neuropsychiatric syndrome that affects 10-15% of older patients after major elective surgery[3,6]. It is characterized by an acute change in attention and awareness, as a consequence of an underlying medical condition[6]. Risk factors that predispose for postoperative delirium include advanced age, pre-existing cognitive disorders, severity of illness and a history of delirium[3]. Precipitating risk factors include complications of surgery, intensive care admission and major surgery[3].

POSTOPERATIVE COGNITIVE DYSFUNCTION

Postoperative cognitive dysfunction (POCD) is regarded as a decline in memory and executive function, that may last from weeks to months after surgery[7]. Incidence of POCD at three months after surgery is around 10%[7,8]. To date, there is no widespread exact definition of POCD, but the recommended assessment according to a consensus statement of 1995 is by using both a preoperative and postoperative cognitive test

battery, and comparison to a control group that did not undergo surgery[9,10]. The latest recommended nomenclature of POCD is mild or major postoperative neurocognitive disorder (NCD)[11], which further specifies that a subjective complaint should be present as well as an objective decline (mild NCD: 1-2 standard deviations decline; major NCD: >2 standard deviations decline), and that a functional decline should be present in the case of major NCD. These recommendations were presented in 2018, and therefore, the current thesis still uses the older definition of POCD. Delirium and POCD can present independently, however, they can also co-occur, although POCD occurs later in the postoperative period than delirium. Other risk factors for POCD include advanced age, peri- and postoperative complications, preoperative cognitive disorders and a low level of education[12].

IMPACT ON SOCIETY

The impact of frailty, delirium and POCD on patients and society are high, stressing the importance of investigating the pathways leading to these conditions. Frailty is associated with an increased risk of falling, cognitive disorders and dementia[1,2]. Postoperative delirium is associated with prolonged hospital stay, admission to another care institution, prolonged cognitive dysfunction and even dementia, thereby also increasing healthcare costs[13,14]. POCD is often a subtle and transient condition, that is also described as a delayed postoperative neurocognitive recovery, thereby lowering quality of life and increasing the healthcare needs of these patients[7,8].

NEUROIMAGING OF FRAILTY, DELIRIUM AND POCD

Magnetic resonance imaging (MRI) of the brain has increased our understanding of disease processes in the brain in normal aging, mild cognitive impairment and specific diseases, such as Alzheimer's disease[15–17]. Applying neuroimaging methods in the investigation of frailty, delirium and POCD could therefore provide new insights into the mechanisms that underlie these conditions. Previous studies that have assessed brain MRI markers in relation to frailty, delirium and POCD have shown inconsistent results however. In frailty, some previous studies have suggested the possibility of a neural substrate, such as regional cerebral atrophy or signs of cerebral small vessel disease[18,19]. In delirium, previous studies have shown that MRI markers of neurodegenerative and neurovascular diseases (e.g. cerebral atrophy, white matter hyperintensities, cerebral infarcts) may predispose for delirium[20–25], although there

is also conflicting evidence[26–28]. Further, some studies reported that delirium may be related to new postoperative brain changes (e.g. loss of white matter integrity, new cerebral infarcts)[29,30]. Neuroimaging of POCD has only been performed in a few small studies that show conflicting results on the association between neurodegenerative and neurovascular brain changes (e.g. cerebral infarcts, cerebral atrophy, white matter hyperintensities) and POCD[24,31,32]. Although these recent efforts have indicated that frailty, delirium and POCD may have a neural substrate, many lacked preoperative imaging, or were underpowered. Therefore, to date, it remains largely unknown which brain alterations predispose to frailty, delirium and/or POCD, and whether these endpoints share a similar predisposing substrate.

Knowledge on the biological basis of frailty could lead to an improved understanding of the physical and cognitive deterioration associated with frailty, and eventually to improved prevention strategies. Further, improved knowledge on delirium and POCD could lead to an improved understanding of the difference in the cognitive trajectories after surgery of these patients. This could assist in an improved preoperative risk assessment and development of targeted treatment and prevention strategies, eventually reducing the burden for patients and society. Therefore, the main aims of this thesis are to assess the brain MRI markers that are related to frailty, to investigate the brain MRI markers that predispose for delirium and/or POCD, and to investigate whether delirium or POCD is related to pre-to postoperative brain changes.

Box 1: Main aims of this thesis

Aim 1: Assess the relation between brain MRI markers and frailty.
Aim 2: Identify brain MRI markers that predispose for delirium and/or POCD.
Aim 3: Investigate whether delirium or POCD is related to preoperative to postoperative MRI brain changes.

OUTLINE OF THIS THESIS

Part I of this thesis is focused on unraveling the brain MRI markers that are associated with the physical frailty syndrome. **Chapter 2** focuses on the association between MRI markers of neurodegenerative and neurovascular brain changes and frailty. In **chapter 3**, we studied the association between cerebral small vessel disease and physical frailty with an in-depth analysis of both commonly used and novel features of cerebral small vessel disease.

Part II of this thesis is focused on delirium and POCD. **Chapter 4** comprises a systematic review of literature on brain MRI markers that may predispose for delirium or POCD, and the relation between delirium or POCD and brain changes in the postoperative period. **Chapter 5** is focused on unraveling preoperative brain MRI markers that may predispose for postoperative delirium in a large group of older patients. **Chapter 6** describes a novel method of identification of MRI phenotypes of the brain and the association of these phenotypes with postoperative delirium. **Chapter 7** assessed the relation between cerebral microbleeds and both postoperative delirium and POCD. In **chapter 8** the association between delirium and preoperative to postoperative brain changes was investigated. Finally, in **chapter 9** the main findings of this thesis are summarized, and the general discussion evaluates the implications for clinical practice and future research possibilities.

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Part I

Frailty

CHAPTER 2

The association between brain volume, cortical brain infarcts and physical frailty

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ABSTRACT

Physical frailty is an age-associated syndrome of decreased reserve leading to vulnerability to physiological stressors, and associated with negative outcomes. The underlying structural brain abnormalities of physical frailty are unclear. We investigated the association between brain volume, cortical brain infarcts and physical frailty. In this multicenter study, 214 non-demented participants were classified as frail (n=32), pre-frail (n=107) or non-frail (n=75) based on the Fried frailty phenotype. The associations between frailty and brain volumes and cortical brain infarcts were investigated by linear or logistic regression analyses. Participants in the frail group showed a lower total brain volume (-19.67 ml (95% Confidence Interval (CI) -37.84 to -1.50)) and lower gray matter volume (-12.19 ml (95% CI -23.84 to -0.54)) compared to non-frail participants. Frailty was associated with cortical brain infarcts (frail 16% (n=5), pre-frail 11% (n=12) and non-frail 3% (n=2)). Reduced total brain volume and gray matter volume and increased cortical brain infarcts seem therefore to be part of the structural substrate of the physical frailty phenotype.

INTRODUCTION

Frailty is defined as an age associated biological syndrome of decreased reserve that leads to a vulnerability to physiological stressors [1,2]. Frail individuals have an increased risk of adverse events, such as hospitalization, falls, institutionalization and complications after surgery including postoperative delirium [3,2]. Frailty is most often described using the physical frailty phenotype [2,4]. This phenotype is assessed with five frailty components: slowness, weakness, exhaustion, weight loss and a low level of activity [2]. A combination of three or more of these components classifies an individual as frail.

Previous studies showed that physical frailty is associated with an increased risk of cognitive decline and dementia [5–7]. These findings may suggest that neurodegenerative or neurovascular changes are the structural substrate of the physical frailty phenotype. However, only few small studies have assessed the underlying structural brain MRI correlates of physical frailty. These studies have shown that signs of neurodegenerative or neurovascular changes, i.e. lower global or regional brain volume, a higher number of cerebral microbleeds and a higher burden of white matter hyperintensities of presumed vascular origin (WMH), were related to frailty in older individuals [8,9,5,10–14]. These studies were however limited to community-dwelling individuals, and included only a low number of frail individuals. Knowledge of the biological basis and development of physical frailty could lead to strategies to prevent dependence, and eventually reduce the burden on an economic, societal and individual level. To date, it is unknown if brain alterations are already present in pre-frail individuals. Furthermore, the association between cortical brain infarcts and physical frailty has never been investigated.

The aim of the present study was to investigate differences in brain volumes, WMH and cortical brain infarcts in physical frail, pre-frail and non-frail older non-demented individuals who were scheduled for elective surgery. In addition, we studied the relation between these brain markers and individual frailty components.

METHODS

Study design and participants

This investigation is part of the BioCog consortium study: an ongoing multicenter prospective cohort study performed in the Charité Universitätsmedizin Berlin and the University Medical Center Utrecht. The general aim of the BioCog study is to identify determinants of perioperative neurocognitive disorders [15]. For the BioCog study participants were included who were: (1) scheduled for major elective surgery of a minimum of 60 minutes, (2) at least 65 years of age, (3) able to undergo cognitive tests (no blindness, deafness, neurological or psychiatric diseases) and MRI scanning and (4) had a mini-mental state exam (MMSE) score of 24 or higher. The present study uses data from the first n=400 participants of the BioCog consortium study. All participants signed an informed consent form and all procedures were approved by the medical ethics committee of both centers under ethical approval number EA2/092/14 (Berlin) and 14-469 (Utrecht).

Procedure

All participants were invited prior to surgery for a visit that included questionnaires, a frailty assessment and an MRI scan. Trained researchers collected data on age, gender, body mass index (BMI), diabetes, smoking and history of cardiovascular events. All participants were assessed with the MMSE [16] to determine preoperative cognitive status. An MMSE score of 24 or higher was considered as absence of severe dementia. The American Society of Anesthesiologists (ASA) classification was assessed in a preoperative interview by an anesthesiologist (in training) [17].

Frailty assessment

Frailty was assessed by trained researchers based on a modified version of the Fried frailty phenotype by Rockwood et al., and consisted of five frailty components: slowness, weakness, exhaustion, weight loss and a low level of activity [2,18], see supplementary table A for a detailed description of these components. Participants who had a combination of three or more components were considered frail, participants who had a combination of one or two components were considered pre-frail, and participants who had none of these components were considered non-frail.

MRI scans

Participants were scanned on a Siemens Magnetom TrioTim MRI scanner (Berlin) or a Philips Achieva 3T MRI scanner (Utrecht). The MRI scanning protocol was

standardized and consisted of a three-dimensional (3D) T1-weighted sequence (voxel size =1.0x1.0x1.0 mm^3; Berlin: 3D-T1 magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE), Repetition Time (TR)/echo time (TE) = 2500/4.77 ms; Utrecht: TR/TE= 7.9/4.5 ms) and a fluid-attenuated inversion recovery (FLAIR) sequence (Berlin: TR/TE/Inversion time (TI) = 4800/388/1800 ms; voxel size = 0.49 x 0.49 x 1.00 mm^3; Utrecht: TR/TE/TI = 4800/125/1650 ms; voxel size = 1.11 x 1.11 x 0.56 mm^3).

MRI processing steps and analysis

A robust approach to brain segmentation of multi-center data was used [19,20]. 3D FLAIR images were registered to the 3D T1-weighted images by using statistical parametric mapping software (SPM12, Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/doc/), running on Matlab R2013a (Mathworks, Natick, MA). WMH segmentations were performed on the FLAIR scans by the lesion prediction algorithm (Schmidt, 2017) as implemented in the Lesion Segmentation Toolbox version 2.0.15 (www.statistical-modeling.de/lst.html) for SPM12. All resulting WMH segmentations were visually checked for segmentation errors by trained researchers (IK, YW, EA and IB) and in doubt by a radiologist (JB) with 10 years of experience in brain segmentation. WMH segmentations were thresholded on a 0.5 probability and WMH volumes were calculated using the Lesion Segmentation Toolbox. Lesion filling was performed on the 3D T1-weighted images by using the WMH segmentations. The resulting 'lesion filled' 3D T1-weighted images were subsequently segmented in the CAT12 toolbox for SPM12 (Gaser and Dahnke, Jena University Hospital, Departments of Psychiatry and Neurology, http://www.neuro.uni-jena.de/cat/index.html#About). This resulted in segmentations of gray matter, white matter and cerebrospinal fluid. Intracranial volume (ICV), total brain volume, gray matter volume, white matter volume and CSF volume were calculated by the SPM12 option "tissue volumes". All scans were checked by a neuro-radiologist (JB) for presence of cortical brain infarcts and major artifacts that might hinder accurate segmentations. Subsequently, all brain tissue segmentations were visually checked for segmentation errors (e.g. registration errors, wrong classification of tissue) by a trained researcher (IK). All cases that contained errors were discussed in a consensus meeting with an expert neuro-radiologist (JB). All final decisions on exclusion of MRI data were made in this consensus meeting. All scans that contained cortical brain infarcts over 1.5 cm were excluded from the WMH and brain volume

analysis because of segmentation errors. We have used the threshold of 1.5 cm based on the standards for reporting vascular changes on neuroimaging (STRIVE) criteria for large subcortical infarcts [21]. Brain surfaces were estimated by a fully automated method that estimates cortical thickness and the reconstruction of the central surface in one step [22]. To allow inter-subject analysis, a spherical map was plotted and images were smoothed by a 15mm Gaussian kernel.

Statistical analysis

Demographic variables were compared between the three groups (frail, pre-frail and non-frail) by a one-way ANOVA or chi-square test depending on the type of variable. For analysis of brain volumes, participants with cortical brain infarcts over 1.5 cm were excluded. To study differences in brain volumes (total brain volume, gray matter volume, white matter volume and WMH volume) between frail, pre-frail and non-frail participants, linear regression analyses were performed adjusted for age, gender, ICV and study center. Analyses of WMH volume were additionally corrected for vascular risk factors (hypertension, hypercholesterolemia, smoking, BMI, history of cardiovascular events and diabetes). For the assessment of the difference in presence of cortical brain infarcts over 1.5 cm between frail, pre-frail and non-frail participants, logistic regression analyses were performed with presence of a cortical brain infarct as the dependent variable, adjusted for age, gender and study center. Analyses of brain volume differences and WMH differences per frailty component were performed by linear regression analyses corrected for age, gender, ICV and study center. Presence of cortical brain infarcts was analyzed by a logistic regression analysis corrected for age, gender and study center. All regression analyses of global brain volumes, WMH and cortical brain infarcts were performed in IBM SPSS version 21.

For analysis of cortical thickness differences between frail, pre-frail and non-frail participants, a linear regression model was implemented in CAT12 and SPM12, with age, gender and center as covariates. All cortical thickness analyses were family-wise error (FWE) corrected and thresholded at $p<0.05$. A cluster was considered significant at a minimal amount of 86 vertices, based on the expected number of voxels per cluster.

RESULTS

Of the initial 400 included participants in the BioCog study, 300 completed the preoperative MRI scanning protocol. Of these participants, 20 had to be excluded because of a brain tumor, previous trauma, MRI artifacts or an incomplete MRI scanning protocol (see figure 1). Furthermore, 66 participants had one or more missing frailty components and were thus excluded. This resulted in inclusion of 214 participants (mean age 72.4 years (SD: 4.9 years); 37% female) in the present study (see figure 1). In total, 32 participants (15%) were classified as frail (three or more frail components), 107 participants (50%) were classified as pre-frail (one or two frail components) and 75 participants (35%) were classified as non-frail (no frail components). Frail participants were older ($F(2,211)=3.98$, $p<0.05$, planned contrasts revealed that frail and pre-frail participants were significantly older than non-frail participants ($t(211)=2.42$, $p<0.05$) and that frail participants were significantly older than pre-frail participants ($t(211)=2.21$, $p<0.05$)), more often female ($x^2(2)=7.90$, $p<0.05$) and had higher preoperative ASA scores ($x^2(4)=12.39$, $p<0.05$) compared to pre-frail and non-frail participants (see table 2 for demographics). The frailty groups showed no differences in vascular risk factors. Patients with cortical brain infarcts over 1.5 cm ($n=19$) were excluded from the brain volume analysis due to segmentation errors. The demographics of the brain volume analysis group after exclusion of participants with cortical brain infarcts were comparable to the original group (for demographics of the brain volume analysis group see supplementary table B).

Table 1: Demographics

	Total (n=214)	**Frail (n=32)**	**Pre-frail (n=107)**	**Non-frail (n=75)**	**p-value**
Age	72.4 ± 4.9	74.7 ± 5.4	72.3 ± 5.0	71.6 ± 4.5	0.020
Female gender	80 (37%)	19 (59%)	37 (35%)	24 (32%)	0.019
MMSE	29 (28 , 30)	28 (27 , 29)	29 (28 , 30)	29 (28 , 30)	0.021
Center					0.11
Utrecht	74 (35%)	13 (41%)	42 (39%)	19 (25%)	
Berlin	140 (65%)	19 (59%)	65 (61%)	56 (75%)	
ASA score (n=211)*					0.015
I	12 (6%)	0 (0%)	4 (4%)	8 (11%)	
II	134 (64%)	18 (58%)	64 (60%)	53 (71%)	
III	65 (31%)	13 (42%)	38 (36%)	14 (19%)	
Vascular risk factors†					
Diabetes	24 (11%)	4 (13%)	12 (12%)	8 (12%)	0.22
BMI	27 (24 , 29)	29 (26 , 33)	26 (24 , 29)	27 (24 , 28)	0.42
Hypertension	128 (60%)	22 (69%)	66 (62%)	40 (53%)	0.11
Hyperlipidemia	54 (25%)	10 (31%)	30 (28%)	14 (19%)	0.09
Current smoker	27 (13%)	2 (6%)	15 (14%)	10 (13%)	0.46
Self-reported previous cardiovascular events	6 (3%)	2 (6%)	2 (2%)	2 (3%)	0.04
Frailty components					
Slowness	52 (24%)	25 (78%)	27 (25%)	0 (0%)	
Weakness	63 (29%)	22 (69%)	41 (38%)	0 (0%)	
Weight loss	14 (7%)	4 (13%)	10 (8%)	0 (0%)	
Exhaustion	48 (22%)	23 (72%)	25 (23%)	0 (0%)	
Mobility	82 (38%)	30 (94%)	52 (49%)	0 (0%)	

Data represent n (percentage), mean ± SD or the median (interquartile range). A one-way ANOVA comparison of three groups was performed on continuous data. A chi-square comparison of three groups was performed for categorical data. In preoperative ASA scores, two values were missing, therefore a percentage of n=212 participants was calculated. † In vascular risk factors three values were missing, therefore a percentage of n=211 participants was calculated. Previous cardiovascular events include previous stroke and cortical brain infarcts.

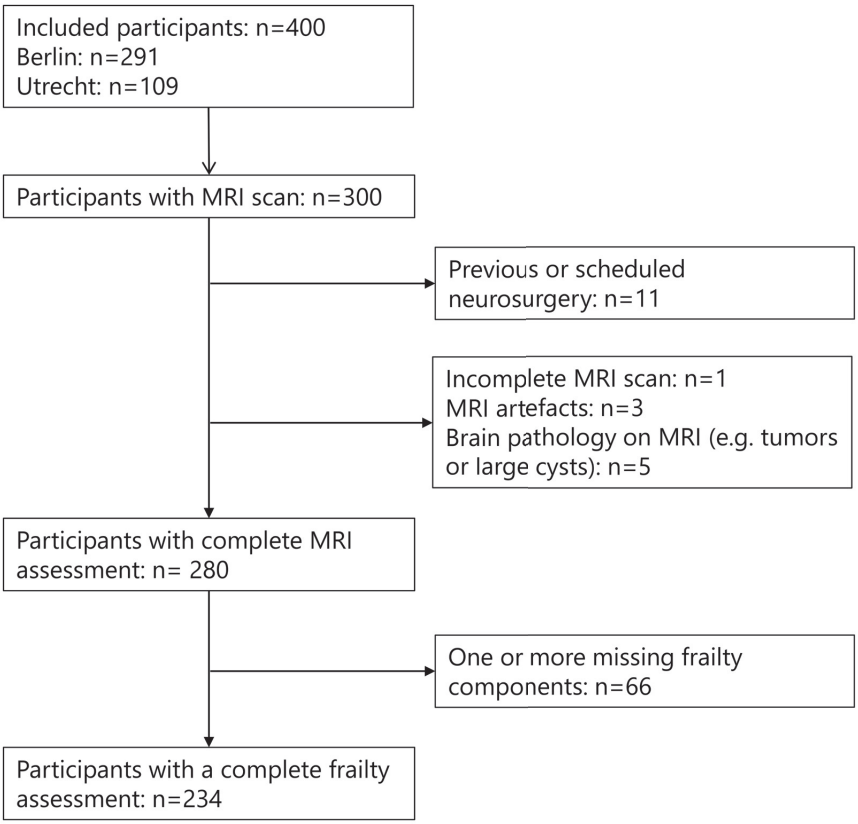

Figure 1: flowchart representing the included participants.

Brain volumes and frailty

Table 2 shows the analyses on the association between total brain volume, gray matter volume, white matter volume, WMH volume and frailty (see supplementary table B). Participants in the frail group showed a lower total brain volume (-19.67 ml (95% Confidence Interval (CI) -37.84 , -1.50)) and lower gray matter volume (-12.19 ml (95% CI -23.84 , -0.54)) compared to participants in the non-frail group. Participants in the frail group further showed a lower total brain volume (-22.40 ml (95% CI -40.38 , -4.41)) and lower gray matter volume (-12.26 ml (95% CI -23.09 , -1.43)) compared to participants in the pre-frail group. No significant differences were found between the pre-frail and non-frail group in total brain volume (1.16 ml (95 % CI -10.78 , 13.11)), gray matter volume (-0.43 (95% CI -8.11 , 7.25)), white matter volume (1.59 (95% CI

-7.09 , 10.27)) and WMH volume (0.32 (95% CI -0.21 , 0.84)) (see table 2). A larger WMH volume was found in the frail group (9.53±13.13 ml) compared to the non-frail group (3.36±3.43 ml), but this difference was not statistically significant (0.45 (95% CI -0.25 , 0.93)) (see table 2). Secondary analyses with additional adjustment for vascular risk factors (hypertension, hypercholesterolemia, smoking, BMI, history of cardiovascular events and diabetes) showed an unchanged, non-significant association between WMH volume and physical frailty (β=0.52 (95% CI-0.01 , 1.04, p=0.05) (see table 2). Analysis of cortical thickness showed a lower global cortical thickness in frail participants compared to pre- and non-frail participants. However, no association between regional cortical thickness and physical frailty was found, as no clusters remained significant after FWE correction for multiple comparisons and cluster size.

Cortical brain infarcts and frailty

In total, 19 participants (9%) had cortical brain infarcts over 1.5 cm (see table 4). The infarct prevalence was associated with frailty status: frail (16%; n=5), pre-frail (11%; n=12) and non-frail (3%; n=2). One of the participants with a cortical brain infarct had reported a previous cardiovascular event (a transient ischemic attack), this participant was classified as frail. All other participants therefore had silent cortical infarcts. None of these participants has reported a previous myocardial infarction. Although participants in the frail group had more cortical brain infarcts compared to the non-frail group, this did not reach statistical significance (OR = 4.14 (95% CI 0.63, 27.40) see table 3). Participants in the pre-frail group showed a higher odds ratio of having a cortical brain infarct compared to participants in the non-frail group (OR= 4.66 (95% CI 1.00, 21.73).

Table 2: Brain volumes and regression analyses of frail, pre-frail and non-frail participants

	Total brain volume	Gray matter volume	White matter volume	WMH volume	WMH volume model 2
Brain volumes					
Frail	1024.78 ± 100.72	556.64 ± 55.66	468.15 ± 55.56	9.53 ± 13.13	
Pre-frail	1047.10 ± 103.58	567.88 ± 51.89	479.22 ± 59.55	5.81 ± 7.25	
Non-frail	1060.47 ± 110.22	572.45 ± 57.92	488.01 ± 58.20	3.36 ± 3.43	
Regression analyses					
Frail vs. non-frail	-19.67 (-37.84 , -1.50)*	-12.19 (-23.84 , -0.54)*	-7.48 (-20.72 , 5.75)	0.45 (-0.25 , 0.93)**	0.52 (-0.01 , 1.04)
Frail vs. pre-frail	-22.40 (-40.38 , -4.41)*	-12.26 (-23.09 , -1.43)*	-10.14 (-24.05 , 3.77)	0.32 (-0.21 , 0.84)	0.42 (-0.12 , 0.95)
Pre-frail vs. non-frail	1.16 (-10.78 , 13.11)	-0.43 (-8.11 , 7.25)	1.59 (-7.09 , 10.27)	0.11 (-0.23 , 0.44)	0.15 (-0.21 , 0.50)

Brain volumes are in ml and are represented as mean ± SD. Regression analysis adjusted for age, gender, intracranial volume and study center. Regression beta coefficients are presented with a 95% confidence interval. * p-value <0.05. ** p-value = 0.06. WMH volumes were multiplied by 100 and natural log transformed before performing regression analyses. WMH volume model 2 are regression beta coefficients that were additionally corrected for cardiovascular risk factors (hypertension, hypercholesterolemia, BMI, diabetes, previous cardiovascular events, and smoking).

Brain volumes, cortical brain infarcts and individual frailty components

Analyses on individual frailty components across groups and brain volumes, cortical brain infarcts and are shown in table 4. In these analyses, all groups (frail, pre-frail and non-frail) were combined and assessed per component. Most frailty components were associated with brain volumes and occurrence of cortical brain infarcts, but these associations did not reach statistical significance (see table 4).

Table 3: The presence of cortical brain infarcts in relation to physical frailty

	Cortical brain infarcts and physical frailty
Presence of cortical brain infarcts	
Frail	5 (16%)
Pre-frail	12 (11%)
Non-frail	2 (3%)
Logistic regression analyses	
Frail vs. non-frail	4.14 (0.63 , 27.40)
Frail vs. pre-frail	1.48 (0.45 , 4.84)
Pre-frail vs. non-frail	4.66 (1.00 , 21.73)*

Data on presence of cortical brain infarcts over 1.5 cm are presented as n (percentage). Logistic regression analysis adjusted for age, gender, and study center. Corrected odds ratios are presented with a 95% confidence interval. * p-value = 0.05.

Table 4: Brain volume changes and presence of cortical brain infarcts per frailty component for the total group

	Total brain volume (n=195)	**Gray matter volume (n=195)**	**White matter volume (n=195)**	**WMH volume (n=195)**	**Cortical brain infarcts (n=234)***
Slowness	β= -12.60 (-25.91 , 0.70)	β= -5.63 (-14.02 , 2.75)	β= -6.97 (-16.77 , 2.83)	β= 0.23 (-0.14 , 0.60)	OR= 2.28 (0.84 , 6.23)
Weakness	β= -8.08 (-20.75 , 4.59)	β= -4.39 (-12.34 , 3.57)	β= -3.69 (-13.01 , 5.63)	β= 0.01 (-0.34 , 0.36)	OR= 1.31 (0.48 , 3.59)
Weight loss	β= -18.18 (-39.84 , 3.47)	β= -9.12 (-22.74 , 4.50)	β= -9.06 (-25.01 , 6.88)	β= 0.24 (-0.36 , 0.84)	-†
Exhaustion	β= -2.94 (-16.56 , 10.68)	β= -2.93 (-11.47 , 5.61)	β= -0.01 (-10.01 , 9.99)	β= 0.36 (-0.02 , 0.73)	OR= 2.02 (0.73 , 5.56)
Mobility	β= -4.27 (-15.80 , 7.25)	β= -5.23 (-12.43 , 1.97)	β= 0.96 (-7.51 , 9.42)	β= -0.01 (-0.33 , 0.31)	OR=1.78 (0.68 , 4.65)

Linear regression analysis on the association between individual frailty components and total brain volume, gray matter volume, white matter volume and WMH volume per frailty component adjusted for age, gender, intracranial volume and study center. Regression beta coefficients are presented with a 95% confidence interval. *Logistic regression analysis on cortical brain infarcts adjusted for age, gender and study center. Adjusted odds ratios are presented with a 95% confidence interval. †There were no participants who fulfilled the criterion for weight loss and had a cortical brain infarct over 1.5 cm.

DISCUSSION

We investigated differences in brain volumes and cortical brain infarcts between frail, pre-frail and non-frail older individuals in a large group of older individuals. We showed that frail individuals had more neurodegenerative and neurovascular abnormalities compared to pre-frail and non-frail individuals. Frail individuals had a significantly lower total brain volume and lower gray matter volume, and showed a trend for more cortical brain infarcts and a higher WMH volume compared to non-frail individuals. Frail individuals showed a lower global cortical thickness compared to pre- and non-frail individuals, however, no regional clusters of a lower cortical thickness were found. Individual frailty components showed a relation with a lower global gray matter volume, but this did not reach statistical significance. Furthermore, pre-frail individuals had more cortical brain infarcts compared to non-frail individuals.

Quantification of global and regional brain atrophy as a MRI marker for neurodegenerative diseases is widely performed in research on cognitive impairment and dementia [23,24]. However, only few studies have performed these analyses in relation to frailty [8,11]. These studies included a low number of frail individuals and thus combined pre-frail and frail individuals in one group, possibly reducing the contrast between groups [8]. Furthermore, the method of determining frailty differed between studies. Some studies have used the physical frailty phenotype and others the Edmonton Frail Scale, which combines physical and cognitive frailty scores [2,25]. This does not allow direct comparison of results between these studies. In line with the results of Chen et al., we showed an association between physical frailty and a lower gray matter volume [8]. We additionally showed an association between physical frailty and a lower total brain volume and gray matter volume. Chen et al. previously showed that distinct patterns of regional (mainly cerebellar) gray matter volume changes were associated with individual frailty components and with physical frailty. Our results confirm their findings by showing an association of frailty and of all individual components with global gray matter volume changes. However, in contrast to previous findings, analysis of regional cortical thickness showed no significant regional differences in cortical thickness, which is possibly due to the heterogeneous nature of physical frailty.

WMH are common in older individuals and are an MRI marker of cerebral small vessel disease [21]. WMH are related to cognitive decline and physical deterioration

such as gait problems [26–28]. To date, only few studies have investigated the association between WMH and physical frailty [8–12], of which only two studies have assessed WMH quantitatively [8,10]. The association between physical frailty and WMH is unclear, as three previous studies found no association between WMH and frailty [8,11,12], and only one study did find an association [9,10]. We found a trend for an association between increased WMH in the frail versus the non-frail group. Because of the large variability in WMH volumes between individuals, future studies with larger patient groups are needed to prove a potential association between WMH volume and physical frailty. Alternatively, other MRI methods that can investigate the structural integrity of the white matter, such as diffusion tensor imaging, may be performed to detect differences in white matter integrity between frail, pre-frail and non-frail [10].

Cortical brain infarcts are an MRI marker of large vessel disease and are associated with cognitive decline [29]. Only one study has specifically explored the association between brain infarcts and physical frailty [14]. In this study, the presence of brain infarcts greater than 3 mm was associated with physical frailty, however, the authors did not distinguish different infarct types according to underlying pathophysiology (i.e. cortical, subcortical or lacunar brain infarcts) [14]. Another investigation that assessed physical and cognitive frailty in a combined way, showed that brain infarcts occurred more frequently in frail compared to pre-frail and non-frail individuals [11]. Our investigation is the first to assess the association between a physical frailty state and the presence of cortical brain infarcts. Our results confirm the relation between physical frailty and cerebral infarcts that was shown in previous studies [11,14]. Additionally, we have shown an association between a physical pre-frailty state and the presence of cortical brain infarcts and a non-significant increase in presence of cortical brain infarcts between pre-frail and frail participants.

A limitation of our study may be between center differences in MRI-based brain volumes. To minimize the effect of these possible between center differences, MRI protocols were made comparable and we used a brain segmentation pipeline that is relatively robust for between center differences [19]. We also used 'center' as a covariate in the analyses. This approach minimized the between-center differences in brain volumes. Another limitation may be that all participants were scheduled for major elective surgery. Therefore, we cannot rule out a possible association between the reason for elective surgery (e.g. total hip replacement) and components of physical

frailty. Finally, our study is limited by its cross-sectional design. Therefore, we are unable to assess whether smaller brain volume measures were already present before development of the frailty phenotype. A strength of our study is the inclusion of a large group of participants, which enabled the separate analysis of frail, pre-frail and non-frail individuals. This allowed us to study pre-frail individuals separately, which is a group that has received almost no previous attention. Furthermore, the physical frailty phenotype is the most frequently used method to classify frailty in research and clinical practice [4]. Therefore, use of this method enables comparison of our results with recent literature, and gives us insight into the underlying mechanism of this clinical concept.

In conclusion, individuals with physical frailty showed lower global brain volumes and lower global gray matter volumes compared to pre-frail and non-frail individuals. Individuals with physical frailty and pre-frailty also showed more cortical brain infarcts compared to non-frail individuals. These brain changes could be the underlying substrate of the physical frailty phenotype.

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SUPPLEMENTARY MATERIAL

Table A: Components of the adapted version of the Frailty phenotype by Rockwood et al. (Rockwood et al., 2007b).

Component	Measure
Weight loss	Self-reported unintentional weight loss of ≥ 5 % in the prior year or loss of ≥ 3 kilograms in the last three months.
Exhaustion	Self-reported exhaustion identified by statement number 13 of the Dutch version of The Geriatric Depression Scale (GDS) "Do you feel full of energy?" in the last two weeks or by the Hospital Anxiety and Depression scale question "I feel that everything is an effort", in which the answers "all the time" and "often were scored as exhausted.
Mobility	Ability to walk without difficulty or assistance according to (Rockwood et al., 2007a), determined by self-report of a statement about mobility and walking from the EuroQOL five dimensions questionnaire.
Weakness	Low maximal hand grip strength measured with a Smedley spring hand dynamometer adjusted for gender and body mass index.
Slowness	Low gait speed based on the Timed Up and Go test (TUG) (a score lower than or equal to 10 seconds was scored as fast, more than 10 seconds was scored as slow) (Savva et al., 2013).

Table B: Demographics of the group without cortical brain infarcts over 1.5 cm.

