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Delirium

Functional brain network and trail making test changes following major surgery and postoperative delirium: a prospective, multicentre, observational cohort study

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Abstract

Background: Delirium is a frequent complication after surgery in older adults and is associated with an increased risk of long-term cognitive impairment and dementia. Disturbances in functional brain networks were previously reported during delirium. We hypothesised that alterations in functional brain networks persist after remission of postoperative delirium and that functional brain network alterations are associated with long-term cognitive impairment.
Methods: In this prospective, multicentre, observational cohort study, we included older patients who underwent clinical assessments (including the Trail Making Test B [TMT-B]) and resting-state functional MRI (rs-fMRI) before and 3 months after elective surgery. Delirium was assessed on the first seven postoperative days.
Results: Of the 554 enrolled patients, 246 remained after strict motion correction, of whom 38 (16%) developed postoperative delirium. The rs-fMRI functional connectivity strength increased 3 months after surgery in the total study population (β=0.006; 95% confidence interval [CI]: 0.001–0.011; P=0.013), but it decreased after postoperative delirium (β=−0.015; 95% CI: −0.028 to 0.002; P=0.023). No difference in TMT-B scores was found at follow-up between patients with and without postoperative delirium. Patients with decreased functional connectivity strength declined in TMT-B scores compared with those who did not (β=11.04; 95% CI: 0.85–21.2; P=0.034).
Conclusions: Postoperative delirium was associated with decreased brain functional connectivity strength after 3 months, suggesting that delirium has a long-lasting impact on brain networks. The decreased connectivity strength was associated with significant cognitive deterioration after major surgery.
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Editor's key points

- Disturbances in functional brain networks are known to occur during delirium.
- This study assessed whether these changes persist after remission of postoperative delirium and if they are associated with long-term cognitive impairment.
- Postoperative delirium was associated with reduced resting-state functional MRI connectivity strength 3 months after clinical resolution.
- Irrespective of delirium, decreased connectivity strength after major surgery was associated with cognitive deterioration.
- These findings provide further evidence of long-term changes in brain function and connectivity after surgery associated with postoperative delirium and cognitive deterioration.

Delirium, a clinical expression of acute encephalopathy,[1] affects 15–25% of older patients after major elective surgery. Delirium can be accompanied by patient distress and increased length of hospital admission, and it is related to poor outcomes, such as long-term cognitive impairment and dementia.[2]

Resting-state functional connectivity based on functional MRI (fMRI) is thought to reflect interactions between brain areas that are crucial for cognitive function.[3] Delirium is characterised by reduced global functional connectivity strength, with less efficient and less integrated functional brain network organisation.[4–6] Reduced global functional connectivity has been observed 1 week after resolution of delirium, suggesting long-term impact of the disorder on the functional brain network.[5] Reduced global functional connectivity strength and disturbances in functional network efficiency and integration have also been reported in cognitive impairment and dementia.[7–9] However, it is unknown whether alterations in connectivity after surgery relate to the cognitive decline seen in some patients.

A long-lasting reduction in global functional connectivity strength attributable to delirium might give insight into the relationship with impaired outcomes, such as long-term cognitive impairment or dementia. However, studies evaluating delirium in relation to brain network have lacked baseline and follow-up measurements (i.e. fMRI measurements before development of delirium and after its resolution).[5,10] It is not known whether the network disturbances that occur in delirium remain long after hospital discharge and whether such functional disconnection is related to impaired cognitive performance. This study aimed to investigate whether postoperative delirium (POD) is associated with reduced global functional connectivity strength, efficiency, and integration of the functional brain network 3 months postoperatively compared with preoperatively, and whether this decrease is related to impaired executive functioning.

Methods

Study design and population

This study is part of the Biomarker Development for Postoperative Cognitive Impairment in the Elderly project at the University Medical Center Utrecht and Charité Hospital at Berlin (ethical approval numbers 14–469 and EA2/092/14, respectively, and registered at NCT02265263 in October 2014).[11] Patients were included between October 2014 and December 2017 when they met the following inclusion criteria: European ancestry, aged 65 yr or more, scheduled for major elective surgery (i.e. orthopaedic, cardiac, gastrointestinal, gynaecological, urologic, maxillofacial, or otorhinolaryngologic surgