Impact of Perioperative Infarcts After Cardiac Surgery

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Cover title: FLAIR MRI lesions before and after cardiac surgery

Keywords: Cardiac Surgery, Cerebral Infarction, Magnetic Resonance Imaging, Neuropsychology

Subject codes: [36] [38] [58] [127]

Word count: 4866/4500 words

In: Stroke (2015); 46: 680-686, doi: 10.1161/STROKEAHA.114.007533

Abstract

Background and purpose: Brain injury following cardiac surgery is a serious concern for patients and their families. This study uses 3-T Fluid Attenuated Inversion Recovery (FLAIR) MRI to characterise new and pre-existing cerebral ischaemic lesions in patients undergoing cardiac surgery and tests whether the accumulation of new ischaemic lesions adversely affects cognition.

Methods: Digital comparison of 'before and after' FLAIR MRI images was performed for data analysis from 77 cardiac surgery patients. The burden of pre-existing vs. new ischaemic lesions was quantified and compared with the results of baseline and post-operative neuropsychological testing.

Results: Pre-existing ischaemic lesions were observed in 62% of patients, averaging 19.4 lesions totalling 1542 mm^3 (~1%) of total brain tissue per patient. Patients with pre-existing lesions were 10 times more likely to receive new lesions following surgery than patients with no pre-existing disease. Following surgery, new lesions were identified in 31% of patients, averaging 0.5 new lesions per patient with a volume of 67 mm^3 (0.06%) of brain tissue per patient. Lesions in the left hemisphere were significantly smaller and more numerous (29 lesions, mean volume=87±95 mm^3) than those on the right (10 lesions, mean volume=264±412 mm^3), which is consistent with a cardioembolic source of particulate emboli. The incidence of post-operative cognitive decline was 46%, regardless of whether the patients had new, large, or multiple lesions.

Conclusions: New lesions following cardiac surgery typically add a negligible (<3%) contribution to the burden of pre-existing cerebrovascular disease and were not found to adversely affect cognitive function.

248/250

Introduction

The relative contributions of chronic cerebrovascular disease and peri-operative stressors in generating post-operative cognitive decline following cardiac surgery are incompletely understood. Previous MRI studies of brain injury following cardiac surgery have focused primarily on identifying acute ischaemic lesions using DW-MRI.[1-12] Acute ischaemic changes are visible in 32% of patients using DW-MRI[1] and new chronic ischaemic lesions are found in approximately 13% of patients.[13] Some studies report an association between the presence, size or number of new acute lesions and post-operative cognitive decline,[3,9] while others do not.[2,7,11,13] Lesions typically consist of multiple, small round, lesions whose radiographic appearance is strongly suggestive of embolisation.[3,5,7] However, few studies have attempted to quantify the accumulation of new ischaemic injuries against a backdrop of chronic pre-existing cerebrovascular disease. Since cognitive impairment is often transient, and new lesions can also occur without any discernable decline in cognition, whether new ischaemic lesions adversely affect cognition remains unclear.

This is the first study to use 3-T FLAIR MRI to assess the relative contribution of new ischaemic lesions to pre-existing cerebrovascular disease in patients undergoing cardiac surgery. We also perform neuropsychological testing at the same time points as the MRI scan to investigate whether the presence, number, or volume of new lesions significantly alters cognition. Only two studies have previously used FLAIR to detect lesions in conjunction with postoperative neuropsychological assessment.[4,13] Lund *et al.* (2005) detected new lesions (>2 mm) in 9 of 52 (17%) of patients at 3 months post-operatively using 1.5-T FLAIR and found a correlation between new and pre-existing lesions, but as cognitive decline had resolved at 3 months no association was observed between post-operative lesions and cognitive decline.[13] Argarwal (2010) studied 10 CABG patients using 1.5-T FLAIR, but, none of their patients developed either new MR lesions or cognitive decline so the results were inconclusive.[4]

Modern MRI techniques, such as FLAIR, enable confident identification of ischaemic white matter disease.[14] By comparing 3-T MR FLAIR lesions observed before and after surgery, we were able to detect small ischaemic lesions with unprecedented resolution and confidently assess the relative contribution of new lesions to old. Here we quantify the volume of old to new lesions and present the spatial distribution and dimensions of new ischaemic lesions observed following surgery, alongside the results of neuropsychological testing, to investigate whether the presence, number, or size of new lesions is related to impaired neuropsychological test performance.

Patients and Methods

All patients requiring CABG, and/or valve surgery at our institution were eligible for inclusion in this study. Data were collected as part of a larger study investigating brain injury following cardiac surgery funded by the British Heart Foundation. Patients were excluded if they had contraindications to MRI (e.g. a cardiac pacemaker), or if their first language was not English, as this would invalidate the neuropsychological tests. Patient characteristics available for analysis as part of this study included age, sex, smoking status, ischaemic heart disease, hypercholesterolemia, hypertension, and aortic stenosis. All patients provided written informed consent following a protocol approved by the University Hospitals of Leicester NHS Trust and Derbyshire Research Ethics Committee (REC reference:10/H0401/78). The study was sponsored by the University *of* Leicester.

Anaesthetic and surgical procedures

Routine perioperative care was given to all patients, and there were no specific alterations to standard surgical practice. Cold crystalloid cardioplegia was used, and anaesthesia management consisted of a combination of isoflurane, propofol, midazolam and fentanyl. Body temperature was measured every 3 minutes with a nasal pharyngeal temperature probe. Non-pulsatile cardiopulmonary bypass (CPB) was implemented using a with a non-occlusive roller pump with a target CPB perfusion pressure above 50 mmHg. The CPB circuit contained a membrane oxygenator and 40 μm arterial line filter. Arterial blood pressure targets during surgery were based on usual clinical practice.

Neuropsychological assessment

Neuropsychological tests were performed 1-2 weeks before surgery and 6-8 weeks postoperatively at the same time points as the MRI scans. Our test battery included two tests recommended by the Statement of Consensus on Assessment of Neurobehavioral Outcome

after Cardiac Surgery:[15] Trail Making Tests (parts A and B)[16] and the Grooved Pegboard Test[17]. In addition, the Wechsler Memory Scale-Third Edition (WMS-III)[18]and Wechsler Abbreviated Scale of Intelligence (WASI)[19]were performed. Patients also completed a Hospital Anxiety and Depression Scale (HADS) questionnaire.[20] These tests were specifically chosen to allow pair-wise comparison of 'before' and 'after' scores, as well as comparison of baseline scores with well characterised normative data in age-matched healthy controls found within individual test manuals (via *z*-score analysis). Neuropsychological assessments were performed by a trained assessor who was blinded to the results of the imaging data.

Magnetic Resonance Imaging

All MRI examinations were conducted using a 3-T whole body scanner (Magnetom Skyra, Siemens Medical, Erlangen, Germany). Scans were performed in the following order: 3-plane localiser; diffusion-weighted sequence; Time of Flight MR angiography; Susceptibility Weighted Imaging and Fluid-Attenuated Inversion Recovery (FLAIR). FLAIR images were obtained using a slice thickness of 3 mm with the number of slices set to cover the whole brain. Matrix size was 320×352, field of view was 240 mm, TR/TE were 6770/108 ms, and TI was 2170 ms. The total imaging time was approximately 30 minutes.

To distinguish chronic lesions from acute ischaemic changes both MR-FLAIR and DW images were presented to a qualified neuroradiologist who was blinded to the results of neuropsychological assessments. Chronic ischaemic changes were then characterised through registration and subtraction of pre- and post-operative FLAIR images using 'in house' software written in Java (Fig. 1). Images were analysed for the location and volume of both new and pre-existing lesions, which were delineated using a semiautomatic contouring technique. Lesion volumes smaller than 100 mm^3 are reported as '<100 mm^3'. To aid visualisation of the distribution of new lesions, post-operative FLAIR images were registered

to a standard MRI brain atlas,[21] and new lesions were segmented and displayed using the atlas as reference for the 3-D display.

Statistical analysis

Statistical analyses were performed using a statistical software package (Statistical Product and Service Solutions, SPSS, version 20.0, SPSS Inc., IL, USA). Differences with a *p*-value of <0.05 were assumed to be statistically significant. Tests for normality were performed using the Kolmogorov-Smirnov test. Data are presented as mean ± SD, unless stated otherwise. The distribution of lesions between left and right was analysed using a binomial test assuming a null hypothesis that lesions were distributed equally between hemispheres. Differences in average dimensions of lesions between the left and right sides were assessed using Student's *t*-test.

Individual neuropsychological test scores were first converted to *z*-scores through comparison with published data describing the mean (X) and standard deviation (SD) of test scores measured from a population of healthy subjects:

$$z = \frac{x - X}{SD} \qquad [1]$$

Post-operative *z*-scores were then subtracted from preoperative *z*-scores to calculate the pair-wise change in *z*-score; a significant decline in cognition was assumed if there was a drop in *z*-score of more than 1 SD from baseline. For timed tests (Trail Making A/B and Grooved Pegboard tests), the sign of the *z*-score was reversed so that improved performance corresponded to a positive *z*-score. In addition to calculating the *z*-score change for each individual test, *z*-scores were summed and averaged to quantify the overall cognitive performance of each patient as a 'composite' cognitive performance score.[8]

Results

Of 103 patients enrolled to the study, 19 did not receive a pre-operative MRI scan due to scheduling difficulties, 3 were unable to receive a postoperative scan (pacemaker fitted) and 4 patients withdrew. Complete pre- and post-operative MRI and cognitive test data were analysed from 77 patients (72 males; 63±10 years). A detailed table summarising all data relating to this study is provided in online supplement A.

Following surgery, 5/77 patients (7%) had perioperative strokes confirmed by the Radiologist's MRI report: patients 13 and 62 had lacunar infarcts in the right corona radiata, patient 47 had a lacunar infarct in the left corona radiata, patient 63 had two small lacunar infarcts (one located in the right superior parietal lobule and one in the left medial precentral gyrus), and patient 19 had a lacunar infarct in the right frontal lobe. Patient 19 was the only patient with perioperative stroke to also experience cognitive decline at 6-8 weeks.