	Total (n=195)	**Frail (n=27)**	**Pre-frail (n=95)**	**Non-frail (n=73)**	**p-value**
Age	72.3 ± 5.0	74.1 ± 5.6	72.4 ± 5.0	71.4 ± 4.5	0.047
Female gender	72 (37%)	16 (60%)	33 (35%)	23 (32%)	0.03
MMSE	29 (28-30)	28 (27-29)	29 (28-30)	29 (28-30)	0.02
Study center					0.20
Utrecht	66 (34%)	10 (37%)	37 (39%)	19 (26%)	
Berlin	129 (66%)	17 (63%)	58 (61%)	54 (74%)	
ASA score (N=193)*					0.04
I	12 (6%)	0	4 (4%)	8 (11%)	
II	124 (64%)	15 (58%)	58 (62%)	51 (70%)	
III	57 (30%)	11 (42%)	32 (34%)	14 (19%)	
Vascular risk factors†					
Diabetes	21 (11%)	2 (7%)	11 (12%)	8 (11%)	0.24
BMI	27 (24-29)	29 (26-34)	26 (24-30)	27 (24-28)	0.40
Hypertension	114 (58%)	18 (67%)	57 (60%)	39 (53%)	0.17
Hyperlipidemia	45 (23%)	7 (26%)	25 (26%)	13 (18%)	0.16
Current smoker	23 (12%)	1 (4%)	12 (13%)	10 (14%)	0.29
Self-reported previous cardiovascular events	5 (3%)	1 (4%)	2 (2%)	2 (3%)	0.21

Data represent N, N (percentage), mean±SD or the median (interquartile range). A one-way ANOVA comparison of three groups was performed on continuous data. A chi-square comparison of three groups was performed for categorical data. In preoperative ASA scores, two values were missing, therefore a percentage of N=193 participants was calculated. † In vascular risk factors three values were missing, therefore a percentage of N=192 participants was calculated.

CHAPTER 3

The association between frailty and MRI features of cerebral small vessel disease

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ABSTRACT

Frailty is a common syndrome in older individuals that is associated with poor cognitive outcome. The underlying brain correlates of frailty are unclear. The aim of this study was to investigate the association between frailty and MRI features of cerebral small vessel disease in a group of non-demented older individuals. We included 170 participants who were classified as frail (n=30), pre-frail (n=85) or non-frail (n=55). The association of frailty and white matter hyperintensity volume and shape features, lacunar infarcts and cerebral perfusion was investigated by regression analyses adjusted for age and sex. Frail and pre-frail participants were older, more often female and showed higher white matter hyperintensity volume (0.69 [95%-CI 0.08 to 1.31], p=0.03 respectively 0.43 [95%-CI: 0.04 to 0.82], p=0.03) compared to non-frail participants. Frail participants showed a non-significant trend, and pre-frail participants showed a more complex shape of white matter hyperintensities (concavity index: 0.04 [95%-CI: 0.03 to 0.08], p=0.03; fractal dimensions: 0.07 [95%-CI: 0.00 to 0.15], p=0.05) compared to non-frail participants. No between group differences were found in gray matter perfusion or in the presence of lacunar infarcts. In conclusion, increased white matter hyperintensity volume and a more complex white matter hyperintensity shape may be structural brain correlates of the frailty phenotype.

INTRODUCTION

Frailty is a chronic condition of increased vulnerability to physiological stressors that is common in older individuals and is most often described using the physical frailty phenotype[1–3]. Frail older individuals have a higher risk of falling, postoperative complications, dependency and cognitive decline, compared to non-frail counterparts[1,4,5]. The impact of these consequences of frailty on a societal and economic level in an aging population stresses the importance of investigating the pathways leading to a frail condition. To date, the biological pathways leading to the decline of multiple physiological systems remain unknown. The association between frailty and cognitive disorders suggests a structural brain correlate, but this is currently largely unknown.

Cerebral small vessel disease (SVD) is a syndrome that is characterized by manifestations of diseases of the small vessels in the brain, with probably different underlying pathophysiology and etiology[6,7]. SVD is one of the major causes of stroke, cognitive decline and dementia in older individuals[6,8]. The most commonly used MRI features of SVD are white matter hyperintensity of presumed vascular origin (WMH) volume and the presence of lacunar infarcts[6,9].

Previous studies on the association between of frailty with WMH volume or lacunar infarcts have shown inconsistent results[10–16]. Due to the heterogeneous nature of SVD, other MRI features of SVD may provide additional information[17–20]. Recent studies have shown that WMH shape is a novel promising feature related to more severe small vessel changes[19,20]. Furthermore, cerebral perfusion measured by arterial spin labeling (ASL) MRI could detect early hemodynamic changes that may be related to SVD [21–23]. Frailty may therefore be associated with both structural brain changes of SVD as well as quantitative hemodynamic changes.

The aim of this study was to investigate the association between frailty and MRI features of cerebral SVD in a group of non-demented older individuals who were scheduled for major elective surgery. We assessed both commonly used structural features (WMH volume and presence of lacunar infarcts) and novel structural (WMH shape) and hemodynamic features (cerebral perfusion) of cerebral SVD.

METHODS

Study design and participants

Data were obtained from the BioCog consortium study: an international observational study that aims to identify biomarkers of postoperative cognitive disorders[37]. The BioCog study is performed at the Charité Universitätsmedizin Berlin and the University Medical Center Utrecht[37]. The present study uses patient data that were collected at the University Medical Center Utrecht only. Patients who were included in BioCog (1) were at least 65 years of age, (2) were scheduled for major elective surgery of at least 60 minutes, and (3) had a mini-mental state exam (MMSE) score of 24 or higher. The medical ethics committee of both centers approved all procedures under ethical approval number EA2/092/14 (Berlin: Ethikkommission der Charité) and 14-469 (Utrecht: Medisch Ethische Toetsingscommissie Utrecht). All participants signed informed consent. All methods were performed in accordance with all relevant guidelines and regulations that apply to research with human participants.

Procedure

Trained research personnel collected demographic data, data on vascular risk factors (i.e. questionnaires and medical history records, vascular risk factors, obesity[38]) and administered the MMSE during a visit prior to surgery. A hospital anxiety and depression scale (HADS) score on the depression subscale ≥8 was seen as having depressive symptoms[39]. Anesthesiologists (in training) performed the classification for the American Society of Anesthesiologists score.

Frailty assessment

Participants were classified based on five frailty components according to the Fried frailty phenotype[2,40]: slowness, weakness, weight loss, exhaustion and mobility. Slowness was measured by the timed up and go test[41]; when this took over 10 seconds it was scored as slow. Weakness was assessed by low maximal hand grip strength, adjusting for sex and body mass index[2]. Weight loss was determined by a self-reported unintentional weight loss of ≥ 5 % or ≥ 3 kg in the previous year. Exhaustion was determined by self-reported exhaustion in the geriatric depression scale or the hospital anxiety and depression scale. Mobility was scored by a self-reported inability to walk without difficulty from the EuroQOL five dimensions questionnaire[42] and the Barthel index[43]. Participants who did not show presence of any frailty components were classified as non-frail, those who showed presence of

one or two frailty components were classified as pre-frail, and those who scored positive on three or more frailty components were classified as frail (see [14] for more details).

MRI scans

Participants were scanned on a Philips Achieva 3T MRI scanner. The MRI scanning protocol consisted of a three-dimensional (3D) T1-weighted sequence (voxel size = 1.0x1.0x1.0 mm^3; TR/TE= 7.9/4.5 ms), a 3D fluid-attenuated inversion recovery (FLAIR) sequence (voxel size = 1.11 x 1.11 x 0.56 mm^3; TR/TE/TI = 4800/125/1650 ms), a pseudo-continuous arterial spin labeling (pCASL) sequence (voxel size = 3.0x3.0x7.0 mm^3; TR/TE=3919/17 ms, label duration = 1650 ms, post labeling delay = 1525 ms) and a diffusion-weighted image (DWI) (voxel size = 0.96 x 1.19 x 4 mm^3; TR/TE= 3294 / 68 ms). Presence of lacunar infarcts was visually rated on the T1-weighted, FLAIR and DWI images by two experienced neuro-radiologists (JB (11 years of experience) and TW (25 years of experience)) according to the standards for reporting vascular changes on neuroimaging (STRIVE) criteria[26].

Quantification of WMH volume and shape features

3D FLAIR images were registered to the T1-weighted images using statistical parametric mapping version 12 (SPM12; Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/doc/) for Matlab (The MathWorks, Inc., Natick, Massachusetts, United States). WMH segmentations were performed on the registered 3D FLAIR images by the lesion prediction algorithm (Schmidt, 2017, Chapter 6.1[44]) of the lesion segmentation toolbox version 2.0.15 (www.statistical-modeling.de/lst.html) for SPM12. Visual quality control for the WMH segmentations was performed by a trained researcher (IK) and supervised by a neuro-radiologist (JB), see figure 1 for an example. Cortical infarcts were manually delineated by a trained researcher (IK) and removed from the WMH probability maps. Lateral ventricular segmentation on the T1-weighted images was performed using the automated lateral ventricle delineation toolbox (ALVIN) in SPM8. The probabilistic WMH segmentations were thresholded at 10%. WMH within 10 mm from the lateral ventricles into the white matter were considered periventricular WMH. WMH that extended from periventricular to more than 10 mm into the deep white matter were considered confluent WMH. WMH that were located >10 mm from the lateral ventricles were considered deep WMH. WMH shape features were calculated from

the thresholded WMH segmentations[20]. The solidity, convexity, concavity index and fractal dimension of periventricular and confluent WMH were calculated by reconstruction of the convex hull, volume and surface area of all individual lesions. The eccentricity and fractal dimension were calculated of deep WMH (see [20] and supplementary table A for more details). For all WMH shape features, mean values per feature were calculated per patient and used for further analyses.

CBF quantification

ASL images were processed with ExploreASL[45]. Lesion filling of the T1-weighted images was performed by the lesion segmentation toolbox version 2.0.15 (www.statistical-modeling.de/lst.html) for SPM12. The filled T1-weighted images were segmented using CAT12[46]. CBF images were motion corrected and registered to the gray matter partial volume maps[45]. The CBF images were quantified with a single compartment model[47], after which the mean CBF was obtained for a total gray matter perfusion and deep WM region-of-interest (ROI)[48]. The spatial coefficient of variation (spatial CoV) was calculated within the total GM as a proxy parameter of vascular sufficiency (for more details see[23]). All perfusion images were rated as images containing 1) CBF contrast, 2) vascular contrast or no contrast by a trained researcher (IK), supervised by an experienced ASL researcher (HM, 7 years of experience). Images that were classified as CBF contrast were used in the perfusion analysis. Images with vascular contrast were included in the analysis of spatial CoV, but excluded from the perfusion analysis. The no contrast images that contained noise only or large artifacts were excluded from further analysis.

Statistical analysis

For demographic analyses, three groups (frail, pre-frail and non-frail) were compared by a one-way ANOVA or chi-square test depending on the type of variable (i.e. continuous or categorical). WMH volumes, WMH shape features and cerebral perfusion were compared between the frail and non-frail group and between the pre-frail and non-frail group by linear regression analyses adjusting for age and sex. WMH volumes were natural log transformed before linear regression analysis and additionally adjusted for intracranial volume (ICV). A Pearson's correlation coefficient was computed to assess the relation between natural log transformed total WMH volume and global cerebral gray and white matter perfusion. The presence of lacunar

infarcts was compared between the frail and non-frail group and between the pre-frail and non-frail group by logistic regression analyses adjusted for age and sex.

In secondary analyses, WMH shape features were compared between groups by linear regression analyses additionally adjusted for WMH volume, to test if the found associations were WMH volume independent. Exploratory post-hoc analyses of the relation between MRI features of SVD (that showed significant between group differences) and frailty components were performed by linear regression analyses adjusted for age and sex, and for the WMH volume analysis additionally adjusted for ICV. All analyses were performed in SPSS version 25. A p-value of below 0.05 was considered statistically significant.

RESULTS

Of the 178 participants that completed the MRI scanning protocol, a total of 8 participants had to be excluded from all analyses, due to extremely large ventricles that hindered accurate segmentation (n=1), an incomplete FLAIR and ASL sequence (n=1), or major MRI artifacts (e.g. motion; n=6), leaving 170 participants for the current study. Demographics for frail (n=30), pre-frail (n=85) and non-frail (n=55) participants are shown in Table 1. Frail participants were older, more often female, had higher ASA classification scores and a higher body mass index (BMI) compared to pre- and non-frail individuals. No between-group differences in other vascular risk factors or MMSE scores were found. A total of 13 participants had to be excluded from the WMH feature analyses due to major segmentation errors (n=6), FLAIR artifacts (e.g. motion, n=4) or no availability of a FLAIR sequence (n=2). A total of 90 participants had an ASL image of sufficient quality for perfusion analysis, and a total of 156 participants had an ASL image that could be used for spatial CoV analysis of vascular signal.

WMH volume: Frail participants showed a higher total (0.69 [95% CI 0.08 to 1.31]), p=0.03 and periventricular/confluent (0.67 [95% CI 0.06 to 1.30], p=0.03) natural log transformed WMH volume compared to non-frail participants (see Table 2). Pre-frail participants showed also a higher total natural log transformed WMH volume (0.43 [95% CI 0.04 to 0.81, p=0.03 and a higher periventricular and confluent natural log transformed WMH volume (0.43 [95% CI 0.04 to 0.81], p=0.03) than non-frail participants.

Table 1: Demographics

	Frail (n=30)	Pre-frail (n=85)	Non-frail (n=55)	p-value
Age	74 ± 5	72 ± 5	70 ± 4	0.01
Female gender	16 (53%)	24 (28%)	12 (22%)	0.01
MMSE	28 (28 , 29)	29 (27 , 30)	29 (28 , 30)	0.81
Depressive symptoms	4 (13%)	6 (7%)	1 (2%)	0.12
ASA score				0.04
I	1 (3%)	8 (9%)	11 (20%)	
II	15 (50%)	45 (53%)	32 (58%)	
III	14 (47%)	32 (38%)	12 (22%)	
Vascular risk factors				
Diabetes	8 (27%)	12 (14%)	6 (11%)	0.13
BMI	29 ± 6	27 ± 4	26 ± 4	0.01
Obesity	9 (30%)	19 (22%)	6 (11%)	0.08
Hypertension	17 (57%)	45 (53%)	22 (40%)	0.21
Hyperlipidemia	12 (40%)	36 (42%)	16 (29%)	0.28
Current smoker	3 (10%)	8 (10%)	3 (5%)	0.60
TIA / stroke	3 (10%)	5 (6%)	1 (2%)	0.10
Frailty components				
Slowness	23 (77%)	18 (21%)	-	n/a
Weakness	18 (60%)	27 (32%)	-	
Weight loss	11 (37%)	19 (22%)	-	
Exhaustion	24 (80%)	22 (26%)	-	
Mobility	27 (90%)	34 (40%)	-	

Data represent n (percentage), mean ± SD or median (interquartile range). A one-way ANOVA comparison of three groups was performed on continuous data. A chi-square comparison of three groups was performed for categorical data.
MMSE: mini-mental state exam. ASA: classification of disease severity for the American Society of Anesthesiologists. BMI: body-mass index. TIA: transient ischemic attack.

Presence of lacunar infarcts

In total, 20% (n=6) of the frail participants, 27% (n=23) of the pre-frail participants and 22% (n=12) of the non-frail participants had lacunar infarcts. Logistic regression analyses corrected for age and sex showed no between-group differences in the presence of lacunar infarcts (frail versus non-frail: OR (95% CI) = 1.25 [0.35 to 4.42], p=0.73; pre-frail versus non-frail: OR (95% CI) = 1.35 [0.59 to 3.08], p=0.48).

Table 2: The association between physical frailty and WMH volume

	Frail (n=28)	Pre-frail (n=77)	Non-frail (n=52)	Frail vs. non-frail	Pre-frail vs. non-frail
Total WMH volume	10.92 ± 15.80	8.68 ± 11.28	4.89 ± 7.38	0.69 (0.08 , 1.31)*	0.43 (0.04 , 0.82)*
Periventricular and confluent WMH volume	10.52 ± 15.68	8.32 ± 11.09	4.64 ± 7.13	0.67 (0.06 , 1.3)*	0.43 (0.04 , 0.81)*
Deep WMH volume	.40 ± .66	.36 ± .65	.25 ± .49	0.55 (-0.35 , 1.46)	0.27 (-0.34 , 0.87)

Data are represented as mean WMH volume (ml) ± SD. The linear regression analyses were adjusted for age, gender and ICV. Regression beta coefficients are presented with a 95% confidence interval. WMH volumes were multiplied by 100 and natural log transformed before performing regression analyses. *p = 0.03

Table 3: The association between physical frailty and WMH shape features

	Frail (n=28)	Pre-frail (n=77)	Non-frail (n=52)	Frail vs. non-frail	Pre-frail vs. non-frail
Periventricular/confluent WMH					
Solidity[a]	.29 ± .18	.31 ± .20	.36 ± .20	-0.14 (-0.43 , 0.15)	-0.16 (-0.37 , 0.04)
Convexity	1.15 ± .18	1.14 ± .18	1.17 ± .17	-0.04 (-0.13 , 0.05)	-0.02 (-0.08 , 0.05)
Concavity index	1.13 ± .13	1.13 ± .24	1.08 ± .09	0.05 (0.00 , 0.11)	0.04 (0.03 , 0.08)*
Fractal dimension	1.68 ± .26	1.67 ± .22	1.57 ± .22	0.08 (-0.03 , 0.20)	0.07 (0.00 , 0.15)*
Deep WMH					
Eccentricity	.58 ± .15	.56 ± .18	.58 ± .10	0.01 (-0.06 , 0.08)	-0.01 (-0.08 , 0.05)
Fractal dimension	1.83 ± .20	1.81 ± .35	1.88 ± .23	-0.04 (-0.17 , 0.09)	-0.06 (-0.19 , 0.07)

Data are represented as means ± SD. Regression analysis were adjusted for age and gender. Regression beta coefficients are presented with a 95% confidence interval. [a]Solidity was multiplied by 100 and natural log transformed. *Concavity index: p=0.03, Fractal dimension: p =0.05

WMH shape features

Frail participants showed a non-significant trend for a more complex shape of periventricular and confluent WMH (concavity index (0.05 [95% CI 0.00 to 0.11], p=0.06) compared to non-frail participants (see table 3). Pre-frail participants showed a more complex shape of periventricular and confluent WMH (a higher concavity index of 0.04 [95% CI 0.03 to 0.08], p=0.03 and a higher fractal dimension of 0.07 [95% CI 0.00 to 0.15], p=0.05) compared to non-frail participants (see table 3). No between-group differences were found in shape features of deep WMH (eccentricity and fractal dimensions). In secondary analyses, the between group differences in the shape of periventricular and confluent WMH attenuated after additional correction for natural log transformed WMH volume, indicating that these differences were also partly explained by WMH volume (see supplementary table B).

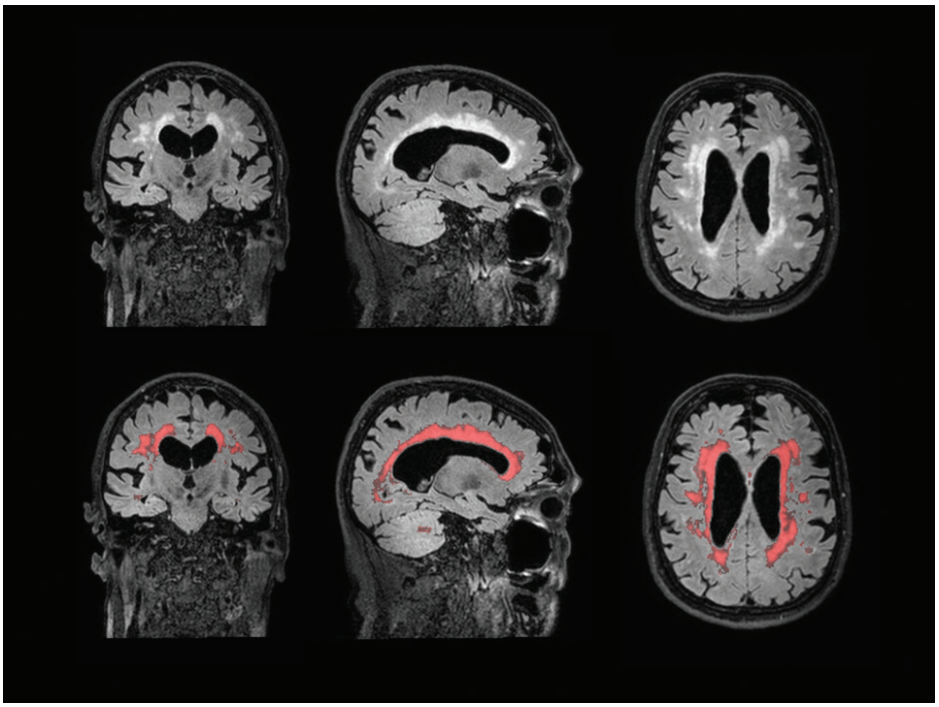

Figure 1: Example of a participant with a high WMH volume and complex WMH shape (top: original 3D FLAIR image; bottom: FLAIR image with overlay of the segmented WMH probability map in red).

Perfusion

Analysis of global cerebral perfusion of gray matter and white matter showed no significant differences between frail and non-frail participants, and no significant differences between pre-frail and non-frail participants. Furthermore, no between group differences were found in spatial CoV of the perfusion images (see table 4).

Exploratory analysis of relevant MRI features of SVD per frailty component

Exploratory analyses were performed of the MRI features of SVD that showed between-group differences (total WMH volume, concavity index, fractal dimensions), see supplementary table C. The physical frailty component slowness showed an association with WMH volume (0.65 [95% CI 0.23 to 1.06], p=0.003) and with a more complex shape of WMH (fractal dimensions: 0.12 [95% CI 0.04 to 0.21], p=0.003). The component exhaustion also showed a relation with WMH volume (0.41 [95% CI 0.00 to 0.82], p=0.048). Other physical frailty components (weakness, weight loss, mobility) showed no significant association with the studied SVD features.

Table 4: The association between physical frailty and cerebral perfusion

	Frail (n=13)	Pre-frail (n=40)	Non-frail (n=37)	Frail vs. non-frail	Pre-frail vs. non-frail
Gray matter perfusion	97 ± 24	82 ± 17	85 ± 20	12.3 (-2.8 , 27.5)	-5.3 (-18.0 , 7.3)
Deep WM perfusion	28 ± 8	26 ± 10	25 ± 8	1.3 (-4.6 , 7.1)	0.7 (-3.8 , 5.1)
Spatial CoV[a]	2.51 ± 0.70	2.52 ± 0.61	2.36 ± 0.56	0.18 (-0.16 , 0.51)	0.15 (-0.07 , 0.36)

Note. Data are represented as mean ± SD. Linear regression analysis were adjusted for age and gender. Regression beta coefficients are presented with a 95% confidence interval. [a]Data represents the spatial coefficient of variation of n=15 frail, n=67 pre-frail and n=48 non-frail individuals.

DISCUSSION

In summary, we observed that frail and pre-frail participants had a higher WMH volume compared to non-frail participants. Furthermore, pre-frail participants showed a more complex shape of periventricular and confluent WMH compared to non-frail participants. No between group differences were found in shape features of deep WMH, cerebral perfusion or presence of lacunar infarcts.

Previous community-based studies showed an inconsistent association between frailty and WMH volume and lacunar infarcts[10–15,24]. Direct comparison with these studies is however hindered by the use of different methods to assess frailty. The frailty assessment of these studies differed between the physical frailty phenotype by Fried et al.[11,12,14,15,24], and frailty scores that included measures of cognition, such as the Edmonton Frail Scale or the frailty index[2,10,13,25]. Four of the previous studies that assessed WMH showed an association between WMH and frailty[10,11,15,24], three other studies that were performed only found a weak or no association[12–14]. Almost all previous studies were community-based studies performed in older adults[10–13,15,24], although the studies that did not find an association included slightly younger individuals, possibly explaining the different findings[12,13]. Our study adds to the body of evidence for an association between frailty and WMH volume[10,12,15].

Comparison of previous studies regarding the association between frailty and lacunar infarcts is difficult due to use of different definitions of lacunar infarcts. Most previous studies did not conform with the size definition of lacunar infarcts (3-15 mm) according to the internationally accepted guidelines that we used on MRI markers of small vessel disease proposed in the STRIVE criteria[26]. One previous study found an association between frailty and cerebral infarcts >3 mm[15], whereas another earlier study showed no association with a frailty score that included cognitive tests and infarcts <20 mm[10]. Another previous study that investigated the relation between physical performance (e.g. gait, walking speed) and lacunar infarcts in memory clinic patients showed no relation between impaired physical performance and the presence of lacunar infarcts according to the STRIVE criteria[27]. Our findings are in accordance with these previous findings, as we did not find an association between frailty and lacunar infarcts[10]. The prevalence of lacunar infarcts in our study (24% in a population with a mean age of 71 ± 5 years of age) is comparable to the prevalence in a general older population (20% in a population with a mean age of 70 ± 7 years of age))[28].

No previous study has been performed on the association between frailty and WMH shape features, and only few studies have been performed on WMH shape features in general[19,20]. A previous cohort study in patients with symptomatic atherosclerotic disease showed that the presence of lacunar infarcts was related to a more complex WMH shape[20]. Furthermore, WMH shape was different in patients with type 2 diabetes mellitus (a condition associated with cerebral SVD) compared to healthy individuals[19]. These investigations indicate that WMH shape may be helpful in examining the heterogeneity of cerebral SVD and that a more complex shape of WMH may be associated with more severe manifestations of cerebral SVD[19,20]. Although our study is the first to show the relation between frailty and a more complex shape of WMH, these associations were not completely independent of WMH volume. A more complex WMH shape combined with increased WMH volume could be part of the structural brain changes that underlie the physical frailty phenotype.

Cerebral perfusion as measured by arterial spin labeling MRI is an indicator of brain metabolism and is one of the early markers for cognitive deterioration. Recently it has been suggested that low perfusion is a marker for SVD, although it is not yet clear whether this precedes or follows the presence of WMH[29]. Previous cross-sectional studies on SVD in both demented and non-demented populations showed that a higher WMH volume is associated with lower total CBF, although this was partly driven by co-occurrence of neurodegenerative diseases[30,31]. Our study is, to the best of our knowledge, the first that assessed the relation between global gray matter perfusion and frailty. We did not find an association between cerebral perfusion and physical frailty. A possible explanation for not finding this association may be that altered brain hemodynamics could be a marker for a more severe type of SVD in comparison to our population[30].

No previous studies on frailty and markers of SVD additionally explored the relation between individual frailty components and features of SVD. However, some previous investigations were performed on separate components without exploring overall frailty, such as gait speed[32], the short physical performance battery[33], mobility[34], and exhaustion[35]. These studies all showed an association between these components and MRI markers for SVD[32–35]. In exploratory analyses in our study, all components were associated with a higher WMH volume and a more complex WMH shape, although only slowness and exhaustion reached statistical significance. For slowness,

this finding is in line with previous findings on gait speed and the short physical performance battery[32,33]. The exhaustion component in our study was derived from one question of a questionnaire on anxiety and depression, and may not be accurate enough. The recommended assessment of exhaustion is by the CES-D depression scale, which could be more sensitive and specific to exhaustion[36]. A possible explanation for the relation between exhaustion and WMH volume might be that exhausted participants were slightly more depressed, which has previously been related to a higher WMH volume[34]. As this was a secondary analysis and there is not much previous evidence, these results should be carefully interpreted.

Strengths of our study include the detailed assessment of both commonly used features of cerebral SVD (WMH volume and lacunar infarcts) and more novel features of cerebral SVD (WMH shape features and cerebral perfusion) together with a detailed assessment of the physical frailty phenotype. Limitations of our study could be the limited number of physically frail individuals, causing a difference in group size between frail, pre-frail and non-frail individuals. Due to these differences, we had a lower statistical power to detect differences between frail and non-frail individuals. This may explain why we did not find a statistically significant difference in WMH shape or perfusion between frail and non-frail individuals. Another limitation is that participants from our study were all scheduled for major elective surgery and may not be comparable to the general population. This could limit the generalizability of our findings to the general population. A limitation in our assessment of slowness is that we did not consider comorbidities such as arthritis and pulmonary disease, which could have influenced the results of walking speed and exhaustion. A technical limitation could be that WMH segmentation methods in general have a limited accuracy for segmentation of especially smaller deep WMH. This may have underestimated possible associations between frailty and shape of deep WMH.

In conclusion, increased WMH volume and a more complex shape of WMH may be structural correlates of the physical frailty phenotype.

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Supplementary table A: description of WMH shape features (also see[2]).

Name	Definition	Explanation of the formula	Interpretation
Convexity (C)	$C = \frac{\text{Convex hull area}}{\text{Area}}$	Area: the surface area of the WMH lesion. Convex hull area: the smallest convex hull that fits the WMH lesion	A description of roughness; a surface with more concavities has a high area. A lower convexity is associated with a more complex shape.
Solidity (S)	$S = \frac{\text{Volume}}{\text{Convex hull volume}}$	Volume is the WMH volume. Convex hull volume is the volume of the smallest convex hull that fits the WMH lesion	A description of roughness; a volume with more concavities has a lower volume within the convex hull and thus a lower solidity. A lower solidity is associated with a more complex shape.
Concavity index (CI)	$CI = \sqrt{(2-C)^2 + (1-S)^2}$	C: Convexity; S: Solidity	A combined measure for convexity and solidity. A higher CI is associated with a more irregular or complex shape.
Fractal dimension (FD)	$FD = \lim_{r \to x_{xyz}} \frac{\log(n_r)}{\log\left(\frac{1}{r}\right)}$	N: number of boxes x_{xyz}: voxel size r: box size	Fractal dimension is calculated by a box counting method. A higher fractal dimension represents a more irregular shape.
Eccentricity (E)	$E = \frac{\text{Minor axis}}{\text{Major axis}}$	Major axis: largest diameter of the WMH in three dimensions. Minor axis: smallest diameter orthogonal to the major axis.	A high eccentricity represents a round shape, while a low eccentricity represents a more oval shape. A low eccentricity therefore relates to "outstretched" or elongated WMH.

Supplementary table B: Exploratory analyses of the association between frailty and WMH shape features additionally corrected for WMH volume

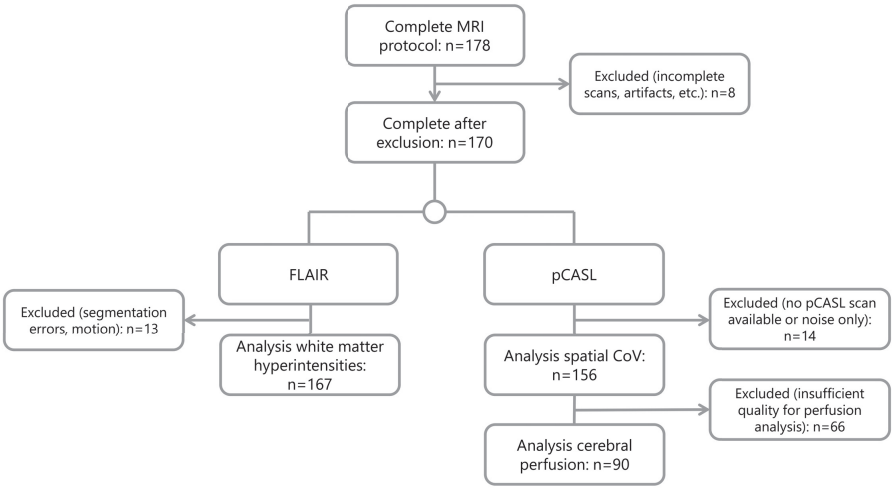
	Frail (n=28)	Pre-frail (n=77)	Non-frail (n=52)	Frail vs. non-frail (Beta (95% CI))	Pre-frail vs. non-frail (Beta (95% CI))
Periventricular/confluent WMH					
Solidity[a]	.29 ± .18	.31 ± .20	.36 ± .20	0.03 (-0.17 , 0.23)	-0.01 (-0.15 , 0.13)
Convexity	1.15 ± .18	1.14 ± .18	1.17 ± .17	-0.04 (-0.13 , 0.06)	-0.02 (-0.08 , 0.05)
Concavity index	1.13 ± .13	1.13 ± .24	1.08 ± .09	0.02 (-0.02 , 0.06)	0.02 (-0.01 , 0.04)
Fractal dimension	1.68 ± .26	1.67 ± .22	1.57 ± .22	-0.01 (-0.03 , 0.01)	0.00 (-0.02 , 0.01)
Deep WMH					
Eccentricity	.58 ± .15	.56 ± .18	.58 ± .10	0.02 (-0.05 , 0.09)	-0.02 (-0.08 , 0.05)
Fractal dimension	1.83 ± .20	1.81 ± .35	1.88 ± .23	-0.05 (-0.18 , 0.09)	-0.06 (-0.19 , 0.07)

Data are represented as means ± SD. Regression analysis were adjusted for age, gender and additionally for natural log transformed WMH volume. Regression beta coefficients are presented with a 95% confidence interval. [a]Solidity was natural log transformed because of a non-normal distribution.

Supplementary table C: Exploratory post-hoc analyses of the relation between MRI features of SVD (that showed significant between group differences) and frailty components

	WMH volume	Concavity index	Fractal dimension
Weakness	0.07 (-0.35 , 0.50)	0.01 (-.02 , 0.05)	0.19 (-0.35 , 0.72)
Weightloss	0.12 (-0.36 , 0.60)	0.01 (-0.04 , 0.05)	0.00 (-0.09 , 0.09)
Slowness	0.65 (0.23 , 1.06)*	0.04 (-0.01 , 0.08)	0.12 (0.04 , 0.21)*
Mobility	0.31 (-0.07 , 0.69)	0.02 (-0.02 , 0.06)	0.04 (-0.03 , 0.12)
Exhaustion	0.41 (0.00 , 0.82)**	0.03 (-0.01 , 0.07)	0.06 (-0.02 , 0.14)

Exploratory post-hoc analyses of the relation between MRI features of SVD (that showed significant between group differences: total WMH volume and the concavity index and fractal dimension of confluent and periventricular WMH) and frailty components were performed by linear regression analyses corrected for age and gender. WMH volume was additionally corrected for ICV. Data are presented as Beta's with 95% confidence intervals. WMH volumes were natural log transformed before performing regression analyses. *p =0.003. ** p=0.048



Supplementary figure A: flowchart of the inclusion of participants

Part II

Delirium and Postoperative cognitive dysfunction

CHAPTER 4

MRI markers of neurodegenerative and neurovascular changes in relation to postoperative delirium and postoperative cognitive decline: a systematic review

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ABSTRACT

Postoperative delirium (POD) and postoperative cognitive decline (POCD) are common in elderly patients. The aim of the present review was to explore the association of neurodegenerative and neurovascular changes with the occurrence of POD and POCD. Fifteen MRI studies were identified by combining multiple search terms for POD, POCD and brain imaging. These studies described a total of 1422 patients and were all observational in design. Neurodegenerative changes (global and regional brain volumes) did not show a consistent association with the occurrence of POD (four studies) or POCD (two studies). In contrast, neurovascular changes (white matter hyperintensities and cerebral infarcts) were more consistently associated with the occurrence of POD (seven studies) and POCD (five studies). In conclusion, neurovascular changes appear to be consistently associated with the occurrence of POD and POCD, and may identify patients at increased risk of these conditions. However, larger prospective studies are needed to study the consistency of these findings and to unravel the underlying pathophysiological mechanisms.

INTRODUCTION

Postoperative delirium (POD) and postoperative cognitive decline (POCD) are common in elderly patients. Postoperative delirium (POD) is a neuropsychiatric disorder characterized by an acute disturbance in attention and cognition that has an incidence of 15-53% in the first days after surgery [1, 2]. Risk factors include increased age, dementia, and coexisting medical conditions [2]. Furthermore, the occurrence of POD during the hospital stay is associated with an increased risk of POCD [3,4].

POCD is generally regarded as postoperative decline in memory and executive functioning that can last for weeks to months after surgery and might even persist for years [5]. To date, there is no exact operational definition of POCD, despite a consensus statement on the assessment of POCD after cardiac surgery [6]. This leads to a variable reported incidence of POCD of 20-50% in the first postoperative weeks. Three to 6 months after surgery the prevalence of POCD is around 10% [3,5,7,8]. Risk factors for the occurrence of POCD are increased age, increased duration of surgery and anesthesia, postoperative complications, a low level of education, a history of depression, or cerebrovascular disease [7–9].

Both POD and POCD have considerable impact on the health care system, as they can lead to prolonged hospital admission, a reduced quality of life and increased dependency [4,10]. To apply preventive measures and better balance the risks and benefits of surgery, we should be able to more accurately identify preoperative patients at increased risk of POD or POCD. However, evidence is lacking to accurately predict these conditions preoperatively.

In population-based studies of patients with (mild) cognitive impairment, structural brain imaging has shown the potential to detect subgroups of patients at risk for increased cognitive decline [11]. Structural brain imaging markers that are widely used to assess neurodegenerative changes are global and regional brain tissue volumes, while markers to estimate neurovascular changes are white matter hyperintensities (WMH), and cortical and lacunar infarcts [12–14]. As neurodegenerative and neurovascular changes may be related to increased vulnerability of patients for future cognitive decline, we reviewed studies that tested the hypothesis if these markers may identify patients at increased risk of POD and POCD.

The aim of this review was to explore the association of neurodegenerative and neurovascular changes, on imaging, with the occurrence of POD and POCD.

METHODS

Study selection

We searched for studies published up to January 2017 that assessed the association of structural neurodegenerative and neurovascular imaging markers (CT or MRI) with POD or POCD. Because there is no universally accepted definition of POCD, we combined search terms for postoperative cognitive dysfunction and cognitive decline. The performed PubMed and Embase search can be found in Appendix 1. All titles and abstracts obtained by the search were screened. Studies in animals, children, neurosurgery patients, ex vivo studies, case studies with less than 10 participants, studies with POCD measurements within one week after surgery and studies with a definition of delirium before publication of the diagnostic and statistical manual of mental disorders, 3rd edition (DSM III) criteria [15] were excluded. The references of all remaining studies were also screened and additional relevant studies were included. The resulting studies were fully read by two independent raters (IK and JB) to evaluate inclusion in the present review. All disagreements were assessed in a consensus meeting with a third rater (AS).

Quality assessment

The assessment of study quality was based on a method that was developed for observational studies on delirium [16]. We have adapted these criteria for use in studies on POD and POCD (see Table 1). All included studies in our review were assessed on these criteria by two independent raters (IK and JB), and disagreements in a consensus meeting with a third rater (AS).

RESULTS

Included studies

Fifteen studies were included in the present study (for details see Figure 1). Together these investigations described the results of 1422 patients. These studies described the association of preoperative (7 studies) and postoperative (2 studies) brain MRI markers with POD, and the association of preoperative (4 studies) and postoperative (2 studies) brain MRI markers with POCD. Appendix 2 includes background information on brain MRI methods and the neurodegenerative and neurovascular changes that were included in this review. Figure 2 shows some examples of these brain changes. No studies on brain CT markers were included, because all of these studies met the exclusion criteria. All included studies were observational in design. For the

assessment of study quality see Table 1 and 2. For an overview of the included studies see Table 3 for neurodegenerative changes and Table 4 for neurovascular changes.

Table 1: Quality criteria, adapted from Soiza et al.[16].

Criterion	Description
1	Main aim of the study is to identify neuroimaging features of POD or POCD.
2	Prospective study design.
3	Sampling bias minimized; at least one third of potential volunteers recruited.
4	POD diagnosed by valid criteria or POCD diagnosed by a cognitive test battery.
5	For case-control studies: non-POD/non-POCD subjects with similar characteristics than the patients. For cohort studies: appropriate information on subject characteristics, including possible confounders.
6	Use of validated methods of scan assessment.
7	Adequate quality control of scan results (e.g. use of two independent raters, reporting of interrater variability or quantitative assessment of scans).
8	Blinding of scan rater (i.e. no volunteer information available to the rater or quantitative assessment of scans).
9	Scan report detail. Quantitative assessment or the presence of at least two of the following in a qualitative assessment: cerebral atrophy, WMH or pathological abnormalities.
10	Use of appropriate statistical methods to compare patients with POD/POCD to subjects without POD/POCD.
11	Inclusion of an appropriate power calculation.

Criterion 1 was rated as 0 if studies were nested in a larger study. Criterion 5 was rated as 0 if POD and non-POD or POCD and non-POCD characteristics were not described separately. Criterion 7 was rated as 1 if one of the brain markers for POD or POCD met with this criterion.

MRI markers of neurodegenerative changes in relation to POD and POCD

Preoperative MRI markers of neurodegenerative changes in relation to POD

Three studies examined the association of preoperative global brain volume and the occurrence of POD (see Table 3) [17–19]. Root et al. and Cavallari et al. did not find an association between preoperative global brain volumes and the occurrence of POD. Shioiri et al. found a smaller preoperative cortical brain volume in patients that developed POD compared to non-delirious patients. Cavallari et al. (hippocampal volume) and Shiori et al. (frontal, temporal, parietal, occipital, limbic, sub-lobar area, cerebellar and brainstem volume [20]) also examined the association of regional brain

volume and POD [17,19]. Cavallari et al. did not find an association between preoperative hippocampal volume and the occurrence of POD [17]. Shioiri et al. found an association between a smaller preoperative cortical brain volume in the temporal and limbic brain regions and the occurrence of POD.

Table 2: Assessment of study quality

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Brown et al., 2015	0	1	0	1	1	1	1	1	1	1	1	10
Cavallari et al., 2015	0	1	0	1	1	1	1	1	1	1	1	9
Cavallari et al., 2016	0	1	0	1	1	1	1	0	0	1	0	6
Hatano et al., 2013	1	0	1	1	1	1	1	1	0	1	0	8
Ito et al., 2012	0	1	0	0	0	0	1	1	0	0	0	3
Maekawa et al., 2008	0	1	1	1	0	0	0	1	1	0	0	5
Maekawa et al., 2014	1	1	1	1	1	1	1	1	1	1	0	10
Nanba et al., 2012	1	1	1	1	1	1	1	1	1	1	0	10
Omiya et al., 2015	1	1	1	1	1	1	0	1	1	1	1	10
Otomo et al., 2013	1	1	1	1	1	1	1	1	1	1	1	11
Patel et al., 2015	0	1	0	1	1	0	0	1	1	1	0	5
Price et al., 2014	1	1	0	1	0	1	1	1	1	1	1	10
Root et al., 2013	1	0	0	1	1	1	1	1	1	1	0	8
Shioiri et al., 2015	1	1	0	1	1	1	1	1	0	1	0	8
Shiori et al., 2010	1	1	0	1	1	1	1	1	0	1	0	8

All included studies in our review were assessed on eleven quality criteria (see Table 1).

Preoperative MRI markers of neurodegenerative changes in relation to POCD

There are no studies on the association between preoperative global, subcortical or cortical brain volume and the occurrence of POCD. However, two studies examined the association between regional brain volumes and the occurrence of POCD. The studies of Price et al. and of Maekawa et al. examined the association between preoperative regional brain volumes and the occurrence of POCD (see Table 2 and 3). In the study of Price et al. no associations were found between preoperative hippocampal and entorhinal cortex volumes and POCD. Maekawa et al. found a relation between a smaller cortical volume of the medial temporal lobe and POCD.

Postoperative MRI markers of neurodegenerative changes in relation to POD and POCD

Only one study investigated the association between postoperative global brain volume and POD (see Table 2 and 3) [21]. They showed that a larger ventricular size was associated with the occurrence of POD. No other studies were found that examined the association between postoperative global, subcortical, cortical or regional brain volumes and POD or POCD.

Overview of evidence for MRI markers of neurodegenerative changes in relation to POD and POCD

Of the four studies that were performed on the association of preoperative global, cortical and subcortical brain volume and the occurrence of POD, two were prospective studies (N=146 and N=84) with a high-quality study design that included preoperative imaging, performed quantitative analysis of MRI scans and excluded demented patients (see Table 3) [17,19]. However, these two studies found contradicting results. The two other studies that also examined the association of preoperative global, cortical and subcortical brain volume and the occurrence of POD had less included patients, a lower study quality and also showed contradicting results [18,21]. One of these studies was probably underpowered as it included only a small number of non-small cell lung cancer patients (N=23) [18]. The other of these studies (N=79) performed only postoperative imaging and only performed qualitative MRI analyses instead of quantitative analyses [21].

Both studies that examined the association of regional brain volumes and the occurrence of POCD had a relatively low number of included patients (N=31 and N=28) and were possibly underpowered [22,23]. These studies showed some leads on certain specific brain regions in the medial temporal lobe that are potential markers, but there is only limited evidence regarding these associations.

In summary, MRI markers of neurodegenerative changes (global and regional brain volumes) are not consistently associated with the occurrence of POD or POCD.

Table 3: Neurodegenerative changes and POD/POCD

Author, Year	Study design	Number of participants	Age in years	Female sex	Type of surgery	Delirium assessment tool or cognitive evaluation	Outcome (time of assessment)	Preoperative cognitive status	MRI sequence	MRI markers	MRI analysis	Conclusion	Comments
Brown et al., 2015	P	79	70 ± 8	22 (27%)	Cardiac surgery	Validated chart review	POD (during hospital stay)	Analysis adjusted for preoperative cognitive status	T1, FLAIR, DWI (2-23 days postoperative)	Ventricular size, cortical sulcal width	Qualitative (0-9 scale)	Postoperative increased ventricular size was associated with POD	Nested study in a larger prospective RCT
Cavallari et al. 2015	P	146	76 ± 4	87 (60%)	Elective non-cardiac surgery	CAM and chart review	POD (daily during hospital stay)	Patients with dementia or low cognitive performance were excluded	FLAIR, T1 (preoperative)	Gray, white, CSF and hippocampal volume	Quantitative (FreeSurfer)	Global brain volume and hippocampal volume were not associated with POD	Part of the SAGES study
Root et al. 2013	R	23, 24 non-delirious	73 (54–86)	26 (55%)	Lung surgery	Chart review	POD (within 4 days after surgery)	Patients with dementia or evidence of cognitive decline in chart were excluded	T1, FLAIR (preoperative)	Gray matter, white matter and CSF volumevolume	Quantitative (SPM8)	Global brain volume was not associated with POD	Scanning protocol was different for delirious and non-delirious patients
Shioiri et al 2015	P	84	64 (27-84)	32(38%)	Cardiac surgery	Psychiatrist (DSM-IV)	POD (daily during hospital stay)	No patients with dementia (MMSE <24) were included	T1, T2 (preoperative)	Gray and white matter volume	Quantitative (SPM8, VBM8)	Lower global and regional brain volume were associated with POD	

Table 3: Continued

Author, Year	Study design	Number of participants	Age in years	Female sex	Type of surgery	Delirium assessment tool or cognitive evaluation	Outcome (time of assessment)	Preoperative cognitive status	MRI sequence	MRI markers	MRI analysis	Conclusion	Comments
Maekawa et al. 2014	P	28	73 ± 8	9 (32%)	Cardiac surgery	Cognitive tests of several domains	POCD (2 weeks after surgery)	Patients with dementia (MMSE <24) were excluded	3D T1, T2, FLAIR, 3D TOF (preoperative)	Medial temporal lobe volume	Quantitative (SPM8, VBM)	Lower volume of the temporal lobe was associated with POCD	
Price et al. 2014	P	31 patients, 12 non-surgery controls	71 ± 7	19 (45%)	Knee arthroplasty surgery	Cognitive tests of several domains	POCD (3 weeks and 3 months after surgery)	Patients with preoperative dementia were excluded	3D T1, FLAIR (preoperative)	Hippocampal and entorhinal cortex volume	Semi-quantitative (manually delineated by experienced raters)	Hippocampal and entorhinal cortex volumes were not associated with POCD	

a Prospective (P) or retrospective (R)

b Age in years presented in mean± SD or mdn and range

CAM = Confusion Assessment Method; RCT = Randomized controlled trial; SAGES = Successful Ageing after Elective Surgery study

Table 4: Neurovascular changes and POD/POCD

Author, Year	Study design	Number of participants	Age	Female sex	Type of surgery	Delirium assessment tool or cognitive evaluation	Outcome (time of assessment)	Preoperative cognitive status	MRI sequence	MRI markers	MRI analysis	Conclusion	Comments
Brown et al., 2015	P	79	70 ± 8	22 (27%)	Cardiac surgery	Validated chart review	POD (unknown)	Analysis adjusted for preoperative cognitive status	T1, FLAIR, DWI (5-8 days after surgery)	WMH severity	Qualitative (severity scale 0-9)	WMH severity was not associated with POD	Nested study in a larger prospective RCT, duration of delirium assessment based on chart review is unclear
Cavallari et al. 2016	P	136	76 ± 4	80 (59%)	Elective non-cardiac surgery	CAM and chart review	POD (daily during hospital stay)	Patients with dementia or low cognitive performance were excluded	DTI (preoperative)	White matter integrity (fractional anisotropy and mean diffusivity)	Quantitative (Freesurfer, SPM8)	A lower fractional anisotropy of the cerebellum, hippocampus, thalamus and basal forebrain was associated with POD incidence and severity	Part of the SAGES study
Cavallari et al., 2014	P	146	76 ± 4	87 (60%)	Elective non-cardiac surgery	CAM and chart review	POD (daily during hospital stay)	Patients with dementia or low cognitive performance were excluded	FLAIR, T1 (preoperative)	WMH volume	Semi-quantitative (expectation maximization algorithm)	Global brain volume and hippocampal volume were not associated with POD	Part of the SAGES study

Table 4: Continued

Author, Year	Study design	Number of participants	Age	Female sex	Type of surgery	Delirium assessment tool or cognitive evaluation	Outcome (time of assessment)	Preoperative cognitive status	MRI sequence	MRI markers	MRI analysis	Conclusion	Comments
Hatano et al. 2013	R	130	67 ± 11	41 (32%)	Cardiac surgery	Chart review	POD (unknown)	No information provided	FLAIR (preoperative)	WMH severity	Qualitative (Fazekas score)	Severity of WMH is associated with POD	Duration of delirium assessment based on chart review is unclear
Ito et al. 2012	P	224 patients with infarcts, 225 patients without infarcts	70 (60-85)	141 (31%)	Cardiac surgery	Hasegawa dementia scale	POCD (unknown)	Patients with preoperative cognitive impairment were not included	T1, T2 (preoperative)	Cerebral infarcts	Qualitative rating on T1 and T2	POCD was more common in the patient group with silent cerebral brain infarcts	Time of POCD measurement is unclear
Maekawa 2008	P	247	70 ± 9	91 (58%)	Cardiac surgery	Cognitive tests of several domains	POCD (one week after surgery)	Patients with preoperative cognitive impairment (HDS < 24) were not excluded	DWI (preoperative)	Acute cerebral infarcts	Qualitative rating	There was no association between preoperative infarcts on DWI and POCD at one week after surgery	
Maekawa et al. 2014	P	28	73 ± 8	9 (32%)	Cardiac surgery	Delirium rating scale and DSM-IV, cognitive tests of several domains	POD (daily assessment until day 7) and POCD (2 weeks after surgery)	Patients with dementia (MMSE <24) were excluded	T1, T2, FLAIR (preoperative)	WMH severity, cerebral infarcts	Qualitative (Fazekas score)	WMH severity and presence of infarcts were associated with POCD	

Table 4: Continued

Author, Year	Study design	Number of participants	Age	Female sex	Type of surgery	Delirium assessment tool or cognitive evaluation	Outcome (time of assessment)	Preoperative cognitive status	MRI sequence	MRI markers	MRI analysis	Conclusion	Comments
Nanba et al., 2012	P	70	68 ± 8	7 (10%)	Carotid endarterectomy	Cognitive tests of several domains	POCD (one month after surgery)	No information provided	DTI (preoperative and one month oostoperative)	White matter integrity (fractional anisotropy)	Quantitative (SPM5)	Fractional anisotropy values were associated with POCD	
Omiya et al., 2015	P	98	69 ± 7	Not reported	Cardiac surgery	Delirium assessments	POD (6-24h after surgery)	No information provided	T2, FLAIR, T2*, DWI (two weeks postoperative)	New cerebral infarcts, WMH severity	Qualitative (Fazekas scale)	New cerebral infarcts and deep WMH were associated with POD	
Otomo et al. 2013	P	153	72 ± 7	44 (29%)	Cardiac surgery	Delirium rating scale, DSM-IV	POD (daily assessment until day 7)	Patients with preoperative cognitive impairment (HDS < 24) were not excluded	FLAIR, T2 (preoperative)	Cerebral infarcts	Qualitative rating	Pre-existing multiple cerebral infarcts were associated with POD	
Patel et al., 2015	P	77	63 ± 10	5 (6%)	Cardiac surgery	Cognitive tests of several domains	POCD (6-8 weeks after surgery)	No information provided	FLAIR, DWI (pre- and 6-8 weeks postoperative)	Number and volume of new cerebral infarcts	Semi-quantitative contouring	New cerebral infarcts were not associated with POCD	
Price et al. 2014	P	31 patients with surgery, 12 without surgery	71 ± 7	19 (45%)	Knee arthroplasty surgery	Cognitive tests of several domains	POCD (three weeks and three months after surgery)	Patients with preoperative dementia were excluded	T1, FLAIR (preoperative)	Combined WMH and lacunar infarct volumes	Quantitative (semi-automatic volume measurement)	Combined WMH and lacunar volumes were associated with POCD	

Table 4: Continued

Author, Year	Study design	Number of participants	Age	Female sex	Type of surgery	Delirium assessment tool or cognitive evaluation	Outcome (time of assessment)	Preoperative cognitive status	MRI sequence	MRI markers	MRI analysis	Conclusion	Comments
Root et al. 2013	R	23 delirious, 24 non-delirious patients	73 (54–86)	26 (55%)	Lung surgery	Chart review	POD (within 4 days after surgery)	Patients with dementia or evidence of cognitive decline in chart were excluded	T1, FLAIR (preoperative)	WMH volume	Semi-quantitative (MRIcron)	WMH volume was associated with POD	Scanning protocol was different for patients and controls
Shiori et al. 2010	P	116	64 (27-84)	38 (33%)	Cardiac surgery	Psychiatrist (DSM-IV)	POD (daily assessment until discharge)	No patients with dementia (MMSE <24) were included	DTI, T1, T2 (preoperative)	White matter integrity (fractional anisotropy)	Quantitative (SPM12)	Reduced fractional anisotropy in four regional areas was associated with POD	

[1] Prospective (P) or retrospective (R)

[2] Age in years presented in mean ± SD or median (range)

CAM = Confusion Assessment Method; RCT = Randomized controlled trial; SAGES = Successful Ageing after Elective Surgery study

MRI markers of neurovascular changes in relation to POD and POCD

Preoperative MRI markers of neurovascular changes in relation to POD

In three studies, the association between preoperative WMH and the occurrence of POD was investigated [17,18,24], see Table 4 for details. Two studies reported an association between WMH and the occurrence of POD [18,24]. In contrast to these findings, the largest prospective study by Cavallari et al. did not find an association between preoperative WMH volume and the occurrence of POD [17].

In two studies, the association of preoperative old cortical brain infarcts and the occurrence of POD was assessed [22,25]. In both studies the presence of cortical brain infarcts was rated qualitatively (no infarcts, a single infarct, multiple infarcts in one location or multiple infarcts in several locations). It was reported that the presence of preoperative cortical brain infarcts was associated with the occurrence of POD [22,25].

Two prospective studies were performed that examined the association between preoperative structural white matter integrity and the occurrence of POD (see Table 4) [26,27]. Shioiri et al. found an association between preoperative reduced fractional anisotropy values in the left frontal lobe and left thalamus and occurrence of POD. Cavallari et al. described an association between reduced fractional anisotropy values of different brain regions (cerebellum, hippocampus, basal forebrain and part of the thalamus) and occurrence of POD.

Preoperative MRI markers of neurovascular changes in relation to POCD

Two studies examined the association between preoperative WMH and the occurrence of POCD (see Table 4) [22,23]. Maekawa et al. showed that the severity of WMH was associated with the occurrence of POCD. Price et al. reported that the combined WMH and lacunar infarct volume was associated with decline of executive functions three weeks postoperatively, and showed a trend three months postoperatively.

Ito et al. examined the association between preoperative old cortical brain infarcts and the occurrence of POCD [28]. They grouped their participants not on POCD status, but on infarct status (silent brain infarcts, symptomatic brain infarcts or no brain infarcts). In the group with silent brain infarcts, POCD was more common than in the group without brain infarcts. Maekawa et al. performed preoperative diffusion-weighted imaging (DWI) and examined whether acute infarcts were associated

with the occurrence of POCD [29] (Table 2 and 4). They found no association between preoperative acute brain infarcts and POCD.

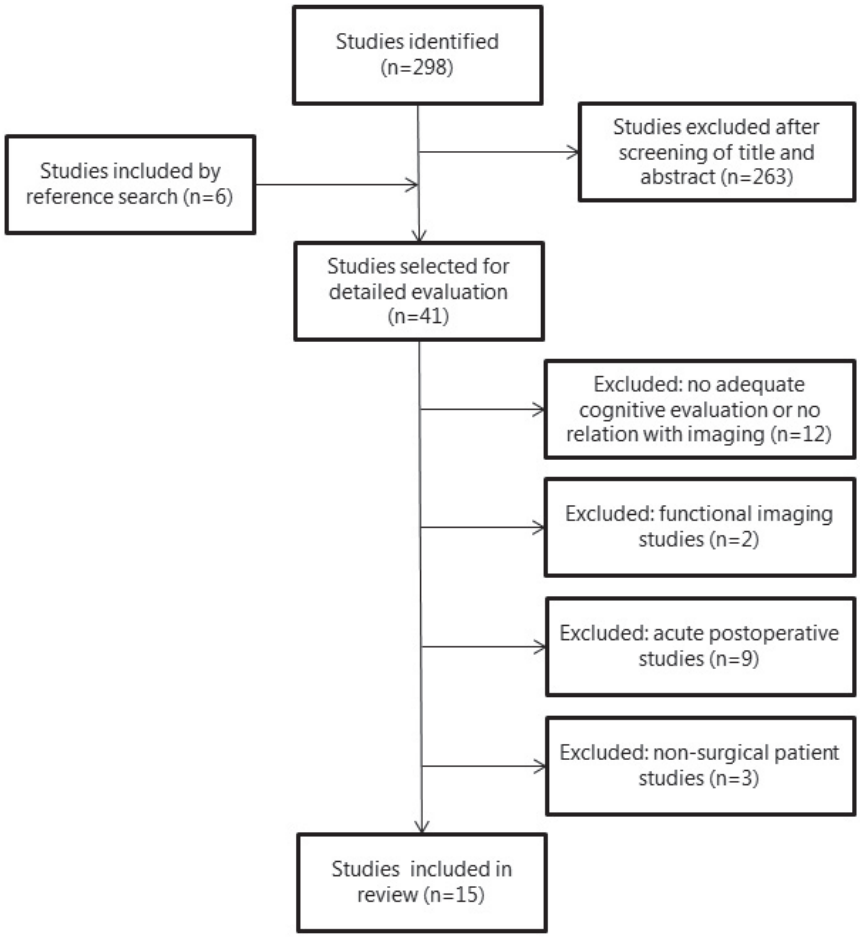

Figure 1: Flow-diagram showing the search and assessment of studies included in this review.

Postoperative MRI markers of neurovascular changes in relation to POD

One study examined the relation between postoperative WMH and POD (See Table 4) [21]. Two studies examined the relation between acute postoperative cerebral infarcts and POD [21,30]. Omiya et al. described that acute postoperative infarcts >2mm were associated with POD[30]. Brown et al., however, found no association between acute postoperative cerebral infarcts and POD [21].

Postoperative MRI markers of neurovascular changes in relation to POCD

Multiple studies have examined the association between acute postoperative cerebral infarcts and POCD. Patel et al. have recently published an extensive review regarding this subject in patients after cardiac surgery [31]. Therefore, we will not include a detailed description of all these individual studies in our review. In the review of Patel et al., most studies showed no association between acute postoperative cerebral infarcts and POCD [31]. Additionally, another more recent study by Patel et al. was performed on the relation between new WMH and acute cerebral infarcts on postoperative MRI scans (compared to preoperative MRI scans) and the occurrence of POCD [32] (see Table 4). No association was found between the presence, size and number of new WMH or acute infarcts and the occurrence of POCD. A prospective study performed by Nanba et al. examined the relation between white matter integrity and the occurrence of POCD [33]. Patients that developed POCD had reduced postoperative fractional anisotropy values at the side of the carotid artery surgery.

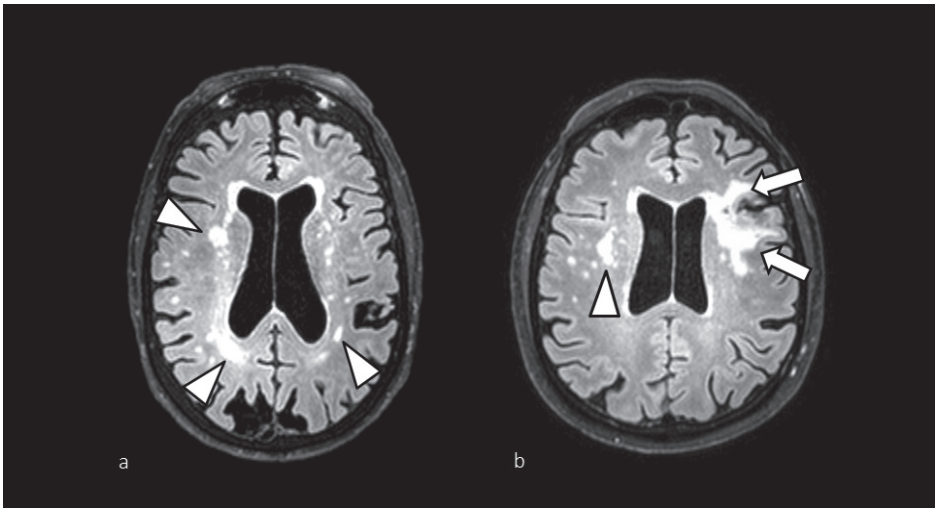

Figure 2: Two example figures of neurovascular brain changes. An example patient (a) of larger (arrowheads) and smaller white matter hyperintensities on a T2 weighted axial Fluid Attenuated Inversion Recovery (FLAIR) image. Some atrophy is also present with brain sulci clearly visible and central atrophy with ventricle enlargement. Another example patient (b) with a combination of white matter matter hyperintensities (arrowhead) and a larger cortical-subcortical infarct (arrows) on a T2 weighted FLAIR image.

Overview of evidence for MRI markers of neurovascular changes in relation to POD and POCD

Six studies examined the association between WMH and POD and found some conflicting evidence [17,18,21,22,24,30]. The study with the largest number of included patients (N=146) that had a high quality prospective design and used quantitative MRI analyses, did not find an association between preoperative WMH and occurrence of POD (see Table 2 and 4) [17]. The other studies that examined the association between WMH and POD included less patients (N=23, N=28, N=79, N=98, N=130). Most of these studies had a good study design and performed qualitative MRI analyses instead of quantitative analyses (see Appendix B and Table 2). Therefore, most evidence was found for an association between WMH volume and occurrence of POD. Two studies were performed on preoperative old cerebral infarcts [22,25]. Both studies were of high quality, but one had a low number of included patients and both included few patients with cerebral infarcts (N= 28 and N=153) (see Table 2). Moreover, the nature of these infarcts (e.g. cortical, subcortical or lacunar) was not specified (see Appendix B). Both studies found an association between cerebral infarcts and occurrence of POD [22,25]. Two prospective studies (N=116 and N=136) were performed that examined the association between markers of white matter integrity and POD [26,27]. Both studies were of high quality, excluded patients with dementia and found an association between markers of white matter integrity and POD.

Two studies consisting of only few patients (N=28, N=31) examined the association between preoperative WMH and POCD [22,23]. In one of these studies, the follow-up period to diagnose POCD was relatively short [22], which might have led to an underestimation of POCD incidence. Both studies found an association between preoperative WMH and occurrence of POCD. Only one study with a relatively low quality design examined the association between cerebral infarcts and POCD (see Table 2) [28]. In this study an association was found between cerebral infarcts and occurrence of POCD. Only one study was performed that examined the association between markers of white matter integrity and POCD[33]. This prospective study (N=70) had a relatively low quality mostly due to study design and patient selection (only patients that underwent carotid endarterectomy). This study showed an association between markers of white matter integrity and occurrence of POCD. In summary, most studies on neurovascular changes found an association with POD or POCD.

DISCUSSION

Neurovascular changes (WMH and cerebral infarcts) are most consistently associated with the occurrence of POD and POCD [18,21–30,33]. Neurodegenerative changes (global and regional brain volumes) are not consistently associated with the occurrence of POD or POCD [17–19,21–23].

MRI markers of neurovascular changes in relation to POD and POCD

The finding that MRI markers of neurovascular changes are most consistently related to the occurrence of POD and POCD is in agreement with population-based studies that showed an association between MRI markers of neurovascular changes and cognitive impairment [11,34]. The imaging signs of neurovascular disease detected by structural MRI sequences might represent the tip of the iceberg of a larger burden of brain tissue changes related to neurovascular disease. We hypothesize that patients with a larger burden of brain tissue lesions (infarcts, WMH) are more vulnerable to hemodynamic changes during the operative period. Alternatively, in these patients there may be a progression of brain tissue lesions, with for instance new infarcts, during the postoperative period. In the direct postoperative period new acute ischemic lesions on diffusion weighted imaging may also be related to POCD and POD [31,35]. From recent studies it is known that cognitive reserve (including education) may be an additional factor in the relation between brain tissue lesions and (postoperative) cognitive changes [36]. Still, the associations of preoperative neurovascular changes and both POD and POCD should be further investigated in larger studies, by assessing promising neurovascular markers, such as WMH burden and presence of cerebral infarcts, taking into account cerebral hemodynamics, new ischemic lesions and cognitive reserve.

MRI markers of neurodegenerative changes in relation to POD and POCD

In most studies no association was found between neurodegenerative changes on MRI scans and POD and POCD. Although some smaller studies suggested a relationship, this could not be confirmed in larger studies such as the recent SAGES study on brain atrophy and POD. It should be noted that in this SAGES study no relation was found between WMH and POD either, and that white matter structure assessed on DTI might be related to occurrence of POD. Based on the current findings we conclude that if a relation between (regional) brain MRI volume and POD and POCD is present, this relation is possibly weak. In most studies on POD and POCD of

this review, demented patients were excluded (see Table 3 and 4). Demented patients are known to have an increased risk of POD and POCD, and vice versa [2]. Due to a lack of studies with preoperative imaging and long-term follow-up, it remains unclear whether patients suffering from POD and POCD are on a trajectory of cognitive decline and dementia.

Strengths and limitations

This is the first review to study the association of MRI markers of neurodegenerative and neurovascular changes of both POD and POCD. The review is strengthened by the systematic search for studies and the detailed quality assessments of all included studies. Therefore, our review provides a detailed overview of the current knowledge in this field.

A limitation of the included studies is the limited sample size of some of these studies. This resulted in only few cases of POD or POCD and therefore limited the power of these studies. Other limitations of the included studies in our review were the heterogeneous study designs and applied quantification techniques, which made it impossible to pool studies in a meta-analysis. Therefore, we chose to group the imaging findings according to groups of underlying pathophysiological mechanisms (neurodegenerative and neurovascular changes). Another limitation could be that the POD assessment varied from a daily assessment by trained research staff to a retrospective chart review. Especially diagnosis of POD by a retrospective chart review only might have led to an underestimation of POD in some studies. The heterogeneous definition and assessment of POCD made comparison of cognitive test results between studies difficult.