Pre-existing chronic ischaemic white matter disease was noted in 64% (49) of patients pre-operatively. Patients had an average of 19.5 pre-existing lesions per person (ranging from 0 to 78) and a total volume of lesions averaging 2329 mm^3 (range: 0, 27950 mm^3) per person. Assuming 1500000 mm^3 and 1320000 mm^3 for the average volume of the male and female brain[22], we estimate that pre-existing lesions in cardiac surgery typically affect up to 1.9% of total brain tissue. The pre-operative test performances were similar to the general population in all tests apart from the grooved pegboard test where our cohort of patients exhibited a moderate decline. The volume of pre-existing ischaemic lesions showed no correlation with lower pre-operative z-score (Pearson's correlation test; p=0.925).

Of the 64% (49) of patients with pre-existing lesions nearly half, 45% (22), went on to develop new lesions post-operatively compared to only 7% (2/28) of patients without pre-existing lesions (i.e. 92% (22/24) of patients with new lesions had pre-existing lesions). An

example showing the location and volume of new (green) and pre-existing lesions (blue) in patient 47 is provided in Fig. 2 (a). Comparison of the contribution from new and pre-existing lesions suggests that the accumulation of new lesions following surgery is relatively minor in comparison with the pre-existing burden due to chronic cerebrovascular disease. Figure 2 summarises the volume of new and pre-existing lesions following surgery for patients (a) with and (b) without new lesions.

New ischaemic lesions were identified using FLAIR MRI in 31% (24/77) of patients. Nine (12%) patients exhibited multiple new MRI lesions (up to a maximum of 5), of which 3 had lesions in more than one vascular territory. Ten patients (13%) received new lesions that were estimated to have volumes >100 mm^3. The largest observed new lesion was 1383 mm^3 in volume (approximately the size of a raspberry) located in the right frontal lobe of patient 13. No significant differences between the characteristics of patients with and without new lesions were observed, other than an association between new lesions and the presence of pre-existing chronic ischaemic white matter disease, (χ^2 test: p=0.001), see table 1.

A 3-dimensional representation of the overall distribution of new MRI lesions, created by superimposing data from the 24 patients with changes following surgery, is presented in panels 3(a) and (b). The majority of new MRI lesions were located in the middle cerebral artery (MCA) territory (64%), followed by the anterior cerebral artery (ACA) territory (13%), posterior cerebral artery (PCA) territory (13%), superior cerebellar artery (SCA) territory (5%), and lateral lenticulostriate artery (LLA) territory (5%), Fig. 3(c). On average, right hemisphere lesions were three times larger (mean volume=264 ± 412 mm^3) than left hemisphere lesions (mean volume=87 ± 95 mm^3), t-test: p=0.034, Fig. 3(d). Lesions were significantly more numerous in the left (74%) hemisphere than the right (26%) (χ^2=9.3: p=0.002).

A decline in neuropsychological test performance following surgery in at least one test was noted in 35 (46%) of 77 patients. Five patients (6%) declined by >1 SD in two or more tests. The most commonly affected domains were attention and psychomotor speed (23% (18); TMT-A: 5% and Grooved pegboard: 18%), visual & executive domains (17% (13); performance: 4% and TMT-B: 13%), immediate memory (8% (6)), and delayed memory (4% (3)). Only one patient declined in the verbal intelligence test (1%). The majority of patients had normal levels of depression and mild levels of anxiety on HADS at pre-operative assessment (anxiety: 6.3±3.8; depression: 3.3±2.7). Depression and anxiety levels were stable or dropped following surgery (anxiety: 3.9±3.1; depression: 2.9±3.2) suggesting that any decline in neuropsychological test scores was not attributable to heightened anxiety or depression. The incidence of cognitive decline in our study population was 46%, which was independent of the presence of new lesions, and irrespective of whether new lesions were large or multiple. There was no association between declining *z*-score and the presence of new MR lesions (indicated by the filled circles in Fig. 4). Grouping patients by neuropsychological outcome showed similar demographic and surgical factors between groups with the exception of increased age (*t*-test, $p= 0.022$) and aortic stenosis (χ^2 test, $p= 0.042$), which were both higher in patients with cognitive decline, table 2.

Of patients who experienced neuropsychological decline, the vast majority, 69% (24/35), had no new postoperative MRI lesions. Conversely, over half (54%) of the 24 patients with new MRI lesions (13/24) did not experience cognitive decline. On average, patients with new MRI lesions did not experience a greater magnitude of decline than patients without new MRI lesions (mean composite *z*-score change, 0.07 versus 0.11, respectively; *t*-test, $p=0.7$) and there was no association between having multiple new lesions and greater magnitude of decline in the composite z-score (*t*-test, $p=0.6$).