Future recommendations

From the results of our review it became clear that large prospective studies are needed to study the consistency of the reported associations between brain MRI markers and the occurrence of POD and POCD. To ensure comparability to existing literature, we would like to recommend future studies to perform preoperative MR imaging, daily delirium screening in the immediate postoperative period, and cognitive tests preoperatively, at three months and at one year follow-up. Furthermore, a matched control group should be included especially to control for learning effects of the cognitive tests.. We recommend to perform POCD assessment by previously published recommendations [37]. Furthermore, we would like to recommend the use

of 3D T1-weighted and 3D FLAIR MRI sequences to assess brain structural changes, combined with more advanced MRI brain imaging to also assess more advanced aspects of brain structure, such as DTI. This review has shown that neurovascular brain changes show the most consistent association with POD and POCD. The presence of lacunar and cortical infarcts was related to the occurrence of POD and POCD in all studies that assessed this marker. WMH volume shows potential as a marker for both POD and POCD. In a few studies with limited participants, white matter integrity also shows potential as a marker for POD and POCD. We would like to recommend future studies to perform quantitative analysis of WMH volume and a qualitative assessment of cerebral infarcts. Functional and hemodynamic MRI markers of the brain vasculature, which were beyond the scope of our review, may also be promising markers to assess in the context of POD and POCD [38,39]. These markers include measurements of brain perfusion with arterial spin labeling MRI sequences, measurement of flow in the larger brain feeding arteries, functional resting-state MRI connectivity markers, functional MRI studies and blood-oxygen-level dependent (BOLD) MRI measures combined with a vascular stimulus such as carbon dioxide to measure the cerebrovascular reserve of the brain vasculature [40,41].

To date, there is insufficient evidence for implementation of these results in clinical practice. Future clinical studies on risk scores need to be performed to be able to assess the added clinical value. In the future, a preoperative assessment could be used to predicts a patient's risk for the development of POD or POCD. This assessment could assist in the decision to operate a patient at high risk of POD or POCD or could influence postoperative management and monitoring. Due to cost restraints, preoperative MRI scans could potentially be reserved only for patients at high risk of POD or POCD following a clinical assessment.

Conclusions

Neurovascular changes appear to be consistently associated with the occurrence of POD and POCD. In the future, these changes may even help to identify patients at increased risk of POD and POCD. Larger prospective studies are needed to study this in more detail and to unravel the underlying pathophysiological mechanisms.

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SUPPLEMENTARY MATERIAL

Appendix A: Search

Pubmed:

((“postoperative period”[MeSH Terms] OR (“postoperative”[All Fields] AND “period”[All Fields]) OR “postoperative period”[All Fields] OR “postoperative”[All Fields]) AND (“delirium”[MeSH Terms] OR “delirium”[All Fields])) OR ((“postoperative period”[MeSH Terms] OR (“postoperative”[All Fields] AND “period”[All Fields]) OR “postoperative period”[All Fields] OR “postoperative”[All Fields]) AND “cognitive”[All Fields]) AND (decline[All Fields] OR impairment[All Fields] OR “dysfunction”[All Fields]) AND ((“tomography, x-ray computed”[MeSH Terms] OR (“tomography”[All Fields] AND “x-ray”[All Fields] AND “computed”[All Fields]) OR “x-ray computed tomography”[All Fields] OR (“computed”[All Fields] AND “tomography”[All Fields]) OR “computed tomography”[All Fields]) OR (“magnetic resonance imaging”[MeSH Terms] OR (“magnetic”[All Fields] AND “resonance”[All Fields] AND “imaging”[All Fields]) OR “magnetic resonance imaging”[All Fields] OR “mri”[All Fields]))

Embase:

postoperative AND period AND (‘delirium’/exp OR delirium) OR ‘postoperative cognitive dysfunction’/exp OR ‘postoperative cognitive dysfunction’ OR ‘postoperative cognitive decline’/exp OR ‘postoperative cognitive decline’ AND (‘imaging’/exp OR imaging OR (magnetic AND (‘resonance’/exp OR resonance) AND (‘imaging’/exp OR imaging)) OR (computed AND (‘tomography’/exp OR tomography))) AND (‘mri’/exp OR mri)

Appendix B: Brain MRI methods and markers

Neurodegenerative markers

The most important MRI methods (i.e., MRI sequences) for structural MRI are the 3D T1-weighted (volumetric) MRI and T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI sequences (either 2D or 3D). The 3D T1-weighted MRI provides excellent contrast between brain tissue and cerebrospinal fluid (CSF) and between gray and white matter. With 3D T1-weighted MRI, gray matter is hypointense (dark) compared to white matter and cerebrospinal fluid is hypointense relative to both white and gray matter. MRI scans can be used by automated brain segmentation methods to segment different brain volumes [42]. Brain segmentation methods can determine the total intracranial volume, which is often used as a reference. Therefore, it is important that the 3D T1-weighted MRI sequence has a good contrast between the inner surface of the skull (tabula interna) and the intracranial compartments. Quantification of brain volumes is further enhanced when an MRI scan is acquired with thin slices that are contiguous. 3D methods are most optimal, as a complete volume is acquired. In most studies the 3D T1-weighted MRI sequence is used with automated segmentation methods to determine brain tissue volumes, but it can also be used in combination with other sequences. Typically, all brain volumes (total brain volume, white matter volume, gray matter volume) are normalized by the total intracranial volume to make the brain volume measurements independent of head size. Total brain volume is a widely studied MRI marker for neurodegenerative diseases such as Alzheimer's Disease [43]. In these diseases, the breakdown of neurons causes brain volume loss, which can be quantified on structural MRI. Brain volume could therefore be associated with an increased risk of POD or POCD. Regional brain volume loss of the medial temporal lobe, especially of the hippocampus and the entorhinal cortex, has previously been identified as a regional structural brain MRI marker for Alzheimer's disease and is associated with mild cognitive impairment [44]. These regional brain MRI markers might therefore also be associated with an increased risk of POD or POCD.

Neurovascular markers

White matter hyperintensities (WMH) are common findings on brain MRI scans in the elderly [45] and also occur in otherwise healthy individuals. WMH and lacunes of presumed vascular origin are regarded as brain MRI markers of small vessel disease [34,45]. These markers are related to cognitive decline in patients with mild cognitive impairment [46]. Cerebral cortical infarcts are also associated with cognitive deficits [47]. The presence of one or a combination of these brain MRI markers could therefore increase the vulnerability for POD or POCD. The T2-weighted FLAIR MRI sequence provides excellent delineation of cerebral cortical infarcts, WMH and lacunes. With the T2-weighted FLAIR sequence, the CSF is nulled (hypointense) and infarcts and WMH are typically hyperintense compared to other brain tissue. When quantitative assessment of these brain abnormalities is of interest, 3D (volumetric) T2-weighted FLAIR sequences have advantages over 2D MRI sequences. Other structural MRI sequences that are often acquired are classic T2-weighted sequences without CSF suppression (as present in T2-weighted FLAIR sequences). T2*-weighted or susceptibility-weighted imaging (SWI) MRI sequences are sensitive to the detection of cerebral hemorrhage and microbleeds. Diffusion-weighted imaging (DWI) can show (acute) cerebral infarcts and diffusion tensor imaging (DTI) can be used as a method to quantify white matter integrity. In the current review we will focus on T1-weighted, T2-weighted FLAIR, DWI and DTI sequences, because these are the most performed structural MRI sequences.

CHAPTER 5

Preoperative brain MRI features of postoperative delirium

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ABSTRACT

The pathophysiology of postoperative delirium remains largely unknown. To increase the understanding of the neural substrate of postoperative delirium, we studied the association between preoperative brain MRI features and the occurrence of postoperative delirium after major elective surgery in a group of 413 non-demented older patients (Mean ±SD: 72 ± 5 years) from a large prospective observational two center study. We measured preoperative brain volumes (total brain, gray matter, white matter), white matter hyperintensity volume and shape, brain infarcts and cerebral perfusion, and used logistic regression analysis to adjust for age, sex, intracranial volume, study center and type of surgery. Postoperative delirium was present in a total of 70 patients (17%). Preoperative cortical brain infarcts increased the risk of postoperative delirium, although this did not reach statistical significance (OR (95%CI): 1.633 (0.838 – 3.183). Further, we found a trend for an association of a more complex shape of white matter hyperintensities with postoperative delirium (OR (95%CI): 0.976 (0.950 – 1.002)). Preoperative brain volumes, white matter hyperintensity volume, and cerebral perfusion were not associated with postoperative delirium. In conclusion, our study suggests that patients with preoperative cortical brain infarcts and those with a more complex white matter hyperintensity shape may be at risk for developing delirium after major surgery.

INTRODUCTION

Postoperative delirium is characterized by an acute change in attention and awareness after surgery[1]. Postoperative delirium is common in older patients with an incidence of 10-15% following major surgery, and associated with longer hospital stay, increased medical costs and impaired cognitive outcome[2,3]. Known predisposing risk factors for postoperative delirium include preoperative cognitive deficits, functional impairment, older age and a history of delirium[2]. Precipitating factors for occurrence of a postoperative delirium include major cardiovascular or orthopedic surgery, and complications of surgery. An increased understanding of the underlying pathophysiology could help further improve the development of prevention and targeted therapy strategies. Furthermore, it could result in improved identification of patients who are at risk for developing postoperative delirium. However, the underlying pathophysiology of delirium remains largely unknown.

To increase the understanding of the neural substrate of postoperative delirium, recent studies have focused on neuroimaging methods using brain magnetic resonance imaging (MRI)[4–14]. Previous studies that assessed MRI markers of the brain showed that possible predisposing markers of postoperative delirium could be a decreased global or regional brain volume[12–14], an increased WMH volume[4,11,15] and multiple brain infarcts[8]. However, there is also conflicting evidence showing no relation with brain volumes[6,15], and no association with WMH volumes or hemodynamics[5,6,12]. An important point to consider is that apart from the SAGES study[16], most of these previous studies were underpowered and/or lacked preoperative brain imaging. Moreover, these studies differed in clinical settings, characteristics of study participants and quality of study design[17]. No previous studies have distinguished between lacunar and cortical brain infarcts (i.e. distinguished infarcts due to cerebral small vessel disease or large vessel disease)[18], or assessed infarct volume as a measure for total infarct burden, or considered new advanced brain MRI features of cerebral small vessel disease like WMH shape. Therefore, a large study that assesses multiple preoperative brain MRI features derived from advanced preoperative MRI methods is needed.

The aim of the present study was to assess whether preoperative brain MRI features are associated with postoperative delirium in a large group of non-demented older patients undergoing major elective surgery. These brain MRI features include

both commonly used and novel MRI brain features assessed with state-of-the art techniques, including global brain volumes, WMH volume, WMH shape features, cerebral hemodynamics and cortical and lacunar infarcts.

METHODS

Study design and participants

The Biomarkers for Postoperative Cognitive Decline (BioCog) study is a large observational multicenter study at Charité Universitätsmedizin (Berlin, Germany) and the University Medical Center Utrecht (Utrecht, The Netherlands) that aims at finding biomarkers for postoperative delirium and postoperative cognitive dysfunction[19]. The study has been reviewed and approved by medical ethics committees of both participating centers under ethical approval number EA2/092/14 (Berlin) and 14-469 (Utrecht). All study participants signed informed consent and were (1) ≥ 65 years of age, (2) non-demented (mini-mental state exam (MMSE) score of ≥ 24), (3) were able to undergo a brain MRI scan and cognitive tests, (4) were scheduled for major elective surgery of at least 60 minutes.

Procedure

Patients who were scheduled for major elective surgery were invited to the hospital for a preoperative visit for a brain MRI scan, questionnaires and cognitive tests. Questionnaires were administered by trained researchers and included the MMSE, frailty questions and questions on medical history and vascular risk factors. The preoperative ASA score was scored by anesthesiologists (in training).

Delirium assessment

Postoperative delirium was defined according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria[1]. Delirium assessment was performed by trained researchers who filled in the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[20] and nursing Delirium Screening Scale (Nu-DESC)[21] twice daily (morning and afternoon) for seven days following surgery, or if discharge was before day seven, until discharge. An additional chart review was performed by trained researchers[22]. Patients were considered delirious in case of ≥ 2 cumulative points on the Nu-DESC and/or a positive CAM-ICU score and/or patient chart review that showed descriptions of delirium (e.g., confused, agitated, drowsy, disorientated, delirious, receiving antipsychotic therapy).

Patients who had one or more delirious episodes in the seven days following surgery were categorized as postoperative delirium, whereas patients who had no delirious episodes were categorized as no delirium.

Brain MRI scans

Participants were scanned on a 3T Magnetom TrioTim (Siemens Healthcare, Erlangen, Germany) MRI scanner (Berlin) or a 3T Achieva (Philips Healthcare, Best, The Netherlands) (Utrecht). The MRI scanning protocol was standardized and consisted of a 3-dimensional (3D) T1-weighted sequence (voxel size 1.0 x 1.0 x 1.0 mm^3; Berlin: repetition time [TR]/echo time [TE] 2500/4.77 ms; Utrecht: TR/TE 7.9/4.5 ms) a fluid-attenuated inversion recovery (FLAIR) sequence (Berlin: TR/TE/inversion time 4800/388/1800 ms; voxel size 0.49 x 0.49 x 1.00 mm^3; Utrecht: TR/TE/inversion time 4800/125/1650 ms; voxel size 1.11 x 1.11 x 0.56 mm^3), a 2D EPI pseudo-continuous arterial spin labeling (pCASL) sequence (Berlin: voxel size 3.0 x 3.0 x 7.0 mm^3; TR/TE 6000/14 ms, label duration 1650 ms, post labeling delay 1525-2275 ms, no background suppression; Utrecht: voxel size 3.0 x 3.0 x 7.0 mm^3; TR/TE 3919/17 ms, label duration 1650 ms, post labeling delay 1525-2225 ms, with background suppression) and a diffusion-weighted image (Berlin: n.a.; Utrecht: (voxel size = 0.96 x 1.19 x 4.00 mm^3; TR/TE 3294/68 ms) for visual inspection only.

MRI processing steps and analysis

For analysis of brain volumes and WMH volumes, a method was used that is robust for scanner differences[23], that was previously used in a BioCog substudy [24]. First, 3D FLAIR images were rigid-body registered to 3D T1-weighted images using statistical parametric mapping software (SPM) version 12 (SPM12; Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/doc/) for Matlab (The MathWorks, Inc., Natick, Massachusetts, United States). WMH probability maps were calculated using an automated algorithm: the lesion prediction algorithm of the SPM12 lesion segmentation toolbox (LST, version 2.0.15, www.statistical-modeling.de/lst.html) for SPM12. The LST lesion filling method using the WMH probability maps was performed on the T1-weighted images. The filled T1-weighted images were segmented in gray matter, white matter and cerebrospinal fluid using the Computational Anatomy Toolbox 12 (CAT12), version r1155 [25], from which the tissue volumes were obtained. All segmented images were visually checked by a trained researcher (IK), supervised by a neuroradiologist (JB).

WMH shape features were determined by an in-house developed automated method[26]. This method has not been validated for between-scanner differences, and was therefore only performed on MRI FLAIR data from Utrecht. In short, the lateral ventricles were segmented and inflated. WMH within 10 mm from the lateral ventricles were considered periventricular, WMH over 10 mm from the ventricles as deep, and WMH that extended from periventricular to deep were considered confluent WMH. The WMH probability maps were thresholded at 10%, after which a convex hull was drawn around the volumes. Based on the convex hull, the convexity, solidity, concavity index, fractal dimension of periventricular/confluent WMH, and the fractal dimension and eccentricity of deep WMH were determined[26].

Cerebral perfusion was calculated using ExploreASL[27]. Intermediate ASL images were motion corrected and registered to the gray matter partial volume maps of the T1-weighted images. The CBF images were quantified with a single compartment model[28], after which the mean CBF of the total gray matter and of the deep white matter regions of interest (ROI) was obtained. Additionally, the spatial coefficient of variation (spatial CoV) of these images was calculated in the total gray matter, as a proxy for cerebrovascular health[29]. Quality assessment of the resulting CBF images was performed by a trained researcher (IK), supervised by an experienced ASL researcher (HM). Images were classified as 1) CBF contrast, 2) vascular contrast or 3) no contrast. Images of category 1 were included in both CBF and spatial CoV analyses, images of category 2 only in the spatial CoV analyses and images in category 3 were excluded from analysis. Presence and classification of brain infarcts was performed on the T1-weighted, FLAIR and DWI images by two experienced neuroradiologists (JB and TW) according to the international standards for reporting vascular changes on neuroimaging (STRIVE) criteria[18]. Manual segmentation of cortical infarcts >1.5 cm was performed by a trained researcher (IK) and supervised by a neuroradiologist (JB).

Statistical analysis

Demographics of delirious and non-delirious patients were compared between both groups by an independent samples T-test for continuous, normally distributed data, a Mann-Whitney U test for continuous skewed data, and a chi-square for comparison of categorical data. The association of MRI features with postoperative delirium was studied with logistic regression analyses with adjustment for age, sex, study center and type of surgery (i.e. cardiothoracic, gastro-intestinal/abdominal, orthopedic

or peripheral). Brain volumes, WMH volumes and cortical infarct volumes were additionally adjusted for intracranial volume.

RESULTS

Patients

In total, 7568 patients were invited, 1033 persons gave informed consent, of whom 100 participants dropped out. Data was collected from a total of 933 patients, of whom 495 participants received a preoperative brain MRI scan. Of these participants a total of 31 participants were excluded due to previous or scheduled neurosurgery (n=17), early quitting of the MRI scan due to claustrophobia (n=8), brain tumors or cysts (n=4) or old brain trauma (n=2). For the current study we further excluded participants who had minor surgery (n=51).

In total, 413 patients were analyzed in the current study. Of these patients, 17% (n=70) developed postoperative delirium during the first seven days after surgery. Patients who developed postoperative delirium were generally older, more often female, had a lower MMSE score and had a higher preoperative ASA score (table 1). For demographics per study center see supplementary table A. Demographics of the total study cohort (n=933) are shown in supplementary table B.

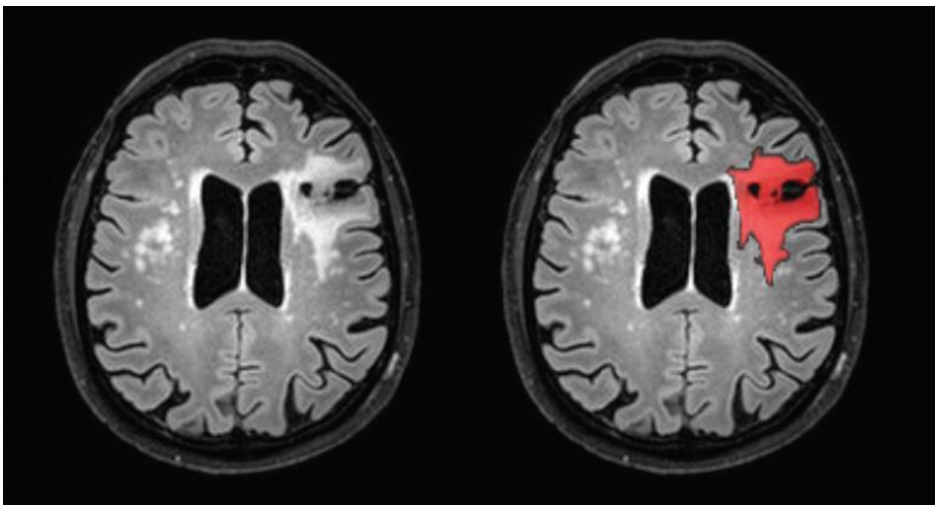

Figure 1: example of a FLAIR image with a manual segmentation of a large cortical brain infarct (left: original image; right: manual segmentation in red).

Table 1: Baseline demographics

	Total (n=413)	Delirium (n=70)	No delirium (n=343)	p-value
Age	72 ± 5	74 ± 4	72 ± 5	0.00
Sex (F, %)	159 (39%)	35 (50%)	124 (36%)	0.03
MMSE	29 (28 – 30)	28 (27 – 30)	29 (28 – 30)	0.01
Frailty	55 (13%)	11 (16%)	44 (13%)	0.56
ASA score				0.02
I	25 (6%)	2 (3%)	23 (7%)	
II	250 (61%)	37 (53%)	213 (62%)	
III	137 (33%)	30 (43%)	107 (31%)	
Vascular risk factors				
Diabetes	91 (22%)	20 (29%)	71 (21%)	0.15
BMI	27 (24 – 29)	26 (23 – 29)	27 (24 – 29)	0.20
Hypertension	251 (62%)	45 (65%)	206 (61%)	0.59
Hyperlipidemia	145 (36%)	28 (41%)	117 (35%)	0.34
Current smoker	45 (11%)	6 (9%)	39 (12%)	0.15
History of TIA/CVA	13 (3%)	5 (7%)	8 (2%)	0.05
Type of surgery				0.01
Cardiac	40 (10%)	12 (17%)	28 (8%)	
Orthopedic	133 (32%)	17 (24%)	38 (11%)	
Gastro-intestinal/ abdominal	147 (36%)	31 (44%)	116 (34%)	
Peripheral*	93 (22%)	10 (14%)	83 (24%)	

Data represent n (percentage), mean ± SD or median (interquartile range). An independent samples T-test was performed on continuous data, and an Mann-Whitney U test for non-normal distributed data. A chi-square comparison of two groups was performed for categorical data. MMSE: mini-mental state exam. ASA: classification of disease severity for the American Society of Anesthesiologists. BMI: body-mass index. TIA: transient ischemic attack. CVA: cerebrovascular accident.
*For a complete lists of types of surgery see supplementary material.

Brain volumes and WMH volume

A total of 387 participants was analyzed for brain volumes, and a total of 382 for WMH volumes (for exclusion reasons see the flowchart in the supplementary material). Total brain volume, gray matter volume and white matter volume were lower in the patients that developed postoperative delirium compared to the patients that did not

develop postoperative delirium, however, this was not a significant association (see table 2). WMH volume was higher in the patients that developed delirium (see table 2), however, this was also not a significant association.

Table 2: Preoperative brain MRI features in relation to postoperative delirium

	Delirium	No delirium	OR (95% CI)
Brain volumes	**n=64**	**n=323**	
Total brain (% ICV)	71 ± 3	72 ± 3	0.998 (0.990 – 1.005)
Gray matter[a] (% ICV)	39 ± 2	39 ± 2	0.998 (0.987 – 1.009)
White matter[a] (% ICV)	32 ± 2	33 ± 2	1.002 (0.991 – 1.013)
White matter hyperintensities	**n=63**	**n=319**	
White matter hyperintensity volume (% ICV)	0.38 ± 0.60	0.31 ± 0.50	0.951 (0.745 – 1.212)

Brain volumes were presented as a percentage of the intracranial volume (ICV). All percentages were presented as the mean ± SD. White matter hyperintensity volumes were natural log transformed before the logistic regression analysis, volumes are shown as percentage of the ICV. Logistic regression analysis was performed, adjusted for age, sex, intracranial volume, study center and type of surgery. Odds ratio's are shown with a 95% confidence interal.
[a]For gray and white matter analysis, patients with large cortical brain infarcts were excluded, due to segmentation errors,, therefore a smaller group was analyzed (delirium: n=57, no delirium: n=306).

WMH shape features

WMH shape features were analyzed in 148 participants (table 3). No significant association was found between any WMH shape features and postoperative delirium. However, the convexity showed a non-significant trend of a lower convexity in the group with postoperative delirium (OR(95% CI): 0.948 (0.974 – 1.001), indicating a more complex shape of confluent and periventricular lesions.

Table 3: White matter hyperintensity shape features

	Delirium	**No delirium**	**OR (95% CI)**
	n=24	n=124	
Periventricular / confluent			
Solidity	0.33 ± 0.22	0.32 ± 0.19	1.011 (0.986 – 1.038)
Convexity	1.08 ± 0.20	1.17 ± 0.18	0.948 (0.974 – 1.001)[a]
Concavity index	1.16 ± 0.17	1.10 ± 0.11	1.031 (0.994 – 1.071)
Fractal dimension	1.64 ± 0.26	1.63 ± 0.23	0.993 (0.971 – 1.015)
Deep			
Fractal dimension	1.83 ± 0.19	1.82 ± 0.30	1.002 (0.985 – 1.019)
Eccentricity	0.59 ± 0.12	0.55 ± 0.12	1.030 (0.982 – 1.080)

All white matter hyperintensity shape features were multiplied by 100 before logistic regression analysis. All features were presented as the mean ± standard deviation. Logistic regression analysis was performed with adjustments for age, sex, study center and type of surgery. Odds ratio's are shown with a 95% confidence interval (95% CI).
[a]p=0.061

Brain hemodynamics

A total of 245 participants had an ASL image of sufficient quality for perfusion analysis, and a total of 325 had an ASL image of sufficient quality for analysis of label distribution, for the indication of cerebrovascular health. There were no significant associations between gray matter perfusion and in white matter perfusion and postoperative delirium. Furthermore, the spatial CoV showed no association with postoperative delirium (see table 4).

Table 4: Perfusion

	Delirium (n=41)	**No delirium (n=204)**	**OR (95% CI)**
Gray matter perfusion	74.2 ± 21.7	74.7 ± 21.0	1.000 (0.981 – 1.018)
Deep white matter perfusion	29.3 ± 9.3	26.8 ± 8.9	1.021 (0.983 – 1.061)
Spatial CoV	0.62 ± 0.24	0.62 ± 0.27	0.720 (0.205 – 2.527)

Cerebral perfusion is presented as the mean ± SD (ml/100g/minute). Logistic regression analyses were performed, adjusted for age, sex, study center and type of surgery. Odds ratio's were shown with a 95% confidence interval (95% CI). Spatial CoV was calculated for a larger sample (delirium: n=56, no delirium: n=269).

Brain infarcts

Brain infarcts were analyzed for 413 participants. In total, 24% (n=17) of the patients with postoperative delirium had cortical brain infarcts, compared to 16% (n=54) of the patients without postoperative delirium (OR (95% CI): 1.633 (0.838 – 3.183), see table 5). Furthermore, 10% (n=7) of the patients with postoperative delirium showed large cortical brain infarcts ((≥1.5 cm), compared to 4% (n=14) of the patients without postoperative delirium. Preoperative cortical brain infarct volume showed no association with postoperative delirium. A subcortical infarct was present in six patients, who did not have a postoperative delirium.

Table 5: Brain infarcts

	Delirium (n=70)	No delirium (n=343)	OR (95% CI)
Presence of lacunar infarcts	13 (19%)	78 (23%)	0.600 (0.300 – 1.205
Presence of cortical infarcts	17 (24%)	54 (16%)	1.633 (0.838 – 3.183)
Cortical infarct volume	1.61 ± 6.29	0.56 ± 5.52	1.028 (0.992 – 1.066)

Presence of cortical and lacunar infarcts was shown as number of participants that had an infarct and the percentage of the group (n (%)). Cortical brain infarct volumes were measured in patients with infarcts > 1.5 cm and are shown as mean ± SD (ml). Logistic regression analyses were adjusted for age, sex, study center and type of surgery. Cortical infarct volume was additionally adjusted for intracranial volume.

DISCUSSION

We found an association between preoperative cortical brain infarcts and postoperative delirium, although this did not reach statistical significance. Furthermore, we detected a trend for an association of a more complex shape of WMH with postoperative delirium. No association was found between WMH volume, presence of lacunar infarcts, global brain volumes and postoperative delirium.

Brain volumes

Previous studies on the association between preoperative global brain volume and postoperative delirium have shown conflicting results. Some small studies showed an association between reduced preoperative brain volumes and postoperative delirium[9,30], however, most studies did not find this association[6,12–15]. Our findings are therefore in accordance with most previous studies. The total brain volume in delirious patients in our study was slightly lower than in non-delirious patients (table

2), however, the effect size was very small, and comparable to previous negative findings in the SAGES study[6].

WMH volume

WMH volume is a key imaging marker of cerebral small vessel disease. In previous studies on the relation between WMH and postoperative delirium, most studies showed an association[4,11,15] or trend[12] between WMH volume and postoperative delirium. However, the largest previous study (SAGES) has concluded that there was no significant association between WMH volume and postoperative delirium or delirium severity[6]. Our study is the largest study to date to assess this relation, and although WMH volume was higher in patients who developed postoperative delirium, this difference did not reach statistical significance.

WMH shape

WMH shape features are novel markers for cerebral small vessel disease, in which a more rough or complex shape of periventricular and confluent lesions, and a more elongated shape of deep lesions potentially represents a more severe manifestation of cerebral small vessel disease (such as lacunes)[26]. WMH shape features have shown the ability to distinguish patients with different diseases, showing that a more complex shape of lesions was related to a more severe disease type, such as diabetes and frailty[26,31]. Our study is the first to assess preoperative WMH shape features in relation to postoperative delirium. Although our study showed no significant between-group differences in these features, a trend was found for the association between a lower convexity of periventricular and confluent lesions and postoperative delirium. This finding indicates that periventricular and confluent WMH might be more complex in patients who will develop postoperative delirium. A lower convexity has previously shown to be related to frailty in a cross-sectional study from the same study cohort[32]. Future studies should be performed to elucidate the exact role of WMH shape in relation to adverse postoperative events.

Brain hemodynamics

Previous studies on cerebral hemodynamics have shown that during a delirious episode, cerebral perfusion was disrupted[33]. Furthermore, evaluation of cerebral hemodynamics has shown the ability to detect neurodegenerative disease such as Alzheimer's disease at an early stage[34]. As dementia is an important predisposing delirium risk factor, altered hemodynamics might already be present before surgery

in patients who are at risk for delirium. One retrospective study showed that cerebral blood flow abnormalities on CT scans in cardiac surgery patients was related to postoperative adverse neurologic outcomes, of which only a small percentage (1.5%) was postoperative delirium. Only one previous SAGES study assessed the association between preoperative perfusion as measured with arterial spin labeling (ASL) MRI and postoperative delirium and showed no association between preoperative perfusion and occurrence of postoperative delirium or delirium severity[5]. The lack of associations in our larger cohort are in line with this previous study. These findings may indicate that impaired cerebral perfusion may not predispose elderly for postoperative delirium, or that any relationship between cerebral hemodynamics and POD is more complex.

Brain infarcts

Brain infarcts can be divided into lacunar, subcortical and cortical brain infarcts. These infarcts reflect different disease processes, as lacunar brain infarcts are regarded as a feature of small vessel disease, whereas cortical brain infarcts are a feature of large vessel disease. Previous studies on the relation between cerebral infarcts and postoperative delirium have not distinguished between lacunar and cortical infarcts[8,35]. These studies have shown an association between having multiple brain infarcts and postoperative delirium in cardiac surgery patients[8,35]. We did not find an association between lacunar infarcts and postoperative delirium, but we did find an association between cortical infarcts and delirium that did not reach statistical significance. Our findings therefore contribute to previous findings by indicating that the effect that was previously found could be driven by the presence of cortical brain infarcts. Possibly, patients with large vessel disease are more at risk for perioperative events resulting in postoperative delirium, such as perioperative micro-embolism due to a higher preoperative cardiovascular burden[10,35,36]. Another explanation may be that patients with larger cortical brain infarcts have a lower brain reserve. A lower brain reserve could increase the vulnerability for precipitating risk factors for delirium in the perioperative period.

Strengths and limitations

Strengths of our study are that it is the largest prospective study on preoperative brain MRI markers in relation to postoperative delirium, with a large sample size and state-of-the-art imaging and analysis techniques. Furthermore, our study included

a heterogeneous group of patients who were scheduled for different types of major elective surgery from two study centers, increasing the generalizability of our results. Limitations of our study could be the extensive work up study protocol for all participants, possibly introducing a selection of patients who were less vulnerable compared to patients who declined participation. This could have underestimated the found associations between preoperative MRI features and postoperative delirium. Another limitation could be that we had to exclude patients with head motion artefacts, especially for the perfusion MRI. This reduced our power to detect between group differences, and possibly led to exclusion of vulnerable patients who were not able to lie still in the MRI scanner. However, there were no differences in the frequency of delirium in the group included in our perfusion analysis compared to the excluded group. Another limitation could be that we used two different types of MRI scanners, introducing a difference between centers. However, we used an image analysis pipeline that is robust for center differences, and we adjusted for center in all analyses.

Conclusion

Our study suggests that patients with preoperative cortical brain infarcts and patients with a more complex white matter hyperintensity shape may be at risk for developing postoperative delirium after major elective surgery.

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SUPPLEMENTARY MATERIAL

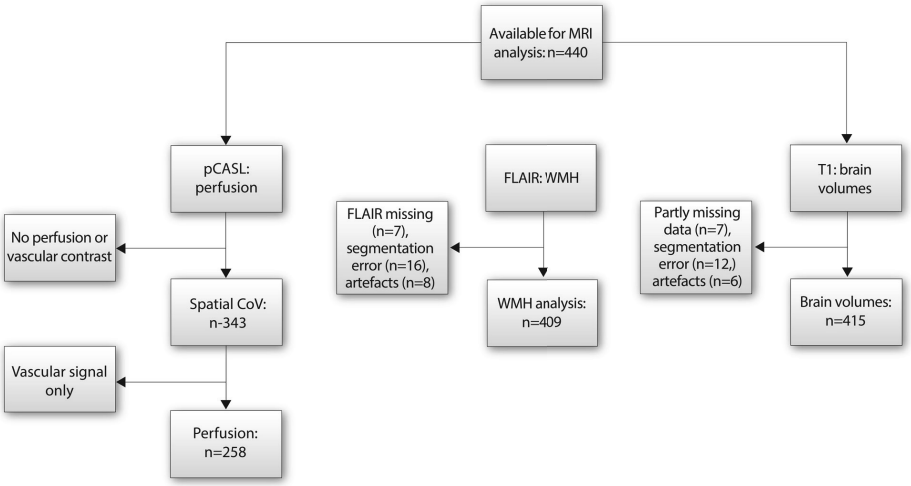

Figure A: flowchart of in- and exclusion of participants per MRI brain feature.

Table A: Baseline demographics per study center

	Utrecht	**Berlin**
Age	71 ± 5	72 ± 5
Sex (F, %)	50 (30%)	109 (45%)
MMSE	29 (28 – 30)	29 (28 – 30)
Frailty	30 (18%)	25 (10%)
ASA score		
I	19 (11%)	6 (2%)
II	93 (55%)	157 (64%)
III	56 (33%)	81 (33%)
Vascular risk factors		
Diabetes	28 (17%)	63 (26%)
BMI	26 (24 – 29)	27 (24 – 29)
Hypertension	82 (50%)	169 (70%)
Hyperlipidemia	61 (37%)	84 (35%)
Current smoker	12 (7%)	33 (14%)
History of TIA/CVA	9 (6%)	4 (2%)
Type of surgery		
Cardiac	39 (23%)	1 (0.4%)
Gastro-intestinal / intra-abdominal	55 (33%)	92 (38%)
Orthopedic	51 (30%)	82 (34%)
Peripheral	23 (14%)	70 (29%)

Data represent n (percentage), mean ± SD or median (interquartile range). An independent samples T-test was performed on continuous data, and an Mann-Whitney U test for non-normal distributed data. A chi-square comparison of two groups was performed for categorical data. MMSE: mini-mental state exam. ASA: classification of disease severity for the American Society of Anesthesiologists. BMI: body-mass index. TIA: transient ischemic attack. CVA: cerebrovascular accident.

Table B: demographics of total study sample

	Total group (n=933)
Age	72 ± 5
Sex (F, %)	394 (42%)
MMSE	29 (28 – 30)
ASA score	
I or II	595 (64%)
III	338 (36%)

Demographic data of total the group that was included and did not drop-out after inclusion (n=933). Data represent n (percentage), mean ± SD or median (interquartile range). MMSE: mini-mental state exam. ASA: classification of disease severity for the American Society of Anesthesiologists.

Table C: List of surgery types included in the current study sample:

Type of surgery (% of total sample)
Abdominal wall surgery: n=13 (3%)
Breast surgery: n=8 (2%)
Cardiac surgery: n=40 (10%)
Ear nose throat: n=23 (6%)
Endocrine surgery: n=5 (1%)
Facial surgery: n=5 (1%)
Gastroenterology: n=55 (13%)
Gynaecology: n=24 (6%)
Hand surgery: n=4 (1%)
Jaw: n=18 (4%)
Lung surgery: n=8 (2%)
Orthopedics: n=133 (32%)
Plastic surgery: n=2 (0.5%)
Urology: n=62 (15%)

CHAPTER 6

Preoperative MRI phenotypes of the brain are related to postoperative delirium in older individuals

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ABSTRACT

The underlying structural correlates of predisposition to postoperative delirium remain largely unknown. Previous studies on this topic assessed only single preoperative brain MRI markers. A combined analysis of preoperative brain MRI markers could better reflect delirium predisposition, which could improve our understanding of the pathophysiology of delirium. Therefore, we aimed to identify different MRI brain phenotypes in older patients scheduled for major elective surgery, and to assess the relation between these phenotypes and postoperative delirium. Markers of neurodegenerative and neurovascular brain changes were determined from MRI brain scans in older patients (n=161, mean age 71, standard deviation 5 years) scheduled for major elective surgery, of whom 24 patients (15%) developed postoperative delirium. A hierarchical cluster analysis was performed on these markers, and different MRI brain phenotypes were studied with logistic regression analysis. We found six distinct groups of patients with different MRI brain phenotypes (limited burden (three groups), mainly atrophy, mainly small vessel disease and atrophy, and multi-burden). Logistic regression analysis showed a higher odds of developing postoperative delirium in individuals with multi-burden pathology (n= 15 (9%), Odds Ratio (95% Confidence Interval): 3.8 (1.1 – 13.0)). In conclusion, these results indicate that different MRI brain phenotypes are related to a different risk of developing delirium after major elective surgery. MRI brain phenotypes could assist in an improved understanding of the structural correlates of predisposition to postoperative delirium.

INTRODUCTION

Postoperative delirium is a common complication of major surgery, characterized by an acute change in attention and awareness[1]. Postoperative delirium has an incidence of 15-51% in older patients undergoing major elective surgery during hospital admission and is associated with an increased risk of adverse outcomes such as prolonged hospital stay and dementia, thereby also increasing healthcare costs[2–4]. Known risk factors for postoperative delirium include advanced age, major surgery (e.g. cardiothoracic or orthopedic), comorbidity, and preoperative cognitive dysfunction.[2] However, the structural brain correlates related to predisposition to postoperative delirium remain largely unknown.

Previous studies on brain MRI markers that may reflect this neural substrate have all focused on the association between one separate preoperative brain MRI marker and the occurrence of postoperative delirium[5–12]. These markers include preoperative brain volumes as markers for neurodegenerative diseases[8,10,11], white matter hyperintensities (WMH) as a marker for small vessel disease[8,9] and brain infarcts as a marker for small and large vessel diseases[12]. However, older patients most often have heterogeneous brain changes due to aging, reflecting disease processes related to both neurodegenerative and neurovascular diseases[13]. Therefore, a combined analysis of these brain MRI markers could be a better representation of the substrate that predisposes to delirium. This could result in an improved understanding of the development of delirium.

We have previously developed an hierarchical clustering approach to analyze brain MRI markers in a combined way, leading to the identification of different MRI brain phenotypes. In this study we have shown that within a group of patients with manifest arterial disease, different MRI brain phenotypes can be identified which were associated with different risks of future stroke and mortality[14]. To the best of our knowledge, no previous studies have focused on the association between distinct MRI brain phenotypes and postoperative delirium.

In the present study, we aimed to (1) identify different MRI brain phenotypes in older patients scheduled for major elective surgery, and (2) assess the relation between these MRI brain phenotypes and the occurrence of postoperative delirium.

METHODS

Study sample

The present investigation is part of the BioCog Study, which is a prospective, observational study that aims to identify biomarkers for postoperative cognitive disorders[15]. Participants for the study 1) were ≥65 years of age, 2) had an mini-mental state exam (MMSE) of ≥24, 3) were scheduled for major elective surgery of ≥60 minutes, and 4) were able to undergo MRI scanning[15]. The present study included participants from one study center (University Medical Center Utrecht). The medical ethical committee has reviewed and approved this study under protocol number 14-469. All participants signed informed consent.

Procedures

Participants who were scheduled for major elective surgery were invited for a hospital visit prior to surgery. The visit included questionnaires by a trained researcher (i.e. demographics, mini-mental state exam (MMSE), functional abilities, medical history, and cardiovascular risk factors) and an MRI scan. The preoperative American Society of Anesthesiologists (ASA) score was determined by anesthesiologists (in training). After surgery, patients were screened for postoperative delirium as outlined below.

Delirium assessment

Delirium was defined according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria[1]. Following surgery, patients were screened by trained researchers using a daily validated chart-review [18],as well as the CAM-ICU[16] and the Nu-Desc[17] twice daily until day 7 or until discharge, whichever occurred first.

Patients were considered delirious in case of ≥2 cumulative points on the Nu-DESC and/or a positive CAM-ICU score and/or patient chart review that showed descriptions of delirium (e.g., confused, agitated, drowsy, disorientated, delirious, receiving antipsychotic therapy).

MRI scans

Participants were scanned on a Philips Achieva 3T MRI scanner. The MRI scanning protocol consisted of a three-dimensional (3D) T1-weighted sequence (voxel size = 1.0x1.0x1.0 mm^3; TR/TE= 7.9/4.5 ms), a 3D fluid-attenuated inversion recovery (FLAIR) sequence (voxel size = 1.11 x 1.11 x 0.56 mm^3; TR/TE/TI = 4800/125/1650

ms), a 2D EPI pseudo-continuous arterial spin labeling (pCASL) sequence (voxel size = 3.0x3.0x7.0 mm^3; TR/TE=3919/17 ms, label duration = 1650 ms, post labeling delay = 1525-2225 ms, with background suppression) and a diffusion-weighted image (DWI) (voxel size = 0.96 x 1.19 x 4 mm^3; TR/TE= 3294 / 68 ms)[19]. Presence of cortical and lacunar brain infarcts was visually rated on the T1-weighted, FLAIR and DWI images by two experienced neuro-radiologists (JB and TW) according to the standards for reporting vascular changes on neuroimaging (STRIVE) criteria[20].

MRI image processing

MRI image processing steps have been described previously[19]. In short, 3D FLAIR images were registered to the 3D T1 weighted images using statistical parametric mapping version 12 (SPM12; Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/doc/) for Matlab (The MathWorks, Inc., Natick, Massachusetts, United States). Thereafter, WMH were automatically quantified using the lesion segmentation toolbox (Schmidt, 2017, Chapter 6.1[21]) of the lesion segmentation toolbox version 2.0.15 (www.statistical-modeling.de/lst.html) for SPM12. A lesion filling method on the T1-weighted images was performed using the lesion segmentation toolbox. The filled T1-weighted images were used for brain tissue segmentation, and cortical surfaces were estimated using the computational anatomy toolbox for SPM12 (CAT12, Gaser and Dahnke, Jena University Hospital, Departments of Psychiatry and Neurology, http://www.neuro.uni-jena.de/cat/index). All segmentations of total gray matter volume, white matter volume, cerebrospinal fluid and WMH were visually checked by trained researchers and in doubt by a neuro-radiologist (JB). Mean cortical thickness was estimated per region of the DK-40 atlas[22]. WMH volumes were thresholded, and distinguished per brain lobe as deep, periventricular or confluent. WMH shape features (solidity, convexity, concavity index, fractal dimensions, eccentricity) were calculated for deep and periventricular or confluent lesions according to an inhouse developed method[19,23]. Perfusion images were analyzed using the ExploreASL toolbox[24], resulting in gray matter perfusion, white matter perfusion and the spatial coefficient of variation (CoV).

Distinguishing MRI brain phenotypes by hierarchical cluster analysis

The brain MRI markers that were included in the cluster analysis were brain volumes (total brain volume fraction, gray matter volume fraction, white matter volume fraction, peripheral CSF fraction, ventricular CSF fraction, mean cortical thickness per region

of the DK-40 atlas), WMH (deep WMH volume per lobe, confluent and periventricular (CP) WMH volume per lobe, convexity, solidity, concavity index, fractal dimension of confluent and periventricular lesions, fractal dimension and eccentricity of deep lesions), brain infarcts (number of cortical infarcts, cortical infarct volume, number of lacunar infarcts) and perfusion (gray matter perfusion, white matter perfusion, spatial CoV). Normally distributed variables were expressed using a Z-score. Non-normally distributed variables were scaled to a range between -2 and 2, by normalizing each value (x) between the new minimum (a) and the new maximum (b):

$x_{normalized} = (b\text{-}a)\frac{x\text{-}min(x)}{max(x)\text{-}min(x)} + a$, where a is equal to -2, and b is equal to 2.

Hierarchical clustering was performed using Ward's method in R version 3.5.1[25] and packages Nbclust[26], factoextra[27], cluster[28] and dendextend[29]. Hierarchical clustering is a method to distinguish groups (clusters) based on the distances between a set of variables. These clusters are organized as a tree, that starts with every patient as a separate cluster, and then repeatedly merges the two closest clusters, updating the distance matrix. Therefore, all clusters are a union of two subclusters, leading to a hierarchical organization. This was repeated until one group (the total group of patients) remains. This approach can be visualized as a dendogram (see left y-axis of figure 1 for an example). To determine the number of groups that is used for further analysis, the dendogram needs to be cut at a certain level. In an optimally clustered sample, the clustered data has a high within cluster cohesion, and a high separation between different clusters. This can be determined using the dunn index (ratio of the smallest distance between observations in different clusters, to the largest between cluster distance), which needs to be maximized. It can also be determined by the heatmap that plots all variables per group of patients. In the current analysis, both methods were used to estimate the optimal number of groups.

Statistical analysis

Between group differences in demographics were assessed using a chi-square test for categorical variables, and a one-way ANOVA for continuous variables. Between group differences of the brain MRI markers were assessed by one-way ANOVA analyses. These analyses were adjusted for multiple comparisons by a false discovery rate (FDR) correction. Logistic regression analysis was performed to assess the relation between the groups with different MRI brain phenotypes and postoperative delirium. All groups were entered to the same model and compared to the reference

group by a single unadjusted logistic regression analysis with postoperative delirium as the dependent variable. A p-value of <0.05 was considered statistically significant.

RESULTS

Study sample

A total of 161 participants (mean age 71, standard deviation (SD) 5 years) were included for the hierarchical cluster analysis with 95 distinct brain MRI markers of neurovascular and neurodegenerative diseases. See table 1 for an overview of the demographics of the total group, and supplementary figure A for a flowchart of the inclusion of participants.

Table 1: Demographics of the study population

	n= 161
Age (years)	71 (5)
Gender (female)	51 (32)
ASA	
1	19 (12)
2	90 (56)
3	52 (32)
MMSE	28 ± 2
BMI	27 ± 4
Current smoking	12 (8)
Diabetes	25 (16)
Hyperlipidemia	58 (37)
Hypertension	78 (49)
Prior Stroke	13 (9)
Prior TIA	8 (5)
Type of surgery	
Cardiothoracic	35 (22)
Intra-abdominal	54 (34)
Orthopedic	47 (29)
Other*	25 (16)

Data represent the mean (standard deviation), or n (percentage). ASA: classification of disease severity for the American Society of Anesthesiologists. MMSE: mini-mental state exam. BMI: body-mass index. TIA: transient ischemic attack.
* Ear nose throat, facial, jaw, and plastic surgery.

Table 2: Main between group differences in brain markers

	Group 1 (n=34)	Group 2 (n=39)	Group 3 (n=30)	Group 4 (n=34)	Group 5 (n=9)	Group 6 (n=15)	
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	p-value
Brain and WMH volumes							
Total brain (% ICV)	73.3 ± 2.0	72.2 ± 2.1	72.1 ± 2.0	69.2 ± 2.1	67.1 ± 2.6	68.7 ± 2.4	<0.001
Gray matter (% ICV)	41.1 ± 1.4	39.8 ± 1.6	39.2 ± 1.2	38.1 ± 1.8	35.5 ± 1.9	37.8 ± 2.0	<0.001
White matter (% ICV)	32.1 ± 1.3	32.4 ± 1.6	32.8 ± 1.6	31.1 ± 1.5	31.6 ± 1.1	30.1 ± 2.6	<0.001
Peripheral CSF (% ICV)	25.1 ± 1.6	25.5 ± 1.6	25.9 ± 1.5	28.1 ± 1.5	29.7 ± 2.4	25.8 ± 4.6	<0.001
Lateral ventricles (% ICV)	1.7 ± 0.6	2.2 ± 1.0	1.9 ± 0.7	2.6 ± 0.7	3.2 ± 1.3	3.5 ± 1.6	<0.001
WMH volume	4.0 ± 7.0	4.1 ± 3.8	1.7 ± 1.3	7.1 ± 5.5	26.6 ± 17.1	23.4 ± 17.8	<0.001
WMH shape features							
ConvexityCP	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.3	1.0 ± 0.2	0.001
SolidityCP	0.4 ± 0.2	0.3 ± 0.2	0.5 ± 0.2	0.2 ± 0.1	0.1 ± 0.0	0.2 ± 0.1	<0.001
CI	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.3 ± 0.2	1.3 ± 0.1	<0.001
FDCP	1.6 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	1.7 ± 0.1	2.0 ± 0.1	1.9 ± 0.2	<0.001
Mean Eccentricity	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.2	0.6 ± 0.1	0.6 ± 0.0	0.5 ± 0.1	0.716
MeanFDD	1.9 ± 0.3	1.8 ± 0.2	1.8 ± 0.6	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.1	0.962
Brain infarcts							
Number of cortical infarcts	0.1 ± 0.2	0.4 ± 0.7	0.4 ± 1.0	0.4 ± 1.1	1.2 ± 1.8	1.7 ± 3.4	0.002

Table 2: Continued

	Group 1 (n=34) Limited burden	Group 2 (n=39) Limited burden	Group 3 (n=30) Limited burden	Group 4 (n=34) Mainly atrophy	Group 5 (n=9) Mainly SVD and atrophy	Group 6 (n=15) Multi-burden (SVD, LVD and atrophy)	p-value
Number of lacunar infarcts	0.1 ± 0.4	0.3 ± 0.6	0.2 ± 0.5	0.4 ± 0.8	0.8 ± 0.8	1.1 ± 1.8	0.002
Cortical_infarct_volume	0.0 ± 0.1	0.5 ± 3.0	0.3 ± 1.7	0.3 ± 1.5	0.1 ± 0.3	5.3 ± 10.9	<0.001
Perfusion							
Gray matter perfusion	82.3 ± 18.1	93.1 ± 21.4	87.6 ± 16.9	79.8 ± 20.0	83.1 ± 32.2	76.7 ± 9.8	0.271

Data are represented as the mean ± the standard deviation per cluster. An ANOVA was performed per variable. P-values were false discovery rate corrected, a p-value <0.05 was considered statistically significant. For a complete overview of MRI brain features and cluster differences see supplementary table 1.

MRI brain phenotypes

The hierarchical cluster algorithm resulted in the dendogram and heatmap shown in figure 1. Based on both the dunn index and the heatmap, the optimal cut-off was determined at 6 different groups with distinct MRI brain phenotypes. These groups consisted of 34 (group 1; limited burden, 21%), 39 (group 2; limited burden, 24%), 30 (group 3; limited burden, 19%), 34 (group 4; mainly atrophy, 21%), 9 (group 5; mainly atrophy and SVD, 6%) and 15 (group 6; multi-burden, 9%) patients. Table 2 shows an overview of the main between group differences in brain MRI markers (for a full list of brain MRI markers that were used in the model, see supplementary table A). Each group had a distinct pattern of brain MRI markers, representing different combinations of neurodegenerative and neurovascular brain changes. The mean age of patients in each group ranged from (mean ± SD) 68.9 ± 3.2 to 75.4 ± 6.4 years.

The "limited burden" groups showed the least brain changes regarding both neurovascular and neurodegenerative diseases (group 1; GM volume (% ICV, mean ± SD): 41.1 ± 1.4, number of cortical brain infarcts (mean ± SD): 0.1 ± 0.2, group 2; GM volume (% ICV, mean ± SD): 39.8 ± 1.6, number of cortical brain infarcts (mean ± SD): 0.4 ± 0.7, group 3; GM volume (% ICV, mean ± SD): 39.2 ± 1.2). The "mainly atrophy" group had an increased overall disease burden of mostly neurodegenerative origin (group 4; GM volume (% of ICV, mean ± SD): 38.1 ± 1.8). The "mainly atrophy and SVD" group showed a high SVD and global atrophy burden (group 5; WMH volume: (mean ± SD) 26.6 ± 17.1, GM volume (% ICV, mean ± SD): 35.5 ± 1.9), and the "multi-burden" group showed an overall high disease burden with mostly MRI features of neurovascular diseases, and the highest number of brain infarcts in comparison to other groups (group 6; WMH volume (mean ± SD): 23.4 ± 17.8 ml, number of cortical brain infarcts (mean ± SD): 1.7 ± 3.4, GM volume (mean ± SD): 37.8 ± 2.0). The groups differed significantly on almost all brain MRI markers that were used in the hierarchical clustering algorithm (see table 2 and supplementary table A).

Table 3 shows the patient demographics of the different groups. The groups differed significantly in age, preoperative ASA scores (with the highest percentage of ASA 3 score in the multi-burden group (group 6; n=9 (60%)), hypertension (with the highest percentage of patients with hypertension in the mainly atrophy and SVD group (group 2; n=8 (89%))), and previous stroke / TIA (with the highest percentage of patients with a previous event in the multi-burden group (group 6; TIA: n=3 (20%), stroke: n=5 (36%)).

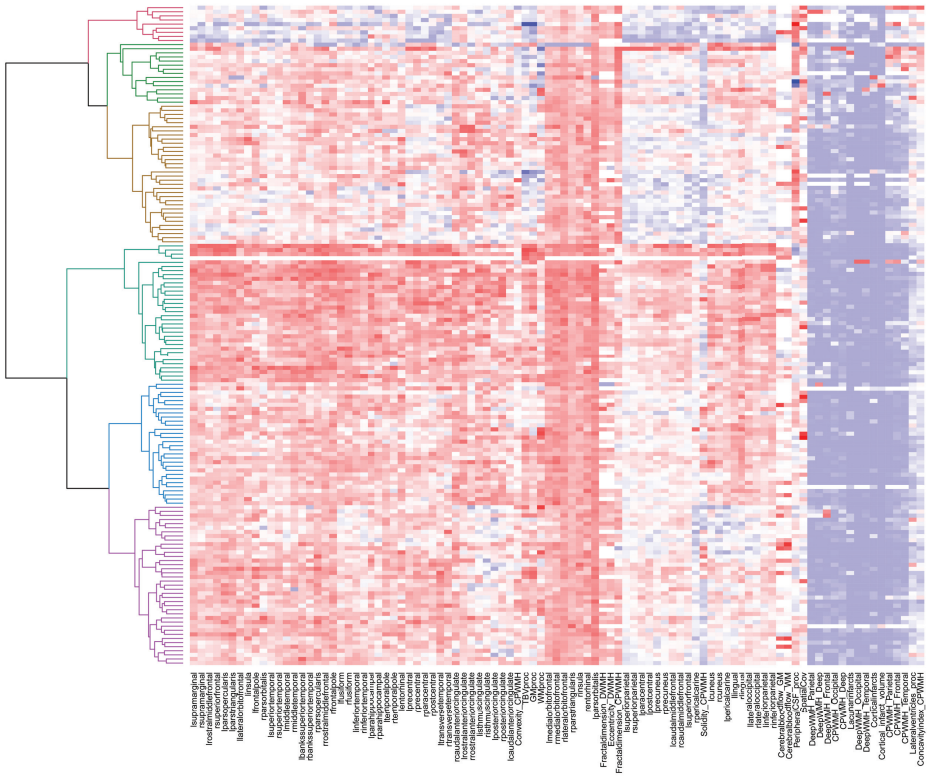

Figure 1: heatmap of the hierarchical clustering algorithm. Every row of this figure represents one participant. Every column represents one brain MRI feature. Blue represents a low value, white represents a value around zero and red represents a high value. The left side of the image shows the hierarchical clustering tree dendogram with the separate groups, respectively in red (atrophy and SVD, n=9), yellow (multi-burden, n=15), blue (mainly atrophy, n=34), purple (limited burden, n= 34), green (limited burden, , n=30), and red (limited burden, , n=39). For example, the blue values in the red group on top represent a relatively low cortical thickness (more atrophy). Another example can be seen in the yellow group, as the right part of the heatmap shows a relatively high WMH burden and a relatively high concavity index (CI) in this group.

Association with postoperative delirium

A total of 24 patients developed postoperative delirium (15%). The percentage of patients with postoperative delirium differed per group from 3% to 36% (see table 3). The groups with limited disease burden were chosen as a combined reference group (group 1, 2 and 3 respectively). Logistic regression analysis showed a higher odds of developing postoperative delirium in the "multi-burden" group (OR (95% CI): 3.8 (1.1 – 13.0)). No association with postoperative delirium was found in the "mainly atrophy and SVD" group (OR (95% CI): 1.0 (0.1 – 8.5)) or the "mainly atrophy" group (OR (95% CI): 1.3 (0.4 – 3.8). .

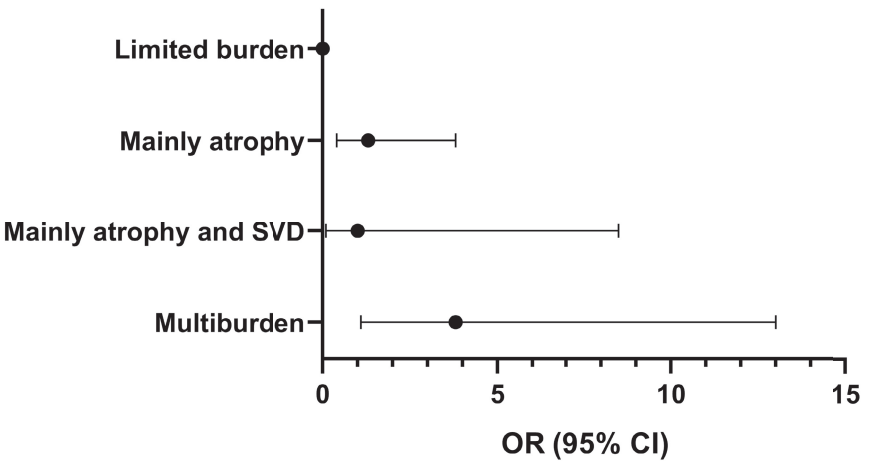

Figure 2: The association between MRI brain phenotypes and postoperative delirium. Odds ratios are shown with a 95% confidence interval.

Table 3: Characteristics of the study population per cluster

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	p-value
Age (M ± SD)	68.9 ± 3.2	69.4 ± 3.6	70.8 ± 4.3	74.3 ± 4.5	74.4 ± 4.2	75.4 ± 6.4	<0.001
Gender (female, N (%))	16 (47)	13 (33)	6 (20)	12 (35)	0 (0)	4 (27)	0.070
Delirium (N (%))	1 (3)	4 (11)	8 (28)	5 (16)	1 (13)	5 (36)	-
ASA (N (%))							0.025
1	8 (24)	6 (16)	3 (10)	2 (6)	0 (0)	0 (0)	
2	22 (65)	19 (49)	19 (63)	20 (59)	4 (44)	6 (40)	
3	4 (12)	14 (36)	8 (27)	12 (35.3)	5 (56)	9 (60)	
MMSE	28.9 ± 1.1	28.5 ± 1.7	28.6 ± 1.6	28.2 ± 1.6	27.6 ± 2.1	27.9 ± 1.5	0.299
BMI (M ± SD)	25.3 ± 2.9	27.1 ± 3.4	27.2 ± 4.3	27.5 ± 4.3	26.8 ± 6.7	26.9 ± 5.0	0.125
Current smoker (N (%))	2 (6)	0 (0)	3 (10)	4 (12)	0 (0)	3 (20)	0.132
Diabetes (N (%))	2 (6)	6 (15)	4 (13)	7 (21)	3 (33)	3 (20)	0.35
Hyperlipidemia (N (%))	8 (26)	14 (36)	9 (30)	15 (44)	5 (56)	7 (47)	0.416
Hypertension (N (%))	6 (19)	14 (36)	17 (57)	21 (62)	8 (89)	12 (80)	<0.001
Prior Stroke (N (%))	3 (10)	2 (5)	2 (7)	0 (0)	1 (11)	5 (36)	0.004

Table 3: Continued

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	p-value
Prior TIA (N (%))	2 (7)	0 (0)	0 (0)	2 (6)	1 (13)	3 (20)	0.040
Type of surgery							0.246
Cardiothoracic	2 (6)	11 (28)	8 (27)	7 (21)	1 (11)	6 (40)	
Intra-abdominal	15 (44)	12 (31)	10 (33)	11 (32)	1 (11)	5 (33)	
Orthopedic	12 (35)	11 (28)	5 (17)	12 (35)	5 (56)	2 (13)	
Other*	5 (15)	5 (13)	7 (23)	4 (12)	2 (22)	2 (13)	

* Ear nose throat, facial, jaw, and plastic surgery.

MMSE: mini-mental state exam. ASA: classification of disease severity for the American Society of Anesthesiologists. BMI: body-mass index. TIA: transient ischemic attack.

DISCUSSION

We showed that distinct MRI brain phenotypes can be identified in older patients who are scheduled for major elective surgery. Furthermore, we found a higher odds of developing postoperative delirium in individuals with multi-burden pathology.

Recent developments in machine learning techniques have enabled analysis of patterns using novel clustering methods. Identification of different MRI brain phenotypes can lead to novel insights into the neural correlates of predisposition to delirium. Our results revealed six distinct subgroups of patients with different distributions of brain MRI markers of neurodegenerative and neurovascular diseases. We have shown that a multi-burden brain MRI phenotype (e.g. SVD, LVD and atrophy) may predispose to developing postoperative delirium. Interestingly, it therefore seems that multiple forms of brain pathology are needed to increase the risk of postoperative delirium.

Future steps that need to be taken to improve our understanding of the relation between preoperative MRI brain phenotypes and postoperative delirium include identification of the MRI features that are driving the increased risk of delirium. This could be realized by identification of the discriminating features between these phenotypes, for example by performing a principal component analysis. Future studies on delirium are encouraged to confirm these findings by validating machine learning methods in other cohorts of surgical patients. To enable future clinical implementation of these techniques and increase comparability between research cohorts, image acquisition and processing methods should be standardized and fully automated by implementation of a standard image processing pipeline, which is tested for accuracy and robustness. After these steps have been undertaken, identification of MRI brain phenotypes could also be used as a personalized risk assessment tool for adverse postoperative outcomes, assisting in patient-specific treatment plans and in a more precise planning of postoperative care.

To the best of our knowledge, our study is the first to assess preoperative MRI brain phenotypes in relation to postoperative delirium. Strengths of our study include the use of multiple brain MRI features in one framework. Furthermore, we mostly included features that can be (semi-)automatically detected on brain MRI scans, using state-of-the-art quantification techniques based on publically available software (e.g. CAT12). This increases the possibility of future standardization and implementation

in clinical practice. Our method performed an automated, unsupervised approach to identify groups, possibly leading to new combinations of brain MRI features and novel insights that might not have emerged with a conventional approach. Limitations of our study include that our method has some settings that may seem arbitrary or subjective, such as the number of groups or the brain MRI features that were used. However, we increased objectivity by using the heatmap and the dunn index for the choice of the number of groups, and by choosing validated MRI features that can almost all be automatically quantified. Furthermore, we aimed to describe our choices in a transparent way, enabling reproducibility. Another limitation may be the limited number of patients with postoperative delirium, even though we performed an extensive delirium screening protocol. This could be the result of improved postoperative care such as activation and mobilization resulting in a reduced number of delirious patients[31]. Replication of the current study in a larger sample is therefore encouraged.

In conclusion, we have shown that different MRI brain phenotypes can be identified in older patients who are scheduled for major elective surgery. Our results may indicate that different MRI brain phenotypes are related to a different risk of developing postoperative delirium. MRI brain phenotypes could assist in an improved understanding of the structural correlates that predispose individuals to postoperative delirium.