Discussion

FLAIR is an inversion recovery pulse sequence which uses a combination of T_1 and T_2 weighting to null the signal from fluid so that it appears dark, while tissue damaged by ischaemia remains bright. Although some studies have used 1.5-T FLAIR MRI to identify new chronic ischaemic lesions following surgery,[4,13,23-25] few studies report the characteristics of pre-existing lesions, and only 2 studies have used FLAIR in conjunction with neuropsychological testing.[4,13] In the FLAIR study by Lund *et al.* (2005) cognitive decline had completely resolved at 3 months, and therefore no association between new lesions and neuropsychological impairment could be observed.[13] The second smaller study by Agarwal *et al*. used FLAIR imaging and neuropsychological assessment at 4-6 weeks, but since none of their patients showed any signs of neuropsychological deficit or new MRI lesions, the results were inconclusive.[4] In this study, the higher resolution afforded by MRI at 3 Tesla, coupled with subtraction of 'before' and 'after' FLAIR images, provides a highly sensitive means of detecting small ischaemic lesions and distinguishing new lesions from old.

Our study reveals the extent of pre-existing cerebrovascular ischaemic lesions in patients undergoing cardiac surgery. Our data suggests that new lesions acquired peri-operatively add a negligible burden to the brain in comparison to existing cardiovascular disease. Our estimates suggest that ~1-2 % of total brain volume is typically affected by pre-existing ischaemic white matter disease prior to surgery. New lesions acquired peri-operatively make up less than 3% of the total burden of ischaemic white matter disease post-operatively, and contribute less than 0.1% to the total volume of pre-existing lesions. This may explain why previous studies, focusing purely on the detection of acute ischaemic lesions, have failed to find a link between new lesions following surgery and cognitive decline. In fact, we were unable to detect any discernable impact on cognitive tests results associated with either pre-existing or new lesions.

A second major finding of our study was that patients with pre-existing disease identified pre-operatively using MR-FLAIR were at exceptionally high risk of developing new lesions post-operatively. Patients with pre-existing lesions were ten times more likely to experience new lesions post-surgery than patients without pre-existing disease. These findings agree with those of Lund *et al.* (2005) who found an association between pre-existing and new lesions in 54 patients undergoing CABG with CPB.

A third important finding of our research is that post-operative lesions identified by 3-T FLAIR MRI are more prevalent than previously thought, and can be found in approximately a third (31%) of patients at 6-8 weeks following surgery. Our higher detection rate is most likely due to the use of digital subtraction to help confidently identify ischaemic changes, and higher resolution afforded by 3-T MRI.

Our study also finds that new MRI lesions and cognitive decline are independent. The incidence of cognitive decline was 46% regardless of the presence, number, or size or new lesions, and the proportion of patients with MRI lesions was 31% irrespective of cognitive status. The incidence of cognitive decline of 46% observed in our patients at 6-8 weeks was similar to that reported by other studies using similar criteria (paired *z*-score analysis with 1 SD as significant).[26]

In previous research, the incidence of neurocognitive impairment ranged from 0 to 50% when measured between 1 and 3 months following surgery and has been found to be related to multiple risk factors, including age, pre-existing white matter disease, pre-existing cognition, and complexity of surgery.[27] Our findings confirm that older patients with aortic stenosis are more likely to suffer post-operative neuropsychological impairment (Table 2).

A strength of our study include higher resolution afford by 3-T MRI and larger sample size (compared to the majority of previous MRI studies). Digital registration and subtraction of

MR images, combined with the expertise of a qualified neuroradiologist, enabled us to confidently estimate the size and location of small new lesions. The distribution of new lesions suggests that larger emboli favour the right side of the brain, predominantly coming to rest in territories supplied by the MCA. This is consistent with a cardio-embolic source, in which larger pieces of emboli debris travel along the brachiocephalic artery, which emerges first from the ascending aorta and is consistent with a tendency for larger emboli to take a preferred trajectory that disproportionately favours major vessels.[28]

In future work, pre-operative MRI assessment may be useful for identifying high-risk patients for targeted intervention to reduce embolisation of atheromatous debris during surgery. A deeper understanding of complex interactions between perioperative stressors and chronic cerebrovascular disease will also be beneficial in gaining further insights into the causes of brain injury during cardiac surgery toward personal risk stratification and intervention.

Conclusions

In summary, patients undergoing cardiac surgery often have extensive pre-existing ischaemic white matter disease affecting up to 2% of total brain volume. Pre-existing lesions were observed in 62% of patients and confer an exceptionally high risk of receiving new lesions following surgery. However, in comparison to the considerable burden of pre-existing chronic cardiovascular disease, new lesions observed post-operatively only contributed ~3% to the existing volume of lesions (affecting <0.1% of brain volume). Although 46% of patients experienced neuropsychological decline at 6-8 weeks post-operatively, this was not attributable to the appearance of new lesions. Older patients with aortic disease were confirmed to be more likely to experience cognitive decline, but there was no association between the presence, size, or number of new MR lesions and post-operative cognitive decline.

Acknowledgments

We thank the participants who took part in this study along with theatre staff of the Cardiothoracic Surgery Unit and the MRI radiographers at Leicester Glenfield Hospital.

Sources of Funding

The study was funded by the British Heart Foundation (FS/10/46/288350). N Patel is a University of Leicester PhD student funded by the NIHR Leicester Cardiovascular Biomedical Research Unit.

Disclosures

None.

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Figures:

Figure 1 Comparison of FLAIR MR images obtained 1-2 weeks before and 6-8 weeks after cardiac surgery. Registration and subtraction of MRI data were performed using 'in house' software to confidently distinguish new ischaemic lesions from pre-existing infarcts and provide an estimate of the position and volume of new lesions.