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Supplementary table A: all brain MRI markers that were included in the hierarchical cluster analysis, shown per group

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	Adjusted p-value (FDR)
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	
Global brain volumes							
TBV	73.3 ± 2.0	72.2 ± 2.1	72.1 ± 2.0	69.2 ± 2.1	67.1 ± 2.6	68.7 ± 2.4	<0.001
GM	41.1 ± 1.4	39.8 ± 1.6	39.2 ± 1.2	38.1 ± 1.8	35.5 ± 1.9	37.8 ± 2.0	<0.001
WM	32.1 ± 1.3	32.4 ± 1.6	32.8 ± 1.6	31.1 ± 1.5	31.6 ± 1.1	30.1 ± 2.6	<0.001
Peripheral CSF	25.1 ± 1.6	25.5 ± 1.6	25.9 ± 1.5	28.1 ± 1.5	29.7 ± 2.4	25.8 ± 4.6	<0.001
Lateral ventricles	1.7 ± 0.6	2.2 ± 1.0	1.9 ± 0.7	2.6 ± 0.7	3.2 ± 1.3	3.5 ± 1.6	<0.001
WMH volumes							
CP WMH volume deep	0.5 ± 0.6	1.1 ± 1.1	0.4 ± 0.8	0.8 ± 0.7	1.8 ± 1.6	3.0 ± 4.3	<0.001
CP WMH volume frontal	1.7 ± 3.6	1.5 ± 1.4	0.6 ± 0.5	2.5 ± 2.2	11.5 ± 10.5	9.3 ± 8.2	<0.001
CP WMH volume occipital	0.2 ± 0.3	0.2 ± 0.2	0.2 ± 0.2	0.5 ± 0.5	1.5 ± 0.5	0.9 ± 1.3	<0.001
CP WMH volume parietal	0.9 ± 2.3	0.6 ± 1.3	0.1 ± 0.3	1.7 ± 1.9	7.1 ± 4.6	6.3 ± 5.3	<0.001
CP WMH volume temporal	0.5 ± 0.8	0.6 ± 0.7	0.3 ± 0.3	1.3 ± 1.2	3.5 ± 2.7	3.2 ± 2.4	<0.001
Deep WMH volume deep	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0	0.070
Deep WMH volume frontal	0.1 ± 0.2	0.2 ± 0.5	0.0 ± 0.0	0.2 ± 0.3	0.7 ± 0.6	0.5 ± 0.6	<0.001
Deep WMH volume occipital	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.490
Deep WMH volume parietal	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.3 ± 0.5	0.2 ± 0.1	<0.001
Deep WMH volume temporal	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.323
WMH shape features							

Supplementary table A: Contunued

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	Adjusted p-value (FDR)
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	
CP Concavity index	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.3 ± 0.2	1.3 ± 0.1	<0.001
CP Convexity	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.3	1.0 ± 0.2	0.001
CP Fractal dimension	1.6 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	1.7 ± 0.1	2.0 ± 0.1	1.9 ± 0.2	<0.001
CP Solidity	0.4 ± 0.2	0.3 ± 0.2	0.5 ± 0.2	0.2 ± 0.1	0.1 ± 0.0	0.2 ± 0.1	<0.001
Deep Eccentricity	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.2	0.6 ± 0.1	0.6 ± 0.0	0.5 ± 0.1	0.716
Deep Fractal dimension	1.9 ± 0.3	1.8 ± 0.2	1.8 ± 0.6	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.1	0.962
Brain infarcts							
Number of cortical infarcts	0.1 ± 0.2	0.4 ± 0.7	0.4 ± 1.0	0.4 ± 1.1	1.2 ± 1.8	1.7 ± 3.4	0.002
Number of lacunar infarcts	0.1 ± 0.4	0.3 ± 0.6	0.2 ± 0.5	0.4 ± 0.8	0.8 ± 0.8	1.1 ± 1.8	0.002
Cortical infarct volume	0.0 ± 0.1	0.5 ± 3.0	0.3 ± 1.7	0.3 ± 1.5	0.1 ± 0.3	5.3 ± 10.9	<0.001
Perfusion							
Gray matter CBF	82.3 ± 18.1	93.1 ± 21.4	87.6 ± 16.9	79.8 ± 20.0	83.1 ± 32.2	76.7 ± 9.8	0.271
White matter CBF	25.0 ± 8.6	28.3 ± 9.9	25.9 ± 7.1	23.0 ± 9.2	24.8 ± 11.7	20.9 ± 5.9	0.426
Spatial CoV	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.2	0.5 ± 0.1	0.6 ± 0.2	0.6 ± 0.1	0.009
Regional cortical thickness (DK40 atlas[22])							
Temporal lobe – medial aspect							
L entorhinal	4.2 ± 0.4	4.0 ± 0.4	4.1 ± 0.4	3.9 ± 0.5	3.7 ± 0.3	3.6 ± 0.5	<0.001
R entorhinal	4.5 ± 0.5	4.2 ± 0.4	4.3 ± 0.3	4.1 ± 0.5	3.6 ± 0.6	3.7 ± 0.6	<0.001

Supplementary table A: Contunued

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	Adjusted p-value (FDR)
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	
L parahippocampal	3.1 ± 0.2	2.9 ± 0.2	2.9 ± 0.2	2.8 ± 0.2	2.6 ± 0.3	2.9 ± 0.2	<0.001
R parahippocampal	3.1 ± 0.2	2.9 ± 0.2	3.0 ± 0.2	2.8 ± 0.2	2.5 ± 0.2	2.8 ± 0.2	<0.001
L temporal pole	4.0 ± 0.3	3.9 ± 0.3	3.8 ± 0.3	3.7 ± 0.4	3.5 ± 0.4	3.7 ± 0.4	<0.001
R temporal pole	4.2 ± 0.3	4.0 ± 0.2	3.9 ± 0.3	3.9 ± 0.3	3.5 ± 0.4	3.8 ± 0.3	<0.001
L fusiform	3.1 ± 0.1	2.9 ± 0.1	3.0 ± 0.1	2.9 ± 0.1	2.6 ± 0.2	2.9 ± 0.1	<0.001
R fusiform	3.1 ± 0.1	2.9 ± 0.1	3.0 ± 0.1	2.9 ± 0.1	2.6 ± 0.2	2.9 ± 0.2	<0.001
Temporal lobe – lateral aspect							
L superior temporal	3.0 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.5 ± 0.1	2.8 ± 0.1	<0.001
R superior temporal	3.0 ± 0.1	2.9 ± 0.1	2.9 ± 0.1	2.8 ± 0.1	2.6 ± 0.1	2.8 ± 0.1	<0.001
L middle temporal	3.1 ± 0.1	2.9 ± 0.1	2.9 ± 0.1	2.9 ± 0.1	2.7 ± 0.1	2.9 ± 0.1	<0.001
R middle temporal	3.1 ± 0.1	3.0 ± 0.2	3.0 ± 0.1	2.9 ± 0.1	2.8 ± 0.1	3.0 ± 0.1	<0.001
L inferior temporal	3.0 ± 0.1	2.8 ± 0.1	2.9 ± 0.1	2.7 ± 0.2	2.6 ± 0.2	2.8 ± 0.2	<0.001
R inferior temporal	3.0 ± 0.1	2.8 ± 0.1	2.9 ± 0.1	2.8 ± 0.1	2.6 ± 0.2	2.9 ± 0.1	<0.001
L transverse temporal	2.4 ± 0.1	2.4 ± 0.1	2.2 ± 0.1	2.1 ± 0.2	1.9 ± 0.2	2.2 ± 0.1	<0.001
R transverse temporal	2.5 ± 0.1	2.4 ± 0.1	2.3 ± 0.2	2.2 ± 0.2	2.0 ± 0.2	2.3 ± 0.2	<0.001
L banks superior temporal sulcus	2.9 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.4 ± 0.2	2.7 ± 0.1	<0.001
R banks superior temporal sulcus	2.9 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.2	2.8 ± 0.1	<0.001
Frontal lobe							

Supplementary table A: Contunued

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	Adjusted p-value (FDR)
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	
L superior frontal	2.9 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.8 ± 0.2	<0.001
R superior frontal	3.0 ± 0.1	2.9 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.8 ± 0.1	<0.001
Middle frontal gyrus							
L rostral middle frontal	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	<0.001
R rostral middle frontal	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.2	<0.001
L caudal middle frontal	2.8 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.5 ± 0.2	2.7 ± 0.2	<0.001
R caudal middle frontal	2.8 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.5 ± 0.2	2.7 ± 0.2	<0.001
Inferior frontal gyrus							
L pars opercularis	2.9 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.5 ± 0.1	2.7 ± 0.1	<0.001
R pars opercularis	2.9 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.5 ± 0.2	2.7 ± 0.2	<0.001
L pars triangularis	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.4 ± 0.1	2.5 ± 0.2	<0.001
R pars triangularis	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.4 ± 0.1	2.6 ± 0.4	<0.001
L pars orbitalis	2.9 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.7 ± 0.2	2.6 ± 0.2	2.6 ± 0.4	<0.001
R pars orbitalis	2.9 ± 0.1	2.8 ± 0.2	2.8 ± 0.1	2.8 ± 0.1	2.7 ± 0.2	2.8 ± 0.1	<0.001
Orbitofrontal cortex							
L lateral orbitofrontal	3.1 ± 0.1	3.0 ± 0.1	3.0 ± 0.1	2.9 ± 0.1	2.8 ± 0.2	2.9 ± 0.2	<0.001
R lateral orbitofrontal	3.1 ± 0.2	2.9 ± 0.1	3.0 ± 0.1	2.9 ± 0.1	2.7 ± 0.2	2.8 ± 0.4	<0.001
L medial orbitofrontal	2.8 ± 0.1	2.5 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.3 ± 0.1	2.5 ± 0.3	<0.001
R medial orbitofrontal	2.8 ± 0.1	2.6 ± 0.1	2.7 ± 0.1	2.6 ± 0.2	2.4 ± 0.1	2.5 ± 0.2	<0.001

Supplementary table A: Contunued

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	Adjusted p-value (FDR)
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	
L frontalpole	2.8 ± 0.2	2.8 ± 0.2	2.7 ± 0.2	2.7 ± 0.2	2.5 ± 0.2	2.7 ± 0.2	<0.001
R frontalpole	2.8 ± 0.2	2.7 ± 0.1	2.7 ± 0.2	2.7 ± 0.1	2.5 ± 0.2	2.6 ± 0.3	<0.001
L precentral	2.6 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.3 ± 0.1	2.1 ± 0.1	2.4 ± 0.1	<0.001
R precentral	2.5 ± 0.1	2.4 ± 0.1	2.3 ± 0.1	2.2 ± 0.1	2.1 ± 0.1	2.4 ± 0.2	<0.001
L paracentral	2.5 ± 0.2	2.4 ± 0.1	2.3 ± 0.1	2.2 ± 0.2	2.1 ± 0.2	2.4 ± 0.3	<0.001
R paracentral	2.5 ± 0.2	2.4 ± 0.1	2.3 ± 0.1	2.2 ± 0.1	2.1 ± 0.2	2.4 ± 0.2	<0.001
Parietal lobe							
L post central	2.2 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	2.2 ± 0.2	<0.001
R post central	2.2 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.0 ± 0.1	1.8 ± 0.1	2.1 ± 0.1	<0.001
L supramarginal	2.8 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	<0.001
R supramarginal	2.8 ± 0.1	2.6 ± 0.1	2.7 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	<0.001
L superior parietal	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.3 ± 0.1	2.2 ± 0.2	2.4 ± 0.2	<0.001
R superior parietal	2.4 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.2 ± 0.1	2.1 ± 0.2	2.4 ± 0.2	<0.001
L inferior parietal	2.8 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.2	<0.001
R inferior parietal	2.8 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	<0.001
L precuneus	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.2	<0.001
R precuneus	2.7 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	<0.001
Occipital lobe							
L lingual	2.3 ± 0.1	2.1 ± 0.1	2.3 ± 0.1	2.1 ± 0.1	2.0 ± 0.1	2.2 ± 0.2	<0.001

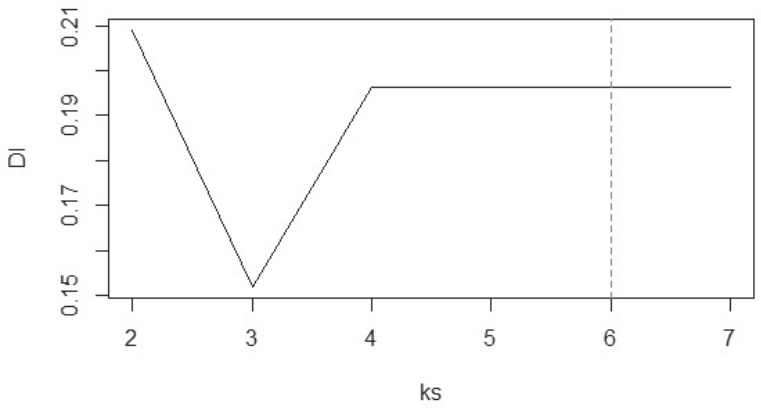
Supplementary table A: Contunued

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	Adjusted p-value (FDR)
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	
R lingual	2.4 ± 0.1	2.1 ± 0.1	2.3 ± 0.1	2.1 ± 0.1	2.0 ± 0.1	2.3 ± 0.1	<0.001
L pericalcarine	2.0 ± 0.1	1.8 ± 0.1	2.0 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	2.0 ± 0.2	<0.001
R pericalcarine	2.1 ± 0.1	1.9 ± 0.1	2.0 ± 0.2	1.9 ± 0.1	1.8 ± 0.1	2.1 ± 0.1	<0.001
L cuneus	2.2 ± 0.1	2.0 ± 0.1	2.2 ± 0.1	2.0 ± 0.1	1.9 ± 0.2	2.1 ± 0.1	<0.001
R cuneus	2.2 ± 0.1	2.0 ± 0.1	2.2 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	2.2 ± 0.1	<0.001
L lateral occipital	2.5 ± 0.1	2.3 ± 0.1	2.5 ± 0.1	2.3 ± 0.1	2.2 ± 0.1	2.4 ± 0.2	<0.001
R lateral occipital	2.5 ± 0.1	2.3 ± 0.1	2.5 ± 0.1	2.3 ± 0.1	2.2 ± 0.2	2.5 ± 0.1	<0.001
Cingulate cortex							
L rostral anterior cingulate	3.2 ± 0.2	2.9 ± 0.2	3.1 ± 0.2	3.0 ± 0.3	2.9 ± 0.2	2.9 ± 0.3	<0.001
R rostral anterior cingulate	3.2 ± 0.2	3.0 ± 0.2	3.1 ± 0.2	3.2 ± 0.2	2.8 ± 0.2	3.0 ± 0.3	<0.001
L caudal anterior cingulate	2.8 ± 0.2	2.6 ± 0.2	2.7 ± 0.2	2.7 ± 0.3	2.6 ± 0.2	2.6 ± 0.3	0.006
R caudal anterior cingulate	2.8 ± 0.2	2.6 ± 0.3	2.7 ± 0.2	2.6 ± 0.3	2.5 ± 0.2	2.5 ± 0.3	<0.001
L posterior cingulate	2.7 ± 0.1	2.5 ± 0.1	2.6 ± 0.1	2.6 ± 0.2	2.5 ± 0.1	2.5 ± 0.1	<0.001
R posterior cingulate	2.7 ± 0.1	2.5 ± 0.1	2.6 ± 0.1	2.5 ± 0.2	2.5 ± 0.1	2.5 ± 0.1	<0.001
L isthmus cingulate	2.8 ± 0.2	2.5 ± 0.2	2.8 ± 0.1	2.7 ± 0.2	2.4 ± 0.2	2.6 ± 0.2	<0.001
R isthmus cingulate	2.8 ± 0.2	2.5 ± 0.2	2.7 ± 0.1	2.6 ± 0.2	2.4 ± 0.1	2.5 ± 0.2	<0.001
L insula	3.7 ± 0.2	3.6 ± 0.1	3.6 ± 0.2	3.5 ± 0.2	3.2 ± 0.2	3.5 ± 0.1	<0.001

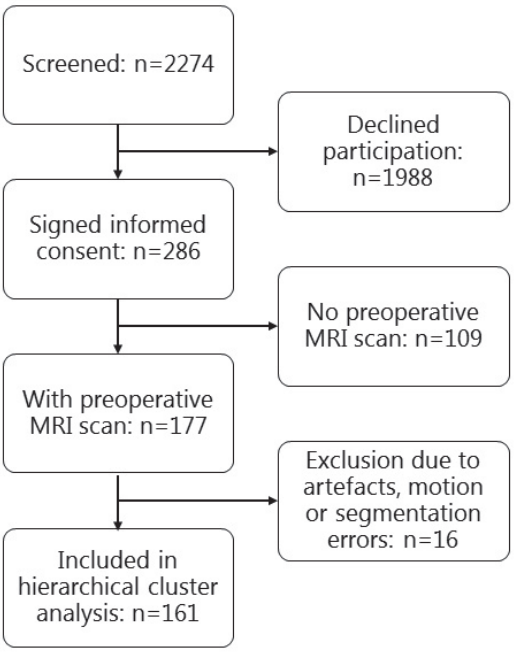
Supplementary table A: Contunued

	1 (n=34)	2 (n=39)	3 (n=30)	4 (n=34)	5 (n=9)	6 (n=15)	Adjusted p-value (FDR)
	Limited burden	Limited burden	Limited burden	Mainly atrophy	Mainly SVD and atrophy	Multi-burden (SVD, LVD and atrophy)	
R insula	3.7 ± 0.2	3.6 ± 0.2	3.6 ± 0.2	3.6 ± 0.2	3.2 ± 0.2	3.4 ± 0.4	<0.001

Data are presented as the mean ± the standard deviation (M ± SD). An ANOVA analysis was performed per MRI brain marker that was used in the model. P-values were FDR-corrected. Percentage missing per variable: global brain volumes: 0%, WMH volumes 6%, brain infarcts 0%, shape markers of periventricular WMH 5%, shape markers of deep WMH 41%, gray and white matter perfusion 47%, spatial CoV 16%, regional cortical thickness 1%. L: left. R: right. CP: confluent and peripheral. Cortical thickness was shown per region in the nomenclature and order as defined by the DK40 atlas[22].



Supplementary figure A: The Dunn index is shown on the y-axis, and on the x-axis the number of groups is shown. The Dunn index should be maximized for an optimal number of groups. The red line represents six groups, which is the number of groups used in our analysis.



Supplementary figure B: flow diagram showing the in- and exclusion of participants in the current study.

CHAPTER 7

Cerebral microbleeds are not associated with postoperative delirium and postoperative cognitive dysfunction in older individuals

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ABSTRACT

Background: Cerebral microbleeds (CMB) occur in the context of cerebral small vessel disease. Other brain MRI markers of cerebral small vessel disease are associated with the occurrence of postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), but for CMB this is unknown. We aimed to study the association between CMB and the occurrence of POD and POCD in older individuals.

Methods: The current study consists of 65 patients (72±5 years) from the BIOCOG study, which is a prospective, observational study of patients who underwent an elective surgery of at least 60 minutes. Patients in the current study received a preoperative cerebral MRI scan including a 3D susceptibility-weighted imaging sequence to detect CMB. The occurrence of POD was screened for twice a day until postoperative day 7 by using the DSM-5, NuDesc, CAM, and CAM-ICU. The occurrence of POCD was determined by the reliable change index model at 7 days after surgery or discharge, respectively, and 3 months after surgery. Statistical analyses consisted of logistic regression adjusted for age and gender.

Results: A total of 39 CMB were detected in 17 patients (26%) prior to surgery. POD occurred in 14 out of 65 patients (22%). POCD at 7 days after surgery occurred in 11 out of 54 patients (20%) and in 3 out of 40 patients at the 3 month follow-up (8%). Preoperative CMB were not associated with the occurrence of POD (OR (95%-CI): 0.28 (0.05, 1.57); p=0.147) or POCD at 7 days after surgery (0.76 (0.16, 3.54); p=0.727) or at 3 months follow-up (0.61 (0.03, 11.64); p=0.740).

Conclusion: We did not find an association between preoperative CMB and the occurrence of POD or POCD.

INTRODUCTION

Postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) occur commonly, particularly in older patients who have multimorbidity. Delirium in general is an acute condition characterized by a deterioration of attention, cognition and awareness that cannot be fully accounted for by a pre-existing neuropsychiatric disease. It might be associated with disturbances of arousal, sleep-wake cycle and affection [1]. Occurrence of POD is associated with a poor outcome and an increased risk of POCD [2, 3]. POCD consists of impairments in memory and executive functioning after surgery that tend to persist over time [4]. POD and POCD have a large incidence (POD (15-53%); POCD (10-54%)) and are currently clinically more recognized due to an increased awareness [5, 6]. Both POD and POCD are associated with a reduced quality of life, longer hospital stay, increased mortality and higher healthcare costs [7].

The exact underlying pathophysiological mechanisms of POD and POCD are still unclear, but certain structural brain changes on magnetic resonance imaging (MRI) are associated with an increased risk [8]. For instance, MRI markers of cerebral small vessel disease like white matter hyperintensities (WMH) are associated with the occurrence of POD and POCD [8]. However, for other MRI markers of cerebral small vessel disease, especially cerebral microbleeds (CMB), this is still unknown [8]. CMB occur in the context of aging and in cerebral small vessel disease and they are associated with an increased risk of cognitive decline and dementia [9]. We therefore aimed to study the association between CMB and the occurrence of POD and POCD in older patients.

METHODS

Study participants

The Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BIOCOG) study is a large prospective multicenter observational study, which aims to establish valid biomarkers for risk analysis and clinical outcome prediction of POD and POCD in a sample of elderly (≥65 years) patients presenting for major elective surgery (>60 min duration) at the Charité - Universitätsmedizin Berlin, Germany [10]. Further inclusion criteria were European descent, the ability to give informed consent and to undergo neuropsychological testing, and eligibility for MRI. Patients were excluded when the Mini-Mental-State-Examination was ≤23 points, when homeless or the patient would not be reachable for follow-up, when participating in another prospective interventional clinical study during hospital stay, when accommodated in an institution due to an official or judicial order, in case of neuropsychiatric morbidity, anacusis or hypoacusis, intake of centrally acting medication or any other condition which could interfere with neurocognitive testing. Overall, 1033 patients were included into the BIOCOG study. Within the BIOCOG study, our substudy was performed consisting of 66 patients who received a 3D susceptibility-weighted imaging (3D SWI) sequence in their preoperative MRI scan. Our substudy was performed in consecutive included patients between April 2016 and October 2017. One patient was excluded due to missing primary endpoints of the BIOCOG study, leaving 65 patients for our current study.

The study was approved by our medical ethics committee (Ethikkommission der Charité – Universitätsmedizin Berlin, EA2/092/14) and all patients signed an informed consent form. This clinical trial meets the requirements set out by the ICH-GCP and Declaration of Helsinki.

Clinical data

Baseline patients demographics (age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, Mini-Mental State Examination (MMSE)) and cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, history of stroke, coronary and chronic heart disease) were obtained at the day of inclusion at a pre-surgery interview and by viewing the medical records. Medical history data were collected by either study physicians (anesthesiologist or anesthesiologist in training) or additional trained research staff (study nurses, psychology or MD students)

under supervision of a physician. Clinical history and long-term medication data were assessed in a structured interview. Medical records were reviewed for additional data whenever a patient had presented in the clinic before. Whenever possible, records of medical findings and physician's letters were obtained from the patients and screened for additional data. Post-hoc, all clinical data have been reviewed and were validated by a study physician (anesthesiologist).

All patients received a preoperative neurocognitive assessment by trained medical staff which consisted of a CANTAB battery [11] (Paired Associates Learning, Verbal Recognition Memory, Simple Reaction Time, Spatial Span Time) as well as Trail Making Tests and Grooved Pegboard.

Peri- and postoperative parameters (surgical time, type of surgery, postoperative complications, intensive care unit (ICU) and in-patient duration, in-patient deaths) were documented by trained medical staff.

POD and POCD

Detection of POD was conducted by screening of the patients twice a day until postoperative day 7 or discharge using the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1], NuDesc [12], CAM [13], and CAM-ICU [14]. POD is defined according to DSM-5 criteria. Patients were considered delirious in case of ≥ 2 cumulative points on the NuDesc and/or positive CAM score and/or positive CAM-ICU score and/or patient chart review that shows description of delirium (e.g., confused, agitated, drowsy, disorientated, delirious, received antipsychotic therapy).

At postoperative day 7 or discharge, respectively, as well as three months after surgery, patients received a follow-up neurocognitive assessment to detect POCD (Fig 1), which was calculated for the whole BIOCOG cohort by the reliable change index model as published by Rasmussen et al. [15]. This method corrects for learning effects and natural variability in repetitive cognitive testing by use of data from the BIOCOG non-surgical control group (n=114), that also served to provide normative data. We imputed missing data according to random forest (technical, organizational or physiological problems) or worst case imputation paradigm (signs of cognitive impairment) whenever parts of the cognitive testing were not performed [16].

MRI scans

MRI scans were performed at the Berlin Institute for Advance Neuroimaging (BCAN), Germany. Scans were acquired in one TIM Trio 3T MRI (Siemens, Erlangen, Germany) with a 32-channel head coil. All patients received a preoperative brain MRI scan with a standardized scan protocol including a 3D susceptibility weighted gradient echo MRI sequence (SWI, voxel size: 0.7×0.6×1.2 mm; field of view: 230×180 mm in 120 transversal slices; TE: 20 ms; TR: 28 ms, 15˚ flip angle) to detect CMB, a fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE/inversion time = 4800/388/1800 ms; voxel size = 0.49x0.49x1.00mm^3) and a 3D T1 magnetization-prepared rapid acquisition gradient echo sequence (TR/TE = 2500 / 4.77 ms; voxel size = 1.00 x 1.00 x 1.00 mm^3) to detect presence of lacunar infarcts and WMH. Additionally, patients had a follow-up MRI scan 3 months after surgery with an identical scan protocol.

MRI processing steps

CMB and presence of lacunar infarcts were determined by a (neuro-)radiologist (JB) who was blinded to patient outcomes. CMB were further categorized as lobar or deep CMB according to the Microbleed Anatomical Rating Scale [17]. Presence of lacunar infarcts was determined according to the STRIVE criteria [18]. WMH volume was determined by an automated method: the lesion prediction algorithm [19] of the lesion segmentation toolbox (LST) version 2.0.15 (www.statistical-modeling.de/lst.html), for statistical parametric mapping software (SPM12, Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/doc/), running on Matlab version R2016b. If present, cortical infarcts were manually segmented and subtracted from the WMH probability maps before calculating the WMH volume. All WMH probability maps were checked for accurate segmentation by a trained researcher (IK).

Statistical analysis

Results for normally distributed data are presented as arithmetic mean ± standard deviation (SD) and for non-normal distributed data as median with quartiles. Categorical data are summarized as frequencies in %. Differences in baseline patient demographics were assessed using Fisher's exact tests for category variables, and Mann-Whitney U tests for contiguous data. Logistic regression models adjusted for age and sex were used to determine the odds ratio's for occurrence of POD and POCD in patients with versus without preoperative CMB. Similar analyses were

used for postoperative CMB patients. In exploratory analyses for POD and POCD, we performed the logistic regression models separately for lobar and deep CMB. Odds ratios (OR) are shown with 95%-confidence intervals (CI). A two-tailed p-value <0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics, Version 25.

RESULTS

Study population

A total of 17 out of 65 patients (26%) had 39 CMB prior to surgery. Of these, 13 patients showed only lobar CMB, 2 patients had only deep CMB and both types of CMB were seen in 2 patients (S1 Table). Baseline patient demographics, peri- and postoperative parameters and cardiovascular risk factors did not differ between the patients with preoperative CMB versus patients without preoperative CMB (Table 1). Types of surgery are shown in S2 Table. Two patients received spinal anesthesia, all other patients were put under general anesthesia. Out of the 65 included patients, all had POD screening, 54 (83%) had a follow-up neurocognitive assessment for POCD at 7 days and 40 (62%) at 3 months after surgery. Results of the cognitive tests at baseline and after three months are presented in the S1 Text. A total of 34 patients (52%) received a follow-up brain MRI scan at 3 months. WMH volumes (p=0.002) were significantly higher in patients with CMB.

Table 1: Patient characteristics and peri- and postoperative parameters.

	Total (n = 65)	**Patients without CMB (n = 48)**	**Patients with CMB (n = 17)**	**P-value**
		Demographics		
Age [years]	72.2 ± 5.2	71.7 ± 5.2	73.7 ± 5.0	0.162
Male gender	30 (46%)	23 (48%)	7 (41%)	0.779
Body Mass Index [kg/m^2]	26.8 ± 3.9	26.9 ± 3.8	26.6 ± 4.3	0.314
ASA score				**0.466**
I	1 (2%)	0	1 (6%)	
II	41 (63%)	33 (69%)	8 (47%)	
III	22 (34%)	14 (29%)	8 (47%)	
IV	0	0	0	
V	1 (2%)	1 (2%)	0	

Table 1: Continued

	Total (n = 65)	Patients without CMB (n = 48)	Patients with CMB (n = 17)	P-value
Baseline MMSE	29 (28, 30)	29 (27, 30)	29 (28, 30)	0.760
Peri- and postoperative parameters				
Surgical time [min]	105 (67, 208)	106 (71, 214)	104 (60, 173)	0.502
Intra-abdominal/-thoracic surgery	16 (25%)	13 (27%)	3 (18%)	0.528
ICU duration [days]	0 (0, 0)	0 (0, 0)	0 (0, 1)	0.724
In-patient duration [days]	7 (4, 9)	7 (4, 9)	6 (4, 10)	0.851
Deceased during hospital stay	2 (3%)	2 (4%)	0	1.000
Cardiovascular risk factors				
Hypertension	41 (63%)	28 (58%)	13 (77%)	0.247
Stroke in history	6 (9%)	3 (6%)	3 (18%)	0.179
Diabetes	14 (22%)	11 (23%)	3 (18%)	0.745
Coronary and chronic heart disease	10 (15%)	6 (13%)	4 (24%)	0.434
Hypercholesterinemia	25 (39%)	15 (31%)	10 (59%)	0.080
MRI markers of cerebral small vessel disease				
WMH volume [ml]	2.1 (0.7, 5.0)*	1.7 (0.5, 3.8)*	6.4 (1.4, 20.2)	**0.002**
Patients with lacunar infarcts	10 (15%)	5 (10%)	5 (29%)	0.111

Continuous variables in mean ± standard deviation (normal distributed data) and median (25%-75% percentiles (non-normal distributed data), frequencies with n (%); ASA, American Society of Anesthesiologists; ICU, Intensive Care Unit; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensities. *one patient had to be excluded from analysis due to previous neurosurgery.

The association of preoperative CMB and occurrence of POD and POCD

POD occurred in 14 out of 65 patients (22%), POCD at 7 days after surgery in 11 out of 54 patients (20%) as well as in 3 out of 40 patients at the 3 month follow-up (8%). Preoperative CMB were not associated with the occurrence of POD (OR (95%-CI): 0.28 (0.05, 1.57); p=0.147) or POCD at 7 days after surgery (0.76 (0.16, 3.54); p=0.727) or at 3 months follow-up (0.61 (0.03, 11.64); p=0.740) (Table 2). In exploratory analysis considering lobar and deep CMB separately, no associations were found with POD or POCD at 7 days or 3 months after surgery.

Patients with preoperative CMB and new CMB after surgery

Of the 34 patients with follow-up MRI scans, 11 patients had preoperative CMB, whereas 4 of these patients (36%) developed new CMB after surgery (S1 Table). No new CMB occurred after surgery in patients without preoperative CMB. Postoperative presence of CMB was not significantly associated with POD (1.15 (0.08, 17.43; p=0.918) or POCD at 7 days (2.66 (0.26, 27.35); p=0.412) or at 3 months (0.34 (0.01, 8.53); p=0.512) after surgery.

Table 2: The association between preoperative CMB and occurrence of POD and POCD.

	Patient without CMB (n = 48)	Patients with CMB (n = 17)	OR (95% CI)	P-value
POD	12 (25%)	2 (12%)	0.278 (0.049, 1.565)	0.147
POCD 7 days after surgery*	8 (21%)	3 (19%)	0.761 (0.164, 3.535)	0.727
POCD 3 months after surgery*	2 (7%)	1 (10%)	0.606 (0.032, 11.637)	0.740

*calculated for 54 patients with POCD assessment after 7 days and 40 patients with POCD assessment after 3 months. Frequencies with n (%); CI, confident interval; OR, odds ratio; POD, postoperative delirium; POCD, postoperative cognitive dysfunction.

DISCUSSION

Our study showed that the presence of preoperative or postoperative CMB was not associated with occurrence of POD or POCD in older individuals. Our study is the first to investigate this association.

CMB are one of the MRI markers for cerebral small vessel disease [20]. Only few previous studies have examined brain MRI markers of cerebral small vessel disease in relation to POD or POCD, and to the best of our knowledge, no study has yet analyzed CMB in post-operative cognitive disorders. A recent review summarized studies investigating associations between POD/POCD and WMH/lacunar infarcts, which are other markers of cerebral small vessel disease [8]. They reported on six studies on the association between POD/POCD and WMH with a total of 504 participants that yielded contradictory results [21-26]. Especially the largest study with 146 participants did not report a significant association between WMH and POD [27]. Previous studies with a total of 71 participants on preoperative WMH and POCD have shown that

WMH were related to POCD [23, 24]. No previous studies have assessed presence of lacunar infarcts as a separate measure. These results have suggested that brain MRI markers for cerebral small vessel disease might play a role in the underlying pathophysiological mechanisms of POD and POCD.

Our findings show that neither preoperative nor (new) postoperative CMB were associated with occurrence of POD or POCD. Preoperative CMB might therefore not play a role in the pathogenesis of POD or POCD. However, previous studies did show an association between other brain MRI markers of cerebral small vessel disease and POD or POCD [8]. Possible explanations for these discrepancies might be that other markers of cerebral small vessel disease are stronger preoperative predictors of POD and POCD risk. Other factors that might have played a role are our limited sample size, reducing the power to detect an association, and the relatively low prevalence of CMB in comparison to other markers for cerebral small vessel disease, such as presence of WMH. The prevalence of CMB was 26% in our cohort, which is somewhat higher compared to population based cohorts like the Rotterdam Study (19% [26]) and the Framingham Heart Study (8% [28]). However, it should be taken into account that our patients were approximately one decade older than patients in the Rotterdam study and Framingham study, while age constitutes a risk factor for CMB [29].

To the best of our knowledge, no previous studies have assessed the relation between CMB progression and occurrence of POD or POCD. However, one previous study has assessed the relation between progression of other markers of cerebral small vessel disease (WMH and infarcts) and occurrence of POCD [25]. They have shown that progression of WMH and lacunar infarcts after surgery was not related to postoperative cognitive status. Nevertheless, Patel and colleagues investigated a sample of patients presenting for cardiac surgery. New infarcts after cardiac surgery are thought to be of thrombembolic origin, although pre-operative atherosclerotic burden has been suggested to increase the risk for new post-operative brain infarcts [30]. On the other hand, intraoperative hypoperfusion is thought to cause perioperative infarcts in patients with preexisting cerebral small vessel disease, which might be similar for surgical procedures other than cardiac surgery [31]. Furthermore, we have found no new CMB after surgery in patients without preoperative CMB, but 4 out of 11 patients with preoperative CMB developed new CMB after surgery. Within

these patients, it is unknown whether progression of CMB is related to progression of cerebral small vessel disease over time or is related to the operation.

Strengths of our study are the pre- and postoperative performed brain MRI scans that enabled us to systematically analyze pre- and postoperative CMB. Furthermore, the assessment of POD was done twice daily after surgery, included multiple screening tools and a chart review, which has increased our sensitivity to detect POD. We have assessed POCD according to the latest guidelines as proposed by Rasmussen et al. [15]. A limitation of our study might be the relatively small number of patients as our study was performed as a substudy. It may further be population biased as only a relatively small number of patients of the overall BIOCOG cohort were analyzed. This might reduce the power to detect an association between CMB and occurrence of POD or POCD. However, there are no previously published studies addressing the association between CMB and the occurrence of POD or POCD. Another limitation might be the relatively low number of participants at the 3 month follow-up for the assessment of POCD (62%) and for the brain MRI (52%). Also, the patients who were lost to follow-up might have been suffering from a worse postoperative cognitive and physical status compared to the patients that returned for follow-up. This could have resulted in some selection bias. Finally, one should consider that patients in our sample have rarely been admitted to the ICU for more than 24 hours. Thus, overall post-operative physical stress in our sample was probably low. This might reflect a relatively low incidence of postoperative triggers for cognitive disorders in our study. The majority of patients in our study might have not developed POD or POCD due to the lack of triggers. Taken together, these factors might have led to an underestimation of the effect of CMB on occurrence of POD or POCD.

In conclusion, we did not find an association between preoperative CMB and the occurrence of POD or POCD.

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SUPPLEMENTARY MATERIAL

Table S1: Distribution of pre- and postoperative counts of CMB

Patients	Preoperative CMB	Postoperative CMB
1	10 (lobar)	12 (lobar)
2	5 (lobar/deep)	5 (lobar/deep)
3	5 (lobar)	5 (lobar)
4	3 (lobar/deep)	5 (lobar/deep)
5	2 (lobar)	3 (lobar)
6	1 (lobar)	3 (lobar/deep)
7	1 (lobar)	1 (lobar)
8	1 (lobar)	1 (lobar)
9	1 (lobar)	1 (lobar)
10	1 (lobar)	1 (lobar)
11	1 (lobar)	1 (lobar)
12	1 (lobar)	-*
13	1 (lobar)	-*
14	2 (lobar)	-*
15	1 (deep)	-*
16	2 (lobar)	-*
17	1 (deep)	-*

Only patients with CMB shown. Rows represent counts of CMB in each single patient. *No MRI scan due to loss to follow-up.

Table S2: Types of surgery.

Types of surgery
Hemihepatectomy 4x
Debulking surgery for ovarian cancer 2x
Pylorus-preserving pancreaticoduodenectomy 3x
Laparoscopic hysterectomy and adnectomy 2x
Laparoscopic IPOM
Orbita biopsy
Decompression L4/5 + Sacrum biopsy
Decompression L2-4 3x
Sequestrectomy
Parathyroidectomy
Spondylodesis C3-6
Orbita excision
Tooth extraction
Total knee arthroplasty 12x
Lumpectomy 2x
Femoral-popliteal bypass
Laparoscopy and HIPEC in mesothelioma
Axillary cancer removal
Laparoscopic parotidectomy
Penile implant change
Total hip arthroplasty 8x
Prostatectomy 4x
FESS
Bladder resection
Open kidney tumor excision
Laser ablation rhinophyma
VATS + atypical resection 2x
Sacropexy 3x
Ureterorenoscopy
Laminectomy C4-7
Tracheoscopy

Results of the cognitive tests at baseline and after three months.