Figure 2 A. The distribution of pre-existing lesions (blue) vs. new lesions (green) was mapped for each patient to estimate the volume of new and pre-existing lesions for each patient. B. Volume of pre-existing lesions in patients who had no new lesions.

Figure 3 The spatial distribution of new ischaemic lesions, compiled from the combined data from all 24 patients, was consistent with a cardio-embolic aetiology. Lesions are highlighted in red against the background of a standard atlas image. A. superior view, B. lateral view. C. The majority (74%) of new lesions were located in the left hemisphere (χ^2 test: p=0.002). Lesions appeared in multiple territories, but particularly favoured regions supplied by the middle cerebral artery (MCA). C. Lesions observed in the left hemisphere tended to be smaller than those on the right.

Figure 4 Summary of changes in neuropsychological test performance (*z*-score change) for 77 patients taking eight cognitive tests. Overall test performance tended to improve slightly on retesting, indicated by a positive mean z-score change (denoted ■). Thirty-five patients (46%) significantly declined in at least 1 test, defined as a drop in *z*-score of more than 1 s.d. (shaded). Five patients declined in 2 or more tests. Visual inspection suggests no obvious correlation between *z*-score decline and the presence or characteristics of new MRI lesions (denoted ⚬).

Tables

Table 1.Comparison of potential risk factors grouped by FLAIR MRI outcome.

	New lesions (*N*=53)	**No new lesions (*N*=24)**	***p*-value**
Male: female	51:2	21:3	0.172*
Age,years (SD)	63±11	64±10	0.606†
CABG: intra-cardiac procedures	21:32	6:18	0.213‡
Smoking, *n* (%)	28 (54)	9 (38)	0.212‡
Hypertension, *n* (%)	40 (76)	15 (63)	0.243‡
Hypercholesterolemia, *n* (%)	41 (77)	17 (71)	0.538‡
Ischaemic heart disease, *n* (%)	31 (59)	12 (50)	0.487‡
Aortic stenosis (mild/severe), *n* (%)	26 (49)	16 (67)	0.151‡
Pre-existing white matter disease, *n* (%)	37 (71)	22 (92)	0.001‡
Neuropsychological decline, *n* (%)	24 (45)	11 (46)	0.964‡

*Fisher's exact test, †*t* test, ‡Chi squared test. Significant risk factors are highlighted.

Table 2.Comparison of potential risk factors grouped by cognitive outcome.

	Cognitive decline *N*=35	**No cognitive decline *N*=42**	***p*-value**
Male: female	33:2	39:3	1.000*
Age, years ± SD	66±7	60±12	0.022†
CABG: intra-cardiac procedures	12:23	15:27	0.896‡
Smoking, *n* (%)	14 (40)	23 (54)	0.254‡
Hypertension, *n* (%)	23 (65)	32 (76)	0.311‡
Hypercholesterolemia, *n* (%)	27 (77)	31 (74)	0.735‡
Ischaemic heart disease, *n* (%)	23 (66)	20 (48)	0.111‡
Aortic stenosis (mild/severe), *n* (%)	17 (49)	11 (26)	0.042‡
Pre-existing white matter disease, *n* (%)	22 (63)	28 (66)	0.727‡
New FLAIR MRI lesions, *n* (%)	11 (31)	13 (31)	0.964‡

*Fisher's exact test, †*t*-test, ‡Chi-squared test. CPB=Cardiopulmonary Bypass; CABG=Coronary Artery Bypass Graft, FLAIR=Fluid Attenuated Inversion Recovery. Significant risk factors are highlighted.

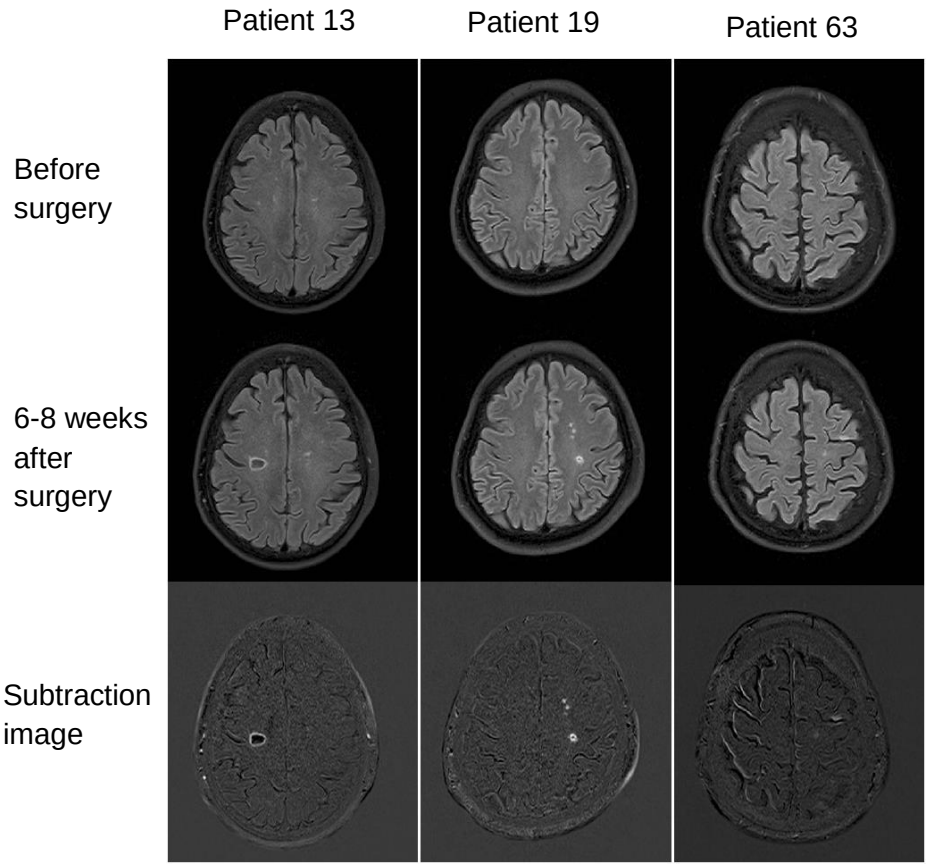
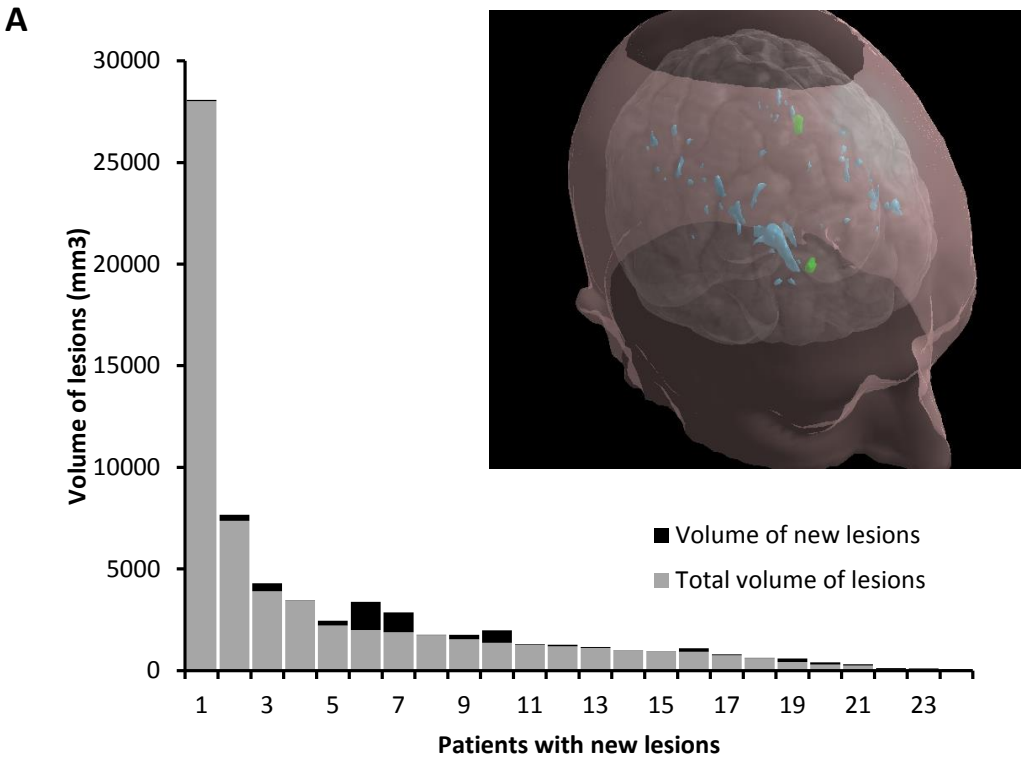

Patient 13
Patient 19
Patient 63
Before surgery
6-8 weeks after surgery
Subtraction image

Fig. 1.


A
30000
25000
20000
15000
10000
5000
0
Volume of lesions (mm3)
Volume of new lesions
Total volume of lesions
1
3
5
7
9
11
13
15
17
19
21
23
Patients with new lesions