Baseline cognitive performance for the whole sample is summarised with median, interquartile and full range. Test performance for patients without cognitive complications, POD and POCD have been summarised with mean and standard deviation.

Repeated measures ANOVA was conducted to test for effects of time, cognitive disorder (POD, POCD) and interaction. SRT latency and time for TMT-B and GPT were log-transformed prior to statistical analysis.

Table S-I summarises cognitive performance in the complete sample. Table S-II summarises baseline test performance in patients with and without postoperative cognitive disorders. Figures S1-S3 display cognitive performance in each test before and after surgery. Significant effects of time, diagnosis or an interaction were found spuriously. TMT-B performance differed between patients without and with POCD ($F_{1,32}$=6.3, p=0.018). The number of correctly recognised items in the VRM was lower at follow-up ($F_{1,38}$=4.4, p=0.043). GPT performance was worse in POD patients at follow-up ($F_{1,38}$=5.3, p=0.028).

Table S-I: Baseline cognitive function in the complete sample

	n	Median	Interquartile range	Min.-max. range
SRT (latency in ms for correct trials)	64	299	258-367	197-904
VRM (correct items in immediate free recall)	64	6	5-8	2-11
VRM (correct recognized items in delayed recall)	63	22	20-23	14-24
Span length (items)	65	5	4-5	3-8
PAL (first trial memory score)	63	13	10-16.5	0-26
GPT (completion time in s)	61	89	76-106	53-250
TMT-B (completion time in s)	60	110	84-142	58-294

Table S-II: Mean and standard deviation for cognitive test performance at baseline in patients with POD, POCD and without cognitive disorder

	No cognitive disorder (n=49)	POD (n=14)	POCD (n=3)
SRT (latency in ms for correct trials)	314±82	301±79	323±55
VRM (correct items in immediate free recall)	6.4±2.3	5.7±2.4	5.7±1.2
VRM (correct recognized items in delayed recall)	21.8±2.3	21.3±2.2	21.3±2.9
Span length (items)	5.1±1.0	4.6±0.9	3.7±1.2
PAL (first trial memory score)	14±5	12±5	10±2
GPT (completion time in s)	89±19	98±21	105±4
TMT-B (completion time in s)	113±37	106±32	211±73

The BioCog study used the MMSE to exclude subjects with pre-existing cognitive deficit from enrollment. Although its wide acceptance as a dementia screening tool, the MMSE is not generally recommended as a diagnostic criterion for dementia (Folstein et al. 1975, Tombaugh and McIntyre 1992). It has further been criticized for not excluding patients with probable or mild dementia at values of 26 to 29 points (Perneczky et al. 2006). Based on analysis of cognitive test data, we compared performance in our sample with reference data to estimate the prevalence of preexisting cognitive deficits in our sample.

Compared to reference data of the age group 70-74 years presented by Tombaugh (2004), median performance in our cohort (109.86s) corresponded to the 30-40. percentiles (105-112s) in the general population, suggesting that we investigated a below-average performing population. Holtzer and colleagues presented TMT-B normative data stratified for prevalent or subsequent development of dementia and loss to follow-up. Median performance in our sample was better than mean performance in the robust cohort without subsequent dementia development (148.9s), but performance in our lowest performing cohort (142.49-293.53s) complied with mean performance in subgroups with prevalent (207.5s) or subsequent diagnosis of dementia (186.2s). In our sample, mean TMT-B performance in patients without postoperative cognitive disorder (112.7s) or POD (106.1s) was thus better than expected from Holtzer's normative data on robust subjects. Nevertheless, patients with POCD

already performed much slower at baseline (210.8s), complying with Holtzer's reference value for demented patients.

Thus, we cannot assume that we have excluded with pre-existing mild cognitive deficits from our study. Nevertheless, since POCD in our study was derived from the reliable change index by Rasmussen, its is by definition independent of patients' baseline performance. Furthermore, our sample represents a wide spectrum of age-related cognitive decline found in the general population. We thus assume that selection bias and ceiling effects in cognitive performance (by enrolling only high-performing subjects willing to undergo the strenuous neuroimaging and testing procedures) are not relevant factors leading to our negative result.

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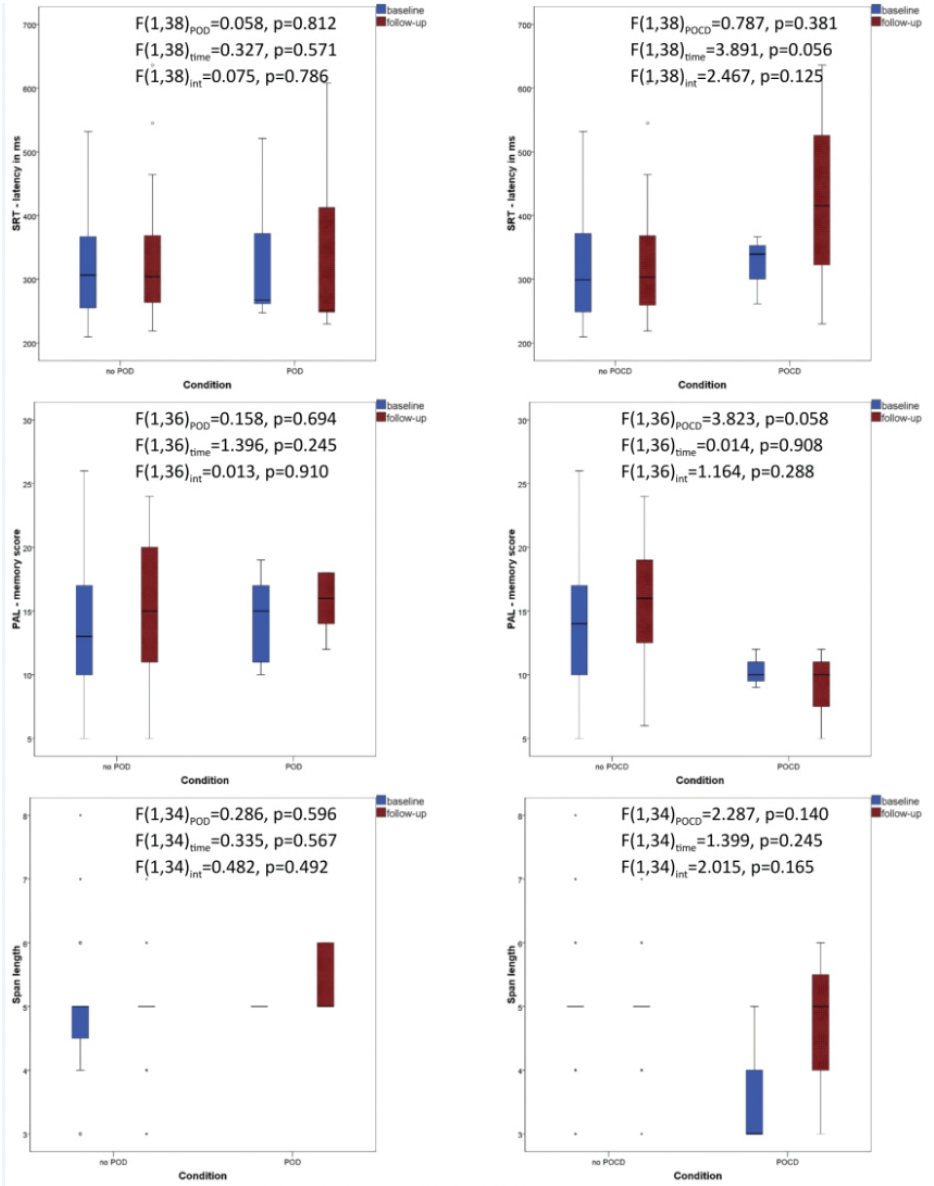

Figure S 1: Results of Simple Reaction Time (SRT), Paired Associate Learning (PAL) and Simple Span Length by diagnosis. Inlays correspond to results from the repeated measures ANOVA.

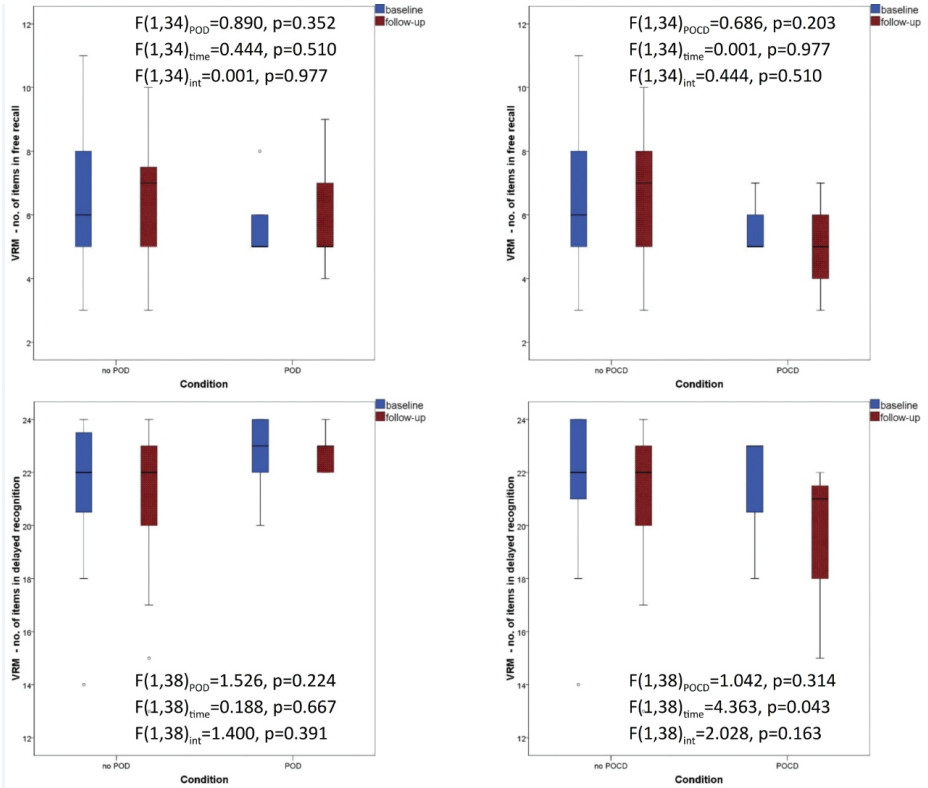

Figure S 2: Results of the Verbal Recognition Memory test (VRM) by diagnosis. Inlays correspond to results from the repeated measures ANOVA.

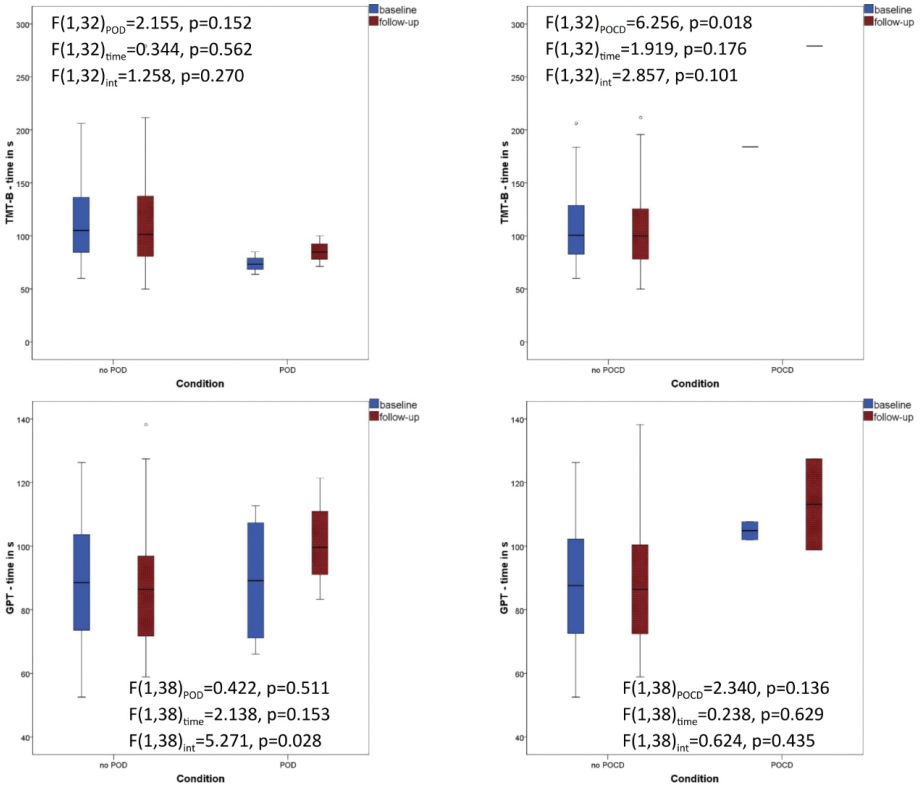

Figure S 3: Results of the Trail Making Test Pt. B (TMT-B) and Grooved Pegboard Test (GPT) by diagnosis. Inlays correspond to results from the repeated measures ANOVA.

CHAPTER 8

Postoperative delirium is associated with postoperative gray matter volume loss and new brain infarcts

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ABSTRACT

Delirium is associated with long-term cognitive dysfunction and with greater brain atrophy. However, it is unclear whether these relationships are causal. Therefore, we investigated postoperative delirium with brain MRIs made before and after the occurrence of surgery and delirium. A total of 299 elderly patients who had major elective surgery and a group of 48 control participants who did not undergo surgery were included. Within the patients group, 37 (12%) developed postoperative delirium. The association between surgery and brain changes, and between postoperative delirium and preoperative to four months postoperative changes in brain volumes, white matter hyperintensities and brain infarcts were investigated. Multiple regression analyses that were adjusted for age, sex, study center, time between measurements and baseline brain volume were performed. Patients showed a greater decrease in gray matter volume than control participants (linear regression: β (95% Confidence Interval (CI)) = -0.44% of intracranial volume (-0.76 to -0.13), p=0.006). In the patient group, delirium was associated with a greater decrease in gray matter volume (β (95%CI): -0.33% of intracranial volume (-0.69 to 0.04)), corresponding to an additional brain volume loss of 5 ml, although this did not reach statistical significance (p=0.08). Furthermore, postoperative delirium was associated with new postoperative brain infarcts (logistic regression: odds ratio (95% CI): 3.3 (1.0 , 10.7), p=0.04). In conclusion, our study suggests that increased progression of gray matter volume loss and occurrence of new brain infarcts in the postoperative period could be part of the underlying structural correlates of long-term adverse outcomes after postoperative delirium.

INTRODUCTION

Delirium is a neuropsychiatric disorder that is characterized by an acute change in attention and awareness[1]. Postoperative delirium is common in older patients, with a reported incidence of 11-51% after major surgery in the immediate postoperative period[2]. Postoperative delirium is a risk factor for long-term cognitive deficits, such as mild cognitive impairment and dementia[3,4]. However, it is unclear whether these relationships are causal and whether this association could be due to postoperative brain changes.

A limited number of neuroimaging studies have been performed that assessed the relation between postoperative delirium and brain changes over time. A study in critically ill patients showed that delirium was associated with a lower brain volume at discharge and three months after discharge[5]. One previous study that performed brain MRI in the immediate postoperative period showed that postoperative delirium was associated with a lower postoperative brain volume[6]. However, no baseline imaging was performed in these studies and therefore the brain changes before and after the occurrence of delirium could not be examined. A small study in cardiac surgery patients showed that postoperative delirium was associated with new brain infarcts in the immediate postoperative period[7].

As previous studies were limited, lacked baseline imaging data or were underpowered, it remains subject of debate whether postoperative delirium is associated with additional brain changes, or whether patients who developed postoperative delirium were already on a trajectory of brain deterioration. Investigating the relation between postoperative delirium and longitudinal brain changes could improve our understanding of postoperative delirium and long-term adverse outcomes.

The aim of the current study was to investigate preoperative to postoperative brain changes, and the association of postoperative delirium with these brain changes. The brain changes that were assessed included brain volumes, white matter hyperintensities and brain infarcts.

METHODS

Study design and participants

This study was part of an observational longitudinal multicenter study that aims to find biomarkers for postoperative delirium and postoperative cognitive dysfunction: the 'Biomarker Development for Postoperative Cognitive Impairment in the Elderly' (BioCog) study, that has been described in detail elsewhere[8]. Patients were invited in two participating centers: Charité Universitätsmedizin Berlin (Berlin, Germany, center 1), and University Medical Center Utrecht (Utrecht, The Netherlands, center 2). Control participants were recruited from general practitioner's offices in Berlin, Germany and in Utrecht, The Netherlands, matched on age and sex on a group level. The study protocol was approved by medical ethical committees from both centers under ethical approval number EA2/092/14 (center 1) and 14/469 (center 2). All participants signed informed consent. Inclusion criteria for patients and control participants were: (1) ≥ 65 years of age, (2) a mini-mental state exam (MMSE) score of ≥ 24, (3) ability to undergo MRI scanning and cognitive testing. The patient group was scheduled for major surgery of ≥ 60 minutes, the control group was not scheduled for surgery in the upcoming 12 months.

Procedure

Patients and control participants were invited for a baseline visit (patients: prior to surgery), which included a brain MRI scan, MMSE and clinical assessments on medical history and vascular risk factors. Trained researchers administered the MMSE, and questionnaires. The preoperative American Society of Anesthesiologists (ASA) score for patients was scored by anesthesiologists (in training). Three months after surgery (control participants: three months after baseline), all participants were invited for a follow-up visit which included a second brain MRI scan, and questionnaires.

Delirium assessment

Delirium was defined according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria[1]. Following surgery, trained researchers performed a delirium assessment twice daily until the seventh postoperative day or until discharge whichever came first, using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[9] and the nursing Delirium Screening Scale (Nu-DESC)[10]. In addition, a validated chart review[11] was performed daily to screen for additional signs of delirium. Patients were considered delirious in case of ≥ 2

cumulative points on the Nu-DESC and/or a positive CAM-ICU score and/or patient chart review that showed descriptions of delirium (e.g., confused, agitated, drowsy, disorientated, delirious, receiving antipsychotic therapy).

Brain MRI scans

Participants were scanned on a 3T Magnetom TrioTim (Siemens Healthcare, Erlangen, Germany) MRI scanner (center 1) or a 3T Achieva (Philips Healthcare, Best, The Netherlands) (center 2). The MRI scanning protocol was standardized between both centers and consisted of a 3-dimensional (3D) T1-weighted sequence (voxel size 1.0 x 1.0 x 1.0 mm^3; center 1: repetition time [TR]/echo time [TE] 2500/4.77 ms; center 2: TR/TE 7.9/4.5 ms) a fluid-attenuated inversion recovery (FLAIR) sequence (center 1: TR/TE/inversion time 4800/388/1800 ms; voxel size 0.49 x 0.49 x 1.00 mm^3; center 2: TR/TE/inversion time 4800/125/1650 ms; voxel size 1.11 x 1.11 x 0.56 mm^3), and a diffusion-weighted image (center 1: n.a.; center 2: (voxel size = 0.96 x 1.19 x 4.00 mm^3; TR/TE 3294/68 ms) for visual inspection only.

MRI processing steps and analysis

The MRI processing method that was used is relatively robust for scanner differences[12] and has previously been described in another BioCog substudy[13]. All processing steps were performed using statistical parametric mapping version 12 (SPM 12; Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/doc/)) for Matlab (The MathWorks, Inc., Natick, Massachusetts, United States). In short, 3D FLAIR images were registered to 3D T1-weighted images. White matter hyperintensity probability maps were calculated on the registered 3D FLAIR images using the lesion segmentation toolbox (LST; version 2.0.15, www.statistical-modeling.de/lst.html) and the lesion prediction algorithm (LPA)). A lesion filling method from the LST was performed on the T1-weighted images. The filled T1-weighted images were segmented in gray matter, white matter, and cerebrospinal fluid, and intracranial volume was estimated by the computational anatomy toolbox (CAT12), version r1155[14]. All segmentations were visually checked by a trained researcher (IK), supervised by a neuroradiologist (JB). All brain volumes were expressed as a percentage of the intracranial volume of that time point, for example, baseline gray matter volumes are shown as a percentage of the baseline intracranial volume (relative brain volume). Differences in brain volumes (delta brain volume) between time points are shown as the crude difference between the relative brain volumes of baseline and follow-up

measurements. Cerebral infarcts were scored by two neuroradiologists (TW and JB), by use of the T1-weighted, FLAIR and DWI images.

Statistical analysis

Demographics of patients and control participants, and within the patients group of patients with and without delirium, were compared by an independent-samples T-test for continuous, normally distributed data, by a chi-square for categorical data or by a Mann-Whitney-U test for continuous skewed data.

Preoperative to postoperative changes in brain volume or white matter hyperintensity volume (delta volume), were assessed by linear regression analysis with volume change (delta volume) as the dependent variable. All linear regression analyses were adjusted for age, sex, time between measurements, center, and baseline brain volume. For example, in gray matter volume, the analysis was adjusted for baseline gray matter volume. The association between delirium and new postoperative cerebral infarcts was studied with logistic regression analysis with new brain infarcts as the dependent variable, and adjustments for age, sex, time between measurements, and center.

In secondary analyses, brain volume changes in patients without delirium were compared to the control participants, and brain volume changes in patients with delirium were compared to control participants by linear regression analyses that were adjusted for the same confounders.

Further, to assess whether the occurrence of new brain infarcts could explain an association between postoperative delirium and a change in gray matter volume, a mediation analysis was performed, according to the method by Preacher and Hayes[15]. Hence, the analysis of delirium on preoperative to postoperative change in gray matter volume was adjusted for new brain infarcts, in addition to all previously named confounders (age, sex, time between measurements, center, baseline gray matter volume). The difference and relative change in the effect estimates of postoperative delirium on the preoperative to postoperative change in gray matter volume was studied.

All statistical analyses were performed in IBM SPSS Statistics version 25. A p-value <0.05 was considered statistically significant.

RESULTS

In total, 299 patients and 48 control participants were included in the present study, who all had a preoperative and postoperative MRI scan (see supplementary material figure A for a flowchart of the reasons for in- and exclusion).

Patients and control participants: demographics

Patients and control participants showed no differences in the distribution of age and sex (table 1). Patients more often had hypertension (table 1). Median time between measurements in the total group of patients was longer than in the group of controls (128 (interquartile range 98 to 147) days versus 108 (interquartile range 91 to 133) days, p=0.02), indicating that this group had a longer timeframe to develop brain changes between both measurements.

Table 1: Demographics of the total group of patients and non-surgical control participants

	Patients (n=299)	Control participants (n=48)	P-value
Age	72 (5)	71 (5)	0.76
Sex (female)	101 (34%)	21 (44%)	0.20
Study center			<0.001
Center 1	155 (52%)	8 (17%)	
Center 2	144 (48%)	40 (83%)	
Baseline MMSE	29 (28 – 30)	29 (28 – 30)	0.58
Vascular factors			
Hypertension	175 (59%)	17 (35%)	0.003
Hyperlipidemia	102 (34%)	13 (33%)[a]	0.89
BMI	27 (24 – 29)	26 (24 – 29)	0.19
Diabetes	52 (17%)	8 (17%)	1.00
Current smoker	32 (11%)	6 (13%)	0.81
History of TIA / stroke	28 (9%)	5 (13%)[a]	0.57

Data represent n (percentage), mean (SD) or median (interquartile range). An independent samples T-test was performed on continuous data, and an Mann-Whitney U test for non-normal distributed data. A chi-square comparison of two groups was performed for categorical data. MMSE: mini-mental state exam. [a]% missing hyperlipidemia and history of TIA / stroke in controls: 17%.

Patients with and without postoperative delirium: demographics

Within the patient group, 37 subjects (12%) developed postoperative delirium during the first seven days after surgery. Patients with postoperative delirium were generally older, had a higher ASA score and were more often scheduled for cardiac surgery than patients without postoperative delirium (table 2). No differences were found in the median follow-up time between the preoperative and postoperative MRI scan in patients with and without postoperative delirium (delirium: 116 (interquartile range 99 to 162) days; no delirium: 114 (interquartile range 97 to 147) days, p=0.36). Patients with postoperative delirium had a longer median duration of hospitalization (delirium: 9 (interquartile range 7 to 14) days, no delirium: 4 (interquartile range 2 to 7) days, p<0.01). Furthermore, patients with postoperative delirium were more often admitted to the ICU (delirium: 46% (n=17), no delirium: 16% (n=41)). Postoperative delirium occurred in 16% of the patients that had a baseline MRI scan. Of the patients that came back for follow-up MRI, delirium occurred in 12%, indicating a greater loss to follow-up in the group with postoperative delirium (supplementary material figure A).

Preoperative to postoperative brain changes in patients and control participants

Compared to control participants, patients showed a larger decrease over time in total brain volume (β (95% Confidence Interval (CI)) = -0.47 % Intracranial volume (ICV) (-0.76 to -0.19), p=0.001), and gray matter volume (β (95% CI) = -0.47 % ICV (-0.79 to -0.16), p=0.003) (table 3). Further, compared to control participants, patients did not show a larger change over time in white matter volume or white matter hyperintensity volume (table 3).

Preoperative to postoperative brain changes in patients with postoperative delirium

Delirium was associated with a greater decrease in preoperative to postoperative gray matter volume (β (95%CI) = -0.33 % ICV (-0.69 to 0.04)), corresponding to approximately 5 ml, although this association did not reach statistical significance (p=0.08) (table 4). White matter volume and white matter hyperintensity volume showed no difference over time between patients with and without postoperative delirium. Patients with postoperative delirium had a higher odds for a new brain infarct in the postoperative period than patients without postoperative delirium (delirium: 12% (n=5), no delirium: 4% (n=11), OR (95% CI): 3.3 (1.0 to 10.7), p=0.04).

Table 2: Demographics of patients with postoperative delirium and without postoperative delirium

	Postoperative delirium (n=37)	**No postoperative delirium (n=262)**	**P-value**
Age	73 (3)	71 (5)	0.04
Sex (female)	14 (38%)	87 (33%)	0.58
Study center			0.49
Center 1	17 (46%)	138 (53%)	
Center 2	20 (54%)	124 (47%)	
Preoperative MMSE	28 (27 – 30)	29 (28 – 30)	0.09
Preoperative ASA			0.02
I	2 (5%)	21 (8%)	
II	19 (51%)	171 (65%)	
III	16 (43%)	70 (27%)	
Type of surgery			0.01
Cardiac	10 (27%)	24 (9%)	
Gastro-intestinal / Abdominal	14 (38%)	85 (33%)	
Orthopedic	7 (19%)	87 (34%)	
Other*	6 (16%)	66 (25%)	
Vascular factors			
Hypertension	22 (60%)	153 (59%)	1.00
Hyperlipidemia	15 (41%)	87 (34%)	0.46
BMI	26 (23 – 28)	27 (24 – 29)	0.16
Diabetes	8 (22%)	44 (17%)	0.49
Current smoker	3 (8%)	29 (11%)	0.82
History of TIA / stroke	7 (19%)	21 (8%)	0.06

Data represent n (percentage), mean (SD) or median (interquartile range). An independent samples T-test was performed on continuous data, and an Mann-Whitney U test for non-normal distributed data. A chi-square comparison of two groups was performed for categorical data. *Other types of surgery: plastic, breast, ear nose throat, endocrine, jaw.

MMSE: mini-mental state exam. ASA: classification of disease severity for the American Society of Anesthesiologists. BMI: body-mass index. TIA: transient ischemic attack. POCD: postoperative cognitive dysfunction at time of the postoperative MRI scan.

Table 3: Preoperative to postoperative brain changes in patients and non-surgical controls

	Patients			**Control participants**			**Beta (95% CI)**
	Preoperative	Postoperative	Δ	Preoperative	Postoperative	Δ	
Total brain	72.1 (2.8)	71.8 (2.7)	-0.3 (0.9)	72.0 (3.2)	72.2 (3.2)	0.2 (0.8)	-0.45 (-0.74 – -0.17)[a]
Gray matter	39.5 (2.0)	39.3 (2.0)	0.0 (0.4)	39.7 (2.0)	40.0 (2.0)	0.1 (0.2)	-0.44 (-0.76 – -0.13)[b]
White matter	32.6 (2.0)	32.5 (2.0)	-0.1 (0.7)	32.3 (2.0)	32.2 (2.2)	-0.1 (0.6)	0.01 (-0.22 – 0.24)
Cerebrospinal fluid	27.9 (2.7)	28.2 (2.7)	0.3 (0.9)	28.0 (3.2)	27.8 (3.2)	-0.2 (0.8)	-
WMH	0.17 (0.07 – 0.36)	0.18 (0.08 – 0.39)	0.02 (0.08)	0.34 (0.07 – 0.58)	0.35 (0.08 – 0.48)	0.02 (0.08)	0.01 (-0.02 – 0.04)

Crude volumes are shown as the percentage of the intracranial volume (ICV) of that time point as mean (standard deviation) or median (interquartile range). Beta coefficients of the difference in volume change over time between patients and control participants (in % ICV) are shown with a 95% confidence interval and were adjusted for age, sex, study center, intracranial volume, time between measurements and baseline volume (for example, in gray matter, the beta was adjusted for preoperative gray matter volume). WMH: white matter hyperintensities. Number of included patients and control participants per analysis: brain volumes patients: n=262, control participants: n=42. White matter hyperintensities patients: n=246, control participants: n=44.[a]p=0.002. [b]p=0.006.

Table 4: The association between postoperative delirium and preoperative to postoperative brain changes

	Postoperative delirium			**No postoperative delirium**			**Beta (95% CI)**
	Preoperative	Postoperative	Δ	Preoperative	Postoperative	Δ	
Total brain	71.9 (2.8)	71.3 (2.9)	-0.5 (1.0)	72.1 (2.8)	71.8 (2.7)	-0.3 (0.8)	-0.23 (-0.56 – 0.10)
Gray matter	39.5 (2.1)	39.0 (2.0)	-0.5 (1.1)	39.5 (2.0)	39.3 (1.9)	-0.2 (0.9)	-0.33 (-0.69 – 0.04)[a]
White matter	32.3 (1.9)	32.3 (1.8)	0.0 (1.0)	32.6 (2.0)	32.5 (2.0)	-0.1 (0.7)	0.11 (-0.16 – 0.38)
Cerebrospinal fluid	28.1 (2.8)	28.6 (2.9)	0.5 (1.0)	27.9 (2.7)	28.2 (2.6)	0.3 (0.8)	-
WMH	0.14 (0.05 – 0.42)	0.19 (0.06 – 0.42)	0.0 (0.1)	0.17 (0.08 – 0.36)	0.18 (0.08 – 0.39)	0.02 (0.08)	-0.01 (-0.05 – 0.02)

Crude volume changes are shown as the delta percentage of the intracranial volume of that time point, mean (standard deviation) or median (interquartile range). Beta coefficients of the difference in volume change over time between patients with and without delirium are shown with a 95% confidence interval and were adjusted for age, sex, study center, intracranial volume, time between measurements and baseline volume (for example, in gray matter, the beta was adjusted for preoperative gray matter volume). ICV: intracranial volume. WMH: white matter hyperintensity. Number of included patients and control participants per analysis: brain volumes, delirium: n=28, no delirium: n=234. White matter hyperintensities, delirium: n=26, no delirium: n=220. Perfusion, delirium: n=17, no delirium: n=124. [a]p=0.08

Preoperative to postoperative brain volume changes in patients with and without delirium and control participants

Delirium was associated with a greater decrease over time in total brain volume and gray matter volume than control participants (total brain volume: β (95%CI) = -0.73% ICV (-1.24 to -0.22), p=0.006; gray matter volume: β (95%CI) = -0.81% ICV (-1.38 to -0.24),p=0.006). Patients without postoperative delirium also showed a larger decrease over time in total brain volume and gray matter volume than control participants (total brain volume: β (95%CI) = -0.41% ICV (-0.70 to -0.13), p=0.004; gray matter volume: β (95%CI) = -0.38% ICV (-0.69 to -0.07), p=0.017).

Mediation analysis

Mediation analysis in which the association between postoperative delirium and preoperative to postoperative change in gray matter volume was additionally adjusted for new brain infarcts, showed a difference in the effect estimate of -0.04 (95% CI -0.21 to 0.02). This corresponds to a non-significant decrease in the effect estimate of 13%, indicating that new brain infarcts had a small contribution to the effect of delirium on gray matter volume loss (see figure B of the supplementary material for all mediation coefficients).

DISCUSSION

In summary, we found that surgical patients showed a greater decrease in gray matter volume than control participants. In the patients group, postoperative delirium was associated with a greater decrease in gray matter volume, corresponding to an additional brain volume loss of 5 ml, which was borderline statistically significant. Furthermore, postoperative delirium was associated with new postoperative brain infarcts.

Patients vs. control participants: brain volume loss

Brain volume loss over time is a feature of normal aging[16], however, accelerated progression of brain volume loss is one of the key features of cognitive impairment and dementia[17]. It is therefore crucial to include a control group of the same age in order to compare the results with normal aging. Our results indicate that surgical patients showed more progression of cerebral atrophy in comparison to control participants. These findings may be explained by a higher disease burden in de patients group. Alternatively, this could be due to the consequences of aesthesia

and surgery, which may lead to an immune response with brain volume loss[18,19]. Other explanations may be medication effects, or postoperative complications. Interestingly, the group of patients without delirium still showed a greater atrophy progression compared to the control participants, indicating that this effect was not only driven by delirium.

Delirium vs. no delirium: brain volume loss

Delirium is consistently associated with dementia, although the nature of this relation remains poorly understood[20]. It has been hypothesized that one of the contributing factors to long-term cognitive deficits after delirium could be an increased brain volume loss[6,21,5], but previous studies lacked baseline imaging. Our study was the first to investigate the association between postoperative delirium and preoperative to postoperative brain volume changes. The increased progression of brain volume loss in patients that had postoperative delirium (-0.33% of the ICV in four months), corresponds to a total brain volume loss of -1.2% within one year. This corresponds to a 3-fold increased rate of annual total brain volume as observed in cohorts of community-dwelling older adults[22–26]. A possible explanation for the increased brain volume loss in patients who had postoperative delirium could be persisting neuroinflammation[27]. It has been hypothesized that in elderly people that are vulnerable for delirium, a trigger event could lead to overactivation of already activated microglia[27]. Overactivated microglia may then release cytotoxic substances that ultimately lead to damage of neurons[27], and this may persist despite recovery of the underlying illness, eventually leading to neurodegeneration[27].