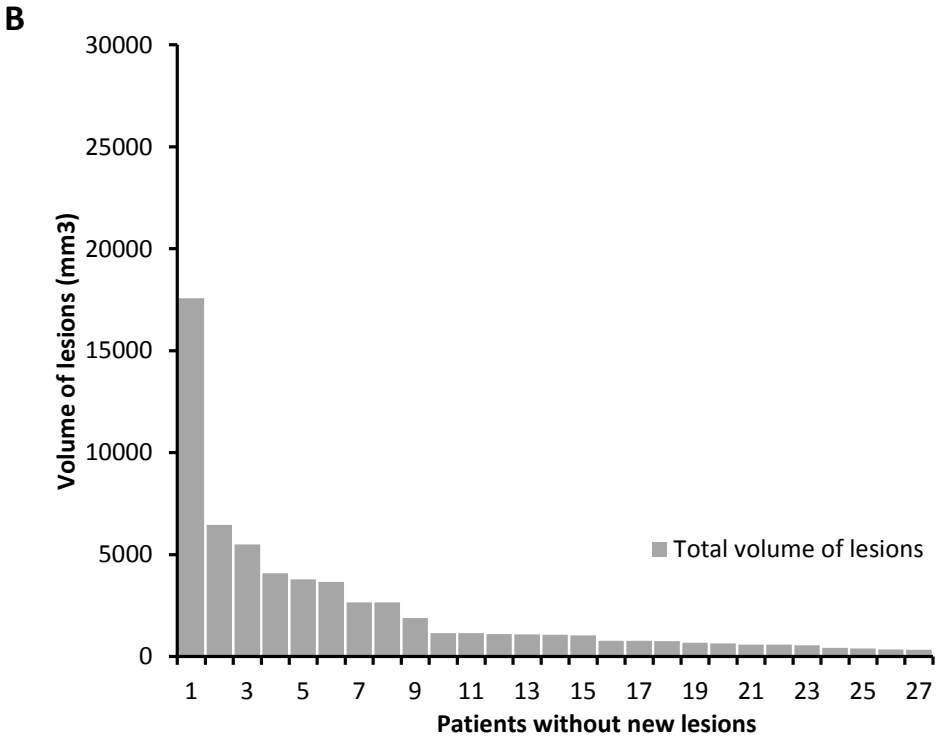

B
30000
25000
20000
15000
10000
5000
0
Volume of lesions (mm3)
Total volume of lesions
1
3
5
7
9
11
13
15
17
19
21
23
25
27
Patients without new lesions

Fig. 2.

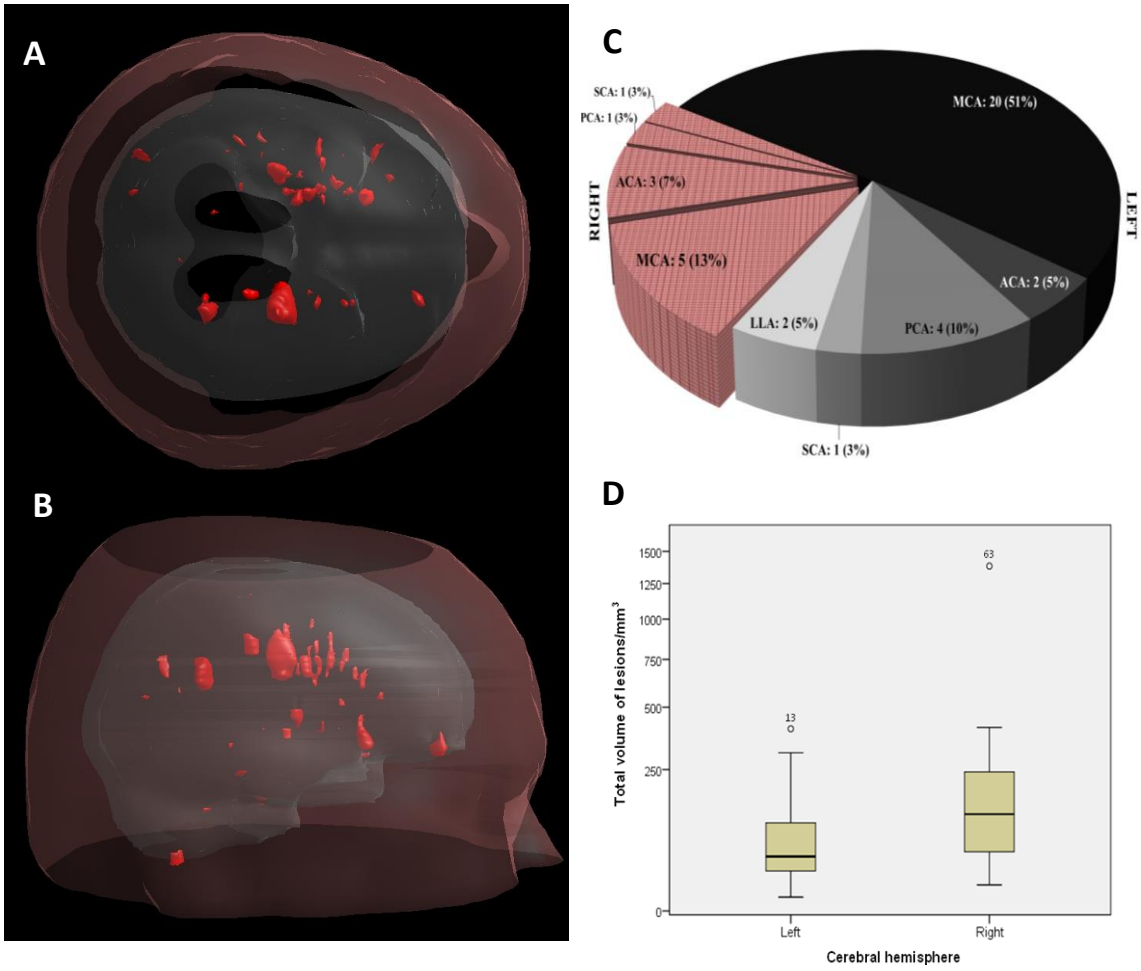

A
B
C
SCA: 1 (3%)
PCA: 1 (3%)
ACA: 3 (7%)
MCA: 5 (13%)
LLA: 2 (5%)
SCA: 1 (3%)
PCA: 4 (10%)
ACA: 2 (5%)
MCA: 20 (51%)
RIGHT
LEFT
D
Total volume of lesions/mm³
1500
1250
1000
750
500
250
0
63
13
Left
Right
Cerebral hemisphere

Fig. 3.