Delirium vs. no delirium: brain infarcts

New brain infarcts after major surgery have often been suggested as a possible contributing factor to adverse neurocognitive outcomes, especially after cardiac surgery[7,28]. Our results have confirmed this previous finding in a more heterogeneous group of patients. In population studies on aging in community-dwelling older individuals, 4-5% of the participants develops a new cerebral infarct within a year[24,29,30]. Our results show that in patients who had postoperative delirium, this percentage was 2-3 times higher within four months.

Most of the infarcts found in our study were neurologically silent, and we were therefore unable to determine the exact moment of infarction. It remains unclear whether these new infarcts resulted from surgery, or occurred later in the

postoperative period. A new peri- or postoperative infarct could thus be one of the precipitating factors leading to delirium, or patients with delirium could be more prone to develop new cerebral infarcts in the postoperative period. The association between delirium and new postoperative infarcts indicates that these patients may be at risk for further cognitive deterioration, as presence of (silent) brain infarcts is related to an increased risk of cognitive decline and dementia[31]. Mediation analysis showed that new brain infarcts after surgery had a small contribution to the effect of delirium on gray matter volume loss, indicating that this effect was mostly not driven by the presence of new brain infarcts.

Strengths and limitations

A major strength of this investigation is that brain MRIs were made before the occurrence of delirium, enabling us to rule out that smaller pre-existing brain volumes explained the association of delirium with brain atrophy. To the best of our knowledge, no other previous study has investigated this association. Other strengths of our study include that this was a two-center study that included a large, heterogeneous group of older patients. Furthermore, we included a control group that did not undergo surgery. Brain volumes and white matter hyperintensities were semi-automatically quantified using a pipeline that is robust for center differences. Limitations of this study include that we had a limited group of delirious patients, partly due to a larger loss to follow-up in patients that experienced postoperative delirium. This could have led to an underestimation of the found effect, as delirious patients probably had a higher disease burden. The relatively low frequency of postoperative delirium compared to other studies[2,4,32], was found despite an extensive delirium screening protocol, and may therefore be the result of improved delirium prevention in both centers[33]. Another limitation may be that the time between the measurements differed between the patient and control group, but follow-up time was adjusted for in the statistical analyses.

Conclusion

In conclusion, our study suggests that in patients that were scanned before and after the occurrence of delirium, increased progression of gray matter volume loss and occurrence of new infarcts in the postoperative period could be part of the underlying structural correlates of long-term adverse outcomes after postoperative delirium.

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SUPPLEMENTARY MATERIAL

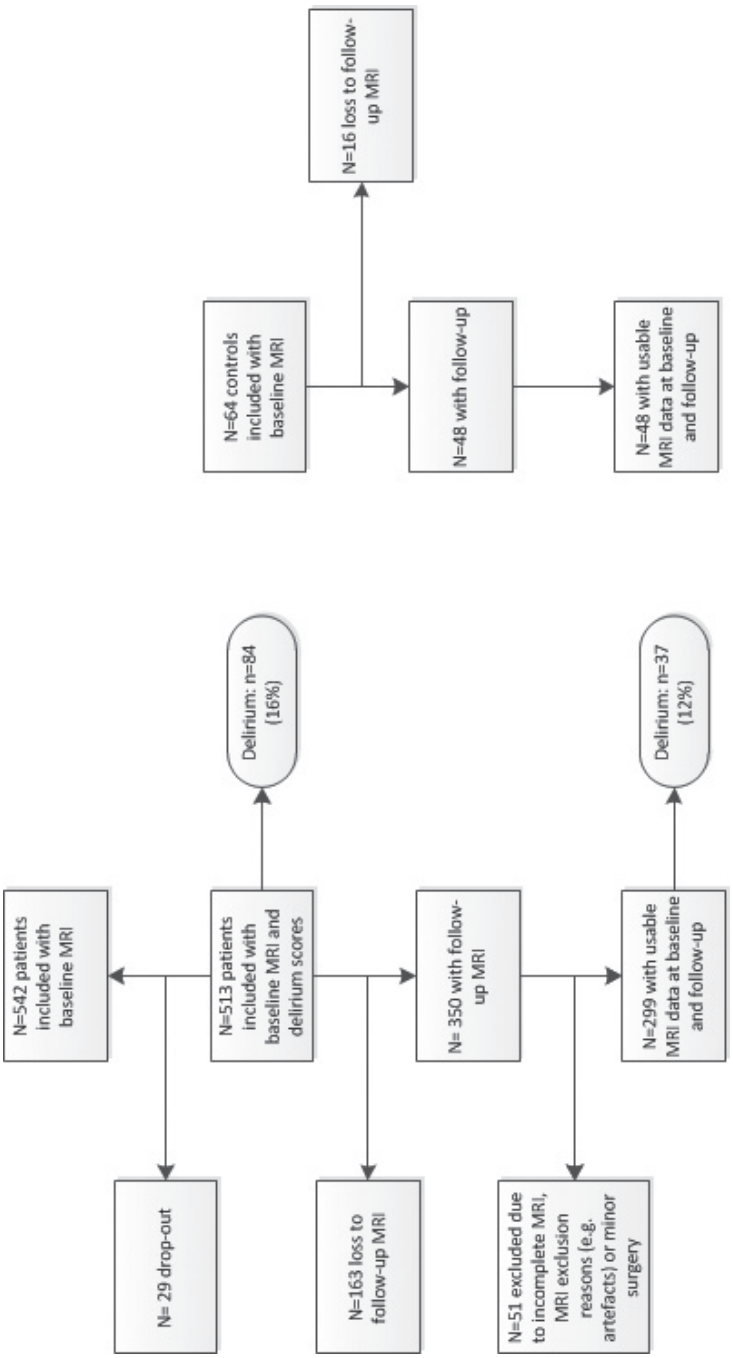

Figure A: Flowchart of patient and control inclusion

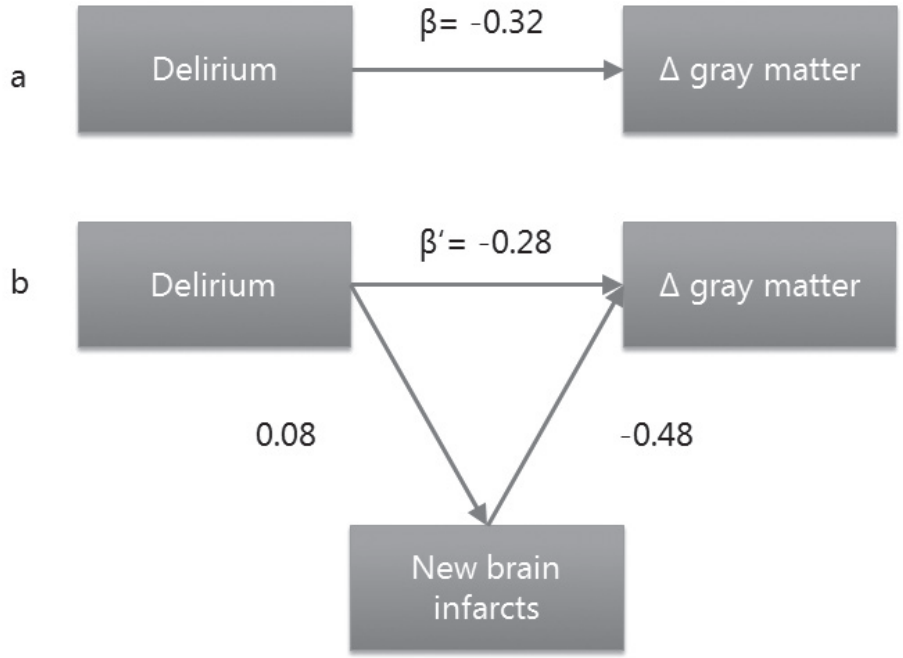

Figure B: Mediation analysis of new brain infarcts on the effect of postoperative delirium on preoperative to postoperative gray matter volume change. Regression coefficients are shown and were adjusted for age, sex, time between measurements, center and baseline gray matter volume. In the first model (a), the adjusted regression beta coefficient is shown. In the second model (b), the association between delirium and gray matter volume change was additionally adjusted for new brain infarcts. The indirect effect of new brain infarcts (i.e. the difference between the effect estimates (β – β')) is -0.04 (-0.21 to 0.01), ns, indicating a non-significant decrease in the effect size of 13%.

Part III

Summary and general discussion

CHAPTER 9

Summary

The objectives of this thesis were to assess the relation between brain MRI markers and frailty, to identify brain MRI markers that predispose to delirium and/or postoperative cognitive dysfunction (POCD) and to investigate whether postoperative delirium or POCD is related to preoperative to postoperative MRI brain changes.

The first part of this thesis focused on frailty. In **chapter 2**, we have shown that frail older patients, in comparison to non-frail patients, have a higher number of cortical infarcts representing large vessel disease, and reduced global brain volumes as a marker of neurodegenerative disease. Interestingly, these differences were found to a lesser extent in pre-frail participants as well. These findings indicate that a reduced brain volume and presence of cortical brain infarcts are part of the neural substrate of the physical frailty phenotype. In **chapter 3** we further investigated the relation between frailty and both commonly used and novel markers of cerebral small vessel disease. Frail participants showed a higher burden of cerebral small vessel disease than non-frail participants, which was demonstrated by a higher white matter hyperintensity volume and a more irregular shape of these white matter hyperintensities. No association was found between frailty and lacunar infarcts, or between frailty and cerebral perfusion.

The second part of this thesis focused on the association between MRI features and delirium and POCD. In **chapter 4**, we provided an overview of previous research on these topics. This overview was divided into research on MRI markers of neurodegenerative diseases, and MRI markers of neurovascular diseases. Overall, MRI markers of neurovascular diseases showed the most consistent association with delirium and POCD. In **Chapter 5** we assessed preoperative brain MRI markers of neurodegenerative and neurovascular diseases in relation to postoperative delirium, in a large cohort of older patients that had major elective surgery, of whom 17% developed postoperative delirium. No association was found between preoperative brain volumes, white matter hyperintensities, cerebral perfusion and postoperative delirium. However, a non-significant trend towards an association between cortical brain infarcts and delirium, and a non-significant trend between shape of white matter hyperintensities and delirium was found. These findings suggest that patients with preoperative cortical brain infarcts and those with a more complex shape of white matter hyperintensity may be at an increased risk for developing delirium after major surgery. **Chapter 6** shows a novel method, in which

a hierarchical clustering approach was performed to analyze brain MRI markers of neurodegenerative and neurovascular diseases. The aim was to identify different MRI phenotypes of the brain in older patients scheduled for major elective surgery, and to assess the relation between these phenotypes and postoperative delirium. Six distinct MRI phenotypes of the brain were found: limited burden (three groups), mainly atrophy, mainly small vessel disease and atrophy, and multi-burden. Patients with a multi-burden phenotype showed a higher odds for developing postoperative delirium, suggesting that MRI phenotypes of the brain could assist in an improved understanding of the structural correlates of predisposition to postoperative delirium. In **chapter 7** the relation between cerebral microbleeds and postoperative delirium and/or POCD was assessed in a group of 65 patients. No association was found between preoperative cerebral microbleeds and the occurrence of postoperative delirium and POCD. Furthermore, new postoperative cerebral microbleeds at three months follow-up were not associated with occurrence of postoperative delirium and POCD. **Chapter 8** assessed the relation between occurrence of postoperative delirium and preoperative to postoperative brain changes. Patients showed a greater decrease in gray matter volume compared to control participants. In the patient group, patients with postoperative delirium showed a greater decrease in gray matter volume compared to patients without postoperative delirium, with an additional loss of around 5 ml in approximately 4 months. Furthermore, in the patient group, occurrence of postoperative delirium was associated with new postoperative brain infarcts. We concluded that a greater decrease in gray matter volume and occurrence of new brain infarcts in the postoperative period could be part of the underlying structural correlates of adverse cognitive outcomes after postoperative delirium.

In conclusion, brain changes on MRI that predispose to postoperative adverse neurocognitive outcomes are probably multifactorial, resulting from both neurodegenerative and neurovascular diseases. Postoperative delirium is also related to new postoperative brain changes of neurodegenerative and neurovascular origin.

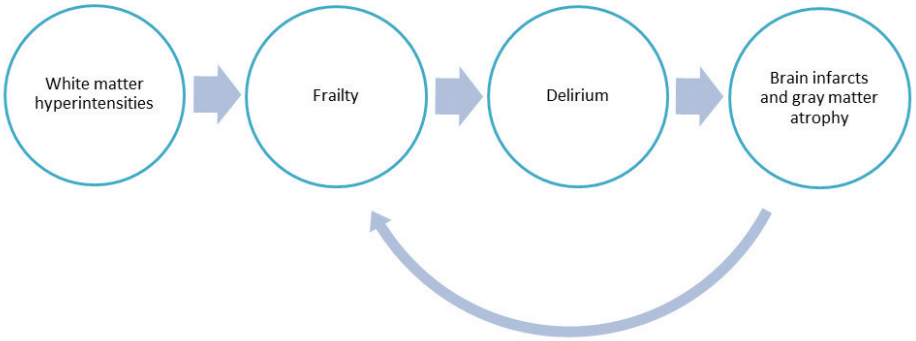

Figure 2: Summary of the findings of this thesis. White matter hyperintensities, cortical brain infarcts and gray matter atrophy are associated with frailty. Frail individuals are at risk for delirium. Delirium is associated with new brain infarcts and an increased rate of gray matter atrophy.

CHAPTER 10

General discussion

In this chapter the methodology that was used, the relation of my findings to other fields of research, and future directions in research and clinical implications will be discussed.

FRAILTY

Defining frailty

Frailty has become an increasingly important topic in research and clinical practice over the last decades[1]. Thereby, several methods of assessing frailty have emerged. These methods vary in underlying concept, components that contribute, and feasibility for routine measurement in clinic care. For instance, there are various frailty assessments that take cognitive function into account, and others that only use physical assessments[2]. Research in the field of frailty has struggled with the lack of a more precise universal definition. The most used frailty assessment is the definition of physical frailty introduced by Fried and colleagues[3], which was used in this thesis. Although this definition is widely used, it is also criticized for the seemingly arbitrary way of defining frailty: a total of three of the five components (i.e. weight loss, weakness, exhaustion, slowness and physical activity) defines an individual as frail, regardless of which components are driving this frailty score. The assumption in this model is that frailty is represented by a decline in multiple physiological systems, regardless of which systems are more rapidly declining. Our results in **chapter 3** show that some frailty components mostly drive the association with markers of cerebral small vessel disease, namely slowness and exhaustion. This might indicate that the nature, and not the number of the physical deterioration symptoms is responsible for the relation between frailty and long-term adverse neurocognitive outcomes. Furthermore, the frailty phenotype classifies individuals as non-frail, pre-frail or frail, while the decline of physiological systems probably manifests gradually. A continuous measure of frailty would probably be more precise. An example is the frailty index, in which frailty is assessed as the cumulative score of frail items on a 36 items questionnaire[4,5]. Frailty is strongly related to mortality in both models, although the frailty index shows a more gradual increase of mortality risk[4,5]. Future investigations will benefit from a continuous, dynamic frailty scale that also enables separate analyses per frailty component, to improve the understanding of the relation between frailty and the vulnerable brain.

The vulnerable brain: accelerated brain aging

Frailty is not a disease in itself, but rather an accumulation of decline of multiple physiological systems. It is widely accepted that frailty is a representation of the biological age of an individual, which can inform the clinician more about the future prospects of an older patient than calendar age. However, to be able to understand the association between frailty and long-term adverse outcomes, a deeper understanding of the underlying pathophysiology is needed. The non-specific manifestation of frailty complicates research in this field, as the underlying pathophysiology is probably heterogeneous. It seems that frailty is, until a certain tipping point, a partly reversible state. As for example functional abilities can improve, for instance after surgery (e.g. the patient that can mobilize again after hip replacement)[1]. When the tipping point has been reached, however, an accelerated decline in multiple systems manifests itself as a downward spiral with a lower probability for an individual to improve[6]. Brain aging probably plays an important role in the manifestation of frailty, and in the irreversibility of frailty. Our findings in **chapter 2** and **chapter 3** show that frail and pre-frail individuals have more structural brain changes than non-frail individuals, indicated by both neurodegenerative and neurovascular brain changes. Frailty thus relates to accelerated brain aging, which could explain the strong relation between frailty and delirium and future long-term cognitive decline[7]. The structural brain changes that we found indicate irreversible damage caused by different mechanisms: neurodegenerative disease (lower brain volumes), and large vessel disease (more cortical brain infarcts) (**chapter 2**) and cerebral small vessel disease (higher white matter hyperintensity volumes and a more complex shape of white matter hyperintensities) (**chapter 3**). Brain deterioration, or accelerated brain aging, i.e. the frail brain is thus, like the syndrome itself, heterogeneous. Neuronal damage could be due to an increased vulnerability to minor stressors: inflammation has been proposed as a contributing factor to frailty and its association with long-term cognitive deficits[8,9]. A higher cardiovascular burden and atherosclerosis leads to an increased risk of cortical brain infarcts, thereby increasing the risk of future cognitive dysfunction. Cerebral small vessel disease also contributes to frailty, although not all markers of cerebral small vessel disease showed a convincing association (**chapter 3**). Our findings indicated that the pre-frail group already showed signs of irreversible brain damage, and that this became more apparent in the frail group. This could

indicate that brain deterioration manifests itself early in the process of becoming frail, but this finding should be confirmed by longitudinal studies.

DELIRIUM AND POCD

Studying delirium in clinical practice

As delirium only occurs after an event that triggered the development of delirium (a precipitating factor), it is difficult to assess a patient for risk factors before the development of delirium. Therefore, observational studies that studied the patient before and after delirium remain scarce. One of the aims of the 'Biomarker Development for Postoperative Cognitive Impairment in the Elderly' (BioCog) study[10], from which data was used for most of the chapters in this thesis (**chapter 2, 3, 5, 6, 7 and 8**), was to assess predisposing factors and consequences of postoperative delirium in the brain of older adults. Postoperative delirium is a useful model, as there is a clear baseline with the certainty of a non-delirious state at that time. However, the incidence of delirium in the immediate postoperative period is low (around 15% in this thesis), and therefore, many patients need to be included to be able to achieve an adequate power to detect any differences between groups. Higher incidences have been reported in other studies (11-51%[11]). The reduced incidence of our studies could be a result of the improved delirium prevention programs in participating centers, where improved postoperative activation and early mobilization has been implemented as standard of care[12]. Another reason for the low incidence could be the extensive study protocol of the BioCog study. This could have resulted in a decline for participation of patients who had a higher disease burden or were less mobile, i.e., the most vulnerable patients for postoperative delirium. Therefore, the results that we have shown could be an underestimation due to selection, as more vulnerable patients probably have a higher chance of developing postoperative delirium.

Delirium: underlying mechanisms

Delirium is an event of acute brain failure, that is probably caused by a heterogeneous combination of predisposing and precipitating factors[13]. Possible underlying mechanisms that are reported include disturbed neurotransmitter balances and neuroinflammation[11,13]. Whether there is one common final pathway leading to delirium is not yet clear, but it is hypothesized that delirium is in the end a disconnection syndrome, with loss of integrity of the functional network as the final common

pathway[14]. However, which structural brain changes contribute to the predisposition for the final disruption of the network remains unclear.

This thesis showed that neurovascular brain changes are most consistently related to a predisposition for postoperative delirium (**chapter 4, 5 and 6**). These brain changes were markers for different underlying mechanisms: cerebral small vessel diseases and large vessel disease. Interestingly, not all markers for neurovascular brain changes were consistently related to postoperative delirium: our study (**chapter 5**) showed that although preoperative white matter hyperintensity volume in itself was not associated with postoperative delirium, a more irregular shape of these white matter hyperintensities was. Cerebral small vessel disease is an umbrella term for multiple underlying disease processes of the small perforating arteries in the brain[15]. Different white matter hyperintensity locations and shapes probably have different underlying etiologies[16]. Thus, the underlying etiology of these lesions may be of higher importance to the increased risk of delirium than volume of the lesions alone.

A possible explanation is that some vascular lesions contribute more to the vulnerability for external stressors than others. For instance, it has been reported that location-specific lesions in the white matter influence local and global functional connectivity[17], and that local and global functional connectivity is influenced by cortical brain lesions[18]. In the SAGES study, it was also shown that structural changes in the white matter predisposed for postoperative delirium[19]. In other words, damage to certain areas of the structural network may be key in the vulnerability for the stressor of major surgery. An important step that needs to be taken in future investigations is to study which neurovascular lesions contribute most to the risk of postoperative delirium. In a combined analysis of the characteristics of structural brain changes and functional connectivity, one would be able to identify structural or functional brain changes that characterize the vulnerable brain for postoperative adverse outcomes. This could for example be realized by investigating whether measures of functional connectivity act as a mediator of the relation between specific neurovascular changes and postoperative delirium.

Methodological considerations: POCD and postoperative neurocognitive disorder

Research on POCD is hampered by the lack of an uniform definition and assessment. The new definition by Evered et al. (postoperative minor or major neurocognitive

disorder)[21] was an important step in realizing a definition that focuses on the amount of dysfunction that is important for the quality of life of patients: the subjective complaints. Still, even though the new definition by Evered et al. improved the old definition, the exact method of assessment of postoperative neurocognitive disorder has not yet been defined[21]. The field of research on POCD thus needs a standardization step in both the definition and the assessment tools that should be used for assessment of this disorder. Although frequently reported by patients and healthcare providers, we can only draw conclusions on the exact prevalence and incidence of POCD when there is a standardized cognitive assessment, on a standardized time point after surgery, with comparison to a control group that is adequately chosen (i.e. matched on age, sex, education level and disease burden). Our study showed a low number of patients with POCD three months after surgery according to the reliable change index, and a low number of patients that had both delirium and POCD (**chapter 7**). This finding could indicate that, in a heterogeneous group of patients, the incidence of POCD at three months after surgery is lower than previously reported in other studies that used the same definition of POCD[22]. Further, it could indicate that delirium and POCD are two separate entities, although they share some of the same risk factors, as was also suggested by the findings of the SAGES study cohort[23]. However, these findings are all dependent on the definition of POCD, and thus could be very different when using another definition[24].

We found a very low number of patients with POCD (**chapter 7**), and could not detect which neural correlates underly the occurrence of POCD. Previous studies on POCD were mostly in cohorts of patients that had cardiac surgery and previous results were inconsistent[25–28]. Whether POCD is related to additional brain changes that occurred in the postoperative period remains unclear to date as well. If the previous studies that used neuroimaging in relation to POCD[10,25–28] could be analyzed with the new standardized methods of POCD or postoperative neurocognitive disorder assessment, the comparability would increase and potentially more robust conclusions could be drawn on the potential neural underpinnings of POCD.

PREOPERATIVE TO POSTOPERATIVE TRAJECTORIES

Initially high-functioning patients with a seemingly equal risk of postoperative adverse outcomes (e.g. high age) have different trajectories after surgery. This thesis has

contributed to the understanding of these trajectories by showing that structural brain damage of neurodegenerative and neurovascular origin plays an important role.

Underlying mechanisms of different trajectories

Differences in preoperative to postoperative trajectories between patients are probably driven by multiple mechanisms. Figure 1 shows potential preoperative to postoperative trajectories of different patients that undergo major surgery. In healthy aging, the brain deteriorates over time, showing more structural changes with higher age, following a non-linear curve[29]. These changes do not necessarily lead to adverse outcomes at a younger age, and are part of the normal aging process[29]. However, an accelerated brain aging process such as seen in physical frailty (**chapter 2 and 3**) also leads to accelerated functional decline of patients, and a higher risk of delirium after surgery. These underlying disease processes are probably multifactorial and have different origins (**chapter 5 and 6**): for example neurodegeneration can be due multiple underlying processes such as Alzheimer's disease, Parkinson's disease or secondary due to ischemia, all leading to reduced brain volumes. Large vessel disease leads to a higher number of cortical brain infarcts, and cerebral small vessel diseases lead to a higher number of lacunes, microbleeds and white matter hyperintensities[15]. The high risk of developing postoperative delirium in vulnerable patients is related to a higher multi-burden brain pathology profile, as demonstrated in **chapter 6**.

Hypothesized trajectories

Potential trajectories in Figure 1 show a patient with a healthy aging trajectory (patient 1), who does not experience any cognitive problems during the postoperative period or afterwards. The second trajectory (patient 2) shows a patient that is pre-frail or frail: a mild disease burden in the brain of these patients increases vulnerability to the stressor event of surgery. Although some of these patients will develop delirium, most of them probably will not. However, long-term cognitive deficits may still arise in these patients. These long-term deficits are related to a lingering disease process that continues after surgery, leading to an increased rate of neurodegeneration (**chapter 8**). Potentially, these patients will report mild complaints of cognitive dysfunction in the months following surgery, which resolves after one year in part of the patients[23]. The third trajectory (patient 3) shows an individual who is pre-frail or frail and has a multi-burden MRI phenotype of the brain, and who is at increased risk

of developing postoperative delirium. Perioperative brain infarcts may have occurred, further increasing the risk of postoperative delirium. Delirium itself has a transient nature as the short duration of a disrupted functional network and acute brain failure resolves over time. The patient initially returns to baseline, however, although the initial inflammatory reaction to surgery has resolved, persistent neuroinflammation contributes to continued disease progression after the delirious period. This lingering neuroinflammation results in an increased rate of neurodegeneration (**chapter 8**). Eventually, this will lead to long-term cognitive deficits or even dementia[30]. Other possible contributing factors to long-term damage include cerebral small vessel disease resulting in structural abnormalities in white matter[31], and non-resolved changes in the functional network[32].

Influence of precipitating factors

The differences in trajectories between patients may also be explained in part at least by differences in precipitating risk factors that eventually lead to delirium. For example, different types of major surgery can have a different impact on the brain. Cardiac surgery patients are prone to perioperative micro-embolism, thereby increasing the risk of postoperative delirium[26]. Furthermore, risk profiles of patients scheduled for surgery differ; vascular risk factors or (treatment of) oncological diseases may play an important role in the postoperative recovery of a patient[33]. Whether there is a different risk of postoperative structural brain deterioration in different types of surgery should be further investigated.

Longitudinal research

Previous investigations on the association between delirium and brain volume changes have only assessed brain MRIs of patients after the occurrence of a delirious episode[34]. In **chapter 8** we showed that postoperative delirium is associated with additional brain deterioration. A major strength of this investigation was that brain MRIs were made before the occurrence of delirium, enabling us to rule out that smaller pre-existing brain volumes explained the association of delirium with brain atrophy. Still, to be able to draw final conclusions on the preoperative trajectories of older patients undergoing major surgery, longitudinal assessments that include more than one preoperative measurement might be suggested. However, the reason for major surgery often arises shortly before surgery. Therefore, setting up such a study is labour intensive and difficult: one would have to include many patients, and the

added value may be small as the accelerated rate of brain atrophy after delirium was already demonstrated (**chapter 8**). More interesting would be to increase the length of follow-up on our study (**chapter 8**). With an increased follow-up length, one would be able to investigate the long-term trajectory of accelerated brain deterioration in patients that experienced postoperative delirium.

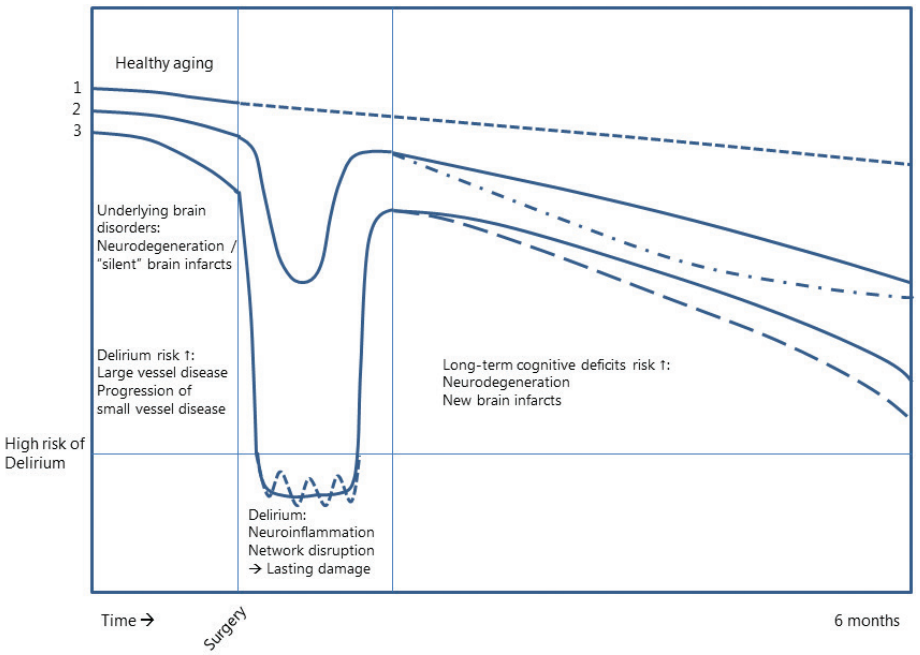

Figure 3: Hypothesized trajectories of three possible patients. Time is shown on the x-axis, the y-axis shows brain function. In healthy aging patients, surgery often has no consequences on the brain or on the cognitive abilities of a patient (case 1, striped line). Case 2 shows a possible trajectory of a patient with mild underlying brain disorders, possibly a pre-frail or frail individual, for whom the stressor event of surgery has an impact on the brain, but not enough for occurrence of delirium. However, following surgery, there are different possible outcomes: either the patient continues on the trajectory of before the surgery, or increased atrophy and silent brain infarcts lead to a higher chance of temporary (dotted and striped line) cognitive deficits or long term brain deterioration. Case 3 shows a patient with multi-burden brain pathology who is pre-frail or frail, who develops postoperative delirium. During delirium, brain dysfunction has a fluctuating character, illustrated by the dotted line. Following surgery, this patient may initially return to baseline, however, the following period shows an increased rate of brain deterioration: increased neurodegeneration and new brain infarcts, leading to a higher chance of long-term cognitive dysfunction and dementia (indicated by the striped and continued trajectory).

FUTURE DEVELOPMENTS IN RESEARCH AND CLINIC CARE

Deep learning and machine learning: application in research

Increased computing power and evolved statistical methods have enabled machine learning and deep learning methods, which are now increasingly applied in medical research. Machine learning and deep learning algorithms can be used as a classifier to determine known groups (supervised learning), for example to automatically perform image quantification, or to discover new patterns in data that otherwise would be hard to distinguish (unsupervised learning). Classifier algorithms based on deep neural networks (deep learning) are already widely used in the field of radiology research, for example, to classify tissues on brain MRI scans such as in segmentation of white matter hyperintensities[37], infarcts[38,39], or even for discovery of patterns in normal appearing tissues[40]. These new techniques should be applied in future investigations on postoperative neurocognitive disorders, and could result in a more accurate identification of predisposing risk factors to delirium and/or POCD.

Radiomics

Another application of machine learning that is increasingly used is to distinguish patterns in large clinical datasets. In radiology, this emerging field is often referred to as "radiomics", a field of rapidly emerging methods to analyze enormous radiological datasets in order to move towards personalized medicine[41]. These patterns can be used for prediction models that may benefit clinical decision support[42,43], selection of patients that would benefit from certain interventions[43], or to discover new patterns in these datasets that provide new research opportunities[44]. One example of these methods is hierarchical clustering, which we have used in **chapter 6** to distinguish different MRI phenotypes of the brain. Hierarchical clustering has the advantage of being unsupervised, hypothesis-free, and is thus a useful tool to generate hypotheses for future investigations. However, to provide an actual deeper understanding of the disorder that is topic of research (e.g. delirium), techniques need to be developed to take the next step: assess the factors that are driving the difference between different groups of patients. Knowing the factors that drive the differences between MRI phenotypes of the brain could help in learning to understand the MRI brain changes, or the combination of MRI brain changes that are key to develop delirium or other adverse neurocognitive outcomes. Further, large databases are needed: a potential opportunity besides the BioCog data would be to assess the influence of

known risk factors for delirium on MRI brain changes in large, publicly available MRI databases such as the OASIS-3 database[35].

Personalized medicine

Although risk prediction based on brain MRI for postoperative delirium alone is not likely (MRI imaging is expensive and not widely available), identification of individuals at risk for an increased rate of deterioration on the long-term could be a future topic of research. Furthermore, future developments of machine learning techniques allow the intriguing opportunity to classify groups of patients that may or may not benefit from certain prevention or treatment strategies. Investigating groups of individuals with different risk profiles may reveal subgroups that benefit from targeted treatments, that otherwise would not have been identified. For instance, in frailty, pre-frail individuals with certain clinical or MRI phenotypes of the brain may benefit from prevention or therapeutic interventions, while others may not. In the field of delirium, individuals with certain clinical or MRI phenotypes of the brain may benefit from new emerging therapies (e.g. transcranial magnetic stimulation, medication therapy), while others may not. This should be investigated by first assessing the nature of these phenotypes by identification of the driving factors behind this classification. Then the association between these phenotypes and long-term adverse outcomes should be explored in large observational studies. Thereafter, randomized controlled trials should be set up to investigate the actual benefit of treatment in these groups. However, it is important to keep in mind that the quality of the outcomes of machine learning methods and automated clustering are ultimately determined by the quality of the data that is used for the algorithm and feature selection. Findings should be internally and externally validated. In investigations of MRI phenotypes of the brain, image acquisition methods should be standardized and image processing pipelines and quality assessments should also be standardized and automated, and tested for accuracy and robustness. Only after those conditions have been met, clinical relevance of these techniques can be assessed and future clinical implementation can be realized.

CONCLUSION

In conclusion, frailty and delirium are associated with brain changes on MRI. Brain changes on MRI that predispose to postoperative adverse neurocognitive outcomes are multifactorial, resulting from both neurodegenerative and neurovascular diseases. Postoperative delirium is also related to new postoperative brain changes

of neurodegenerative and neurovascular origin. Whether POCD is associated with brain changes on MRI remains unclear. These results stress the importance of future investigation on the preoperative to postoperative trajectories of older patients, and on the prevention and treatment of these disorders.

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