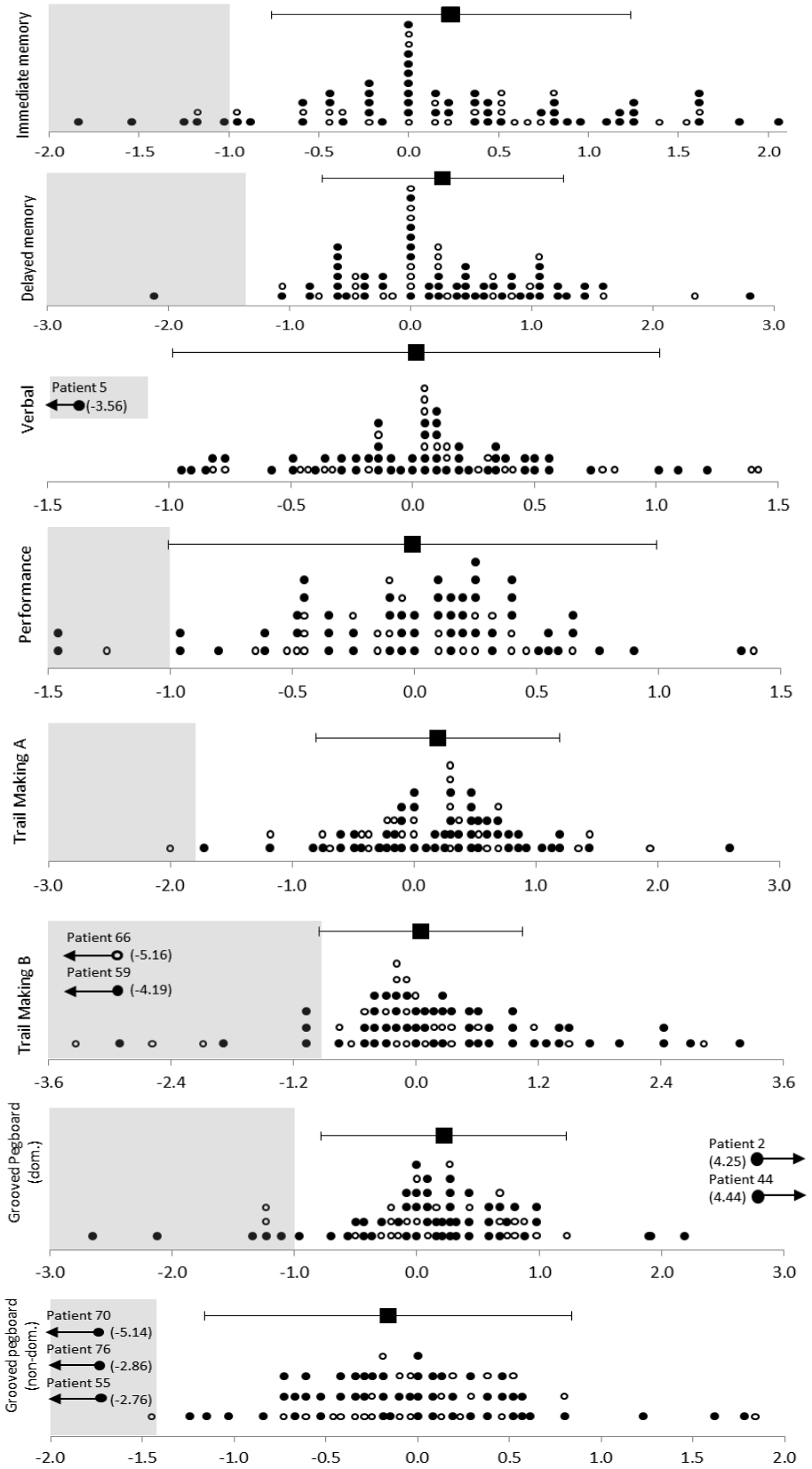

Immediate memory
-2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0
Delayed memory
-3.0 -2.0 -1.0 0.0 1.0 2.0 3.0
Verbal
Patient 5
(-3.56)
-1.5 -1.0 -0.5 0.0 0.5 1.0 1.5
Performance
-1.5 -1.0 -0.5 0.0 0.5 1.0 1.5
Trail Making A
-3.0 -2.0 -1.0 0.0 1.0 2.0 3.0
Trail Making B
Patient 66
(-5.16)
Patient 59
(-4.19)
-3.6 -2.4 -1.2 0.0 1.2 2.4 3.6
Grooved Pegboard (dom.)
Patient 2
(4.25)
Patient 44
(4.44)
-3.0 -2.0 -1.0 0.0 1.0 2.0 3.0
Grooved pegboard (non-dom.)
Patient 70
(-5.14)
Patient 76
(-2.86)
Patient 55
(-2.76)
-2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0

Fig. 4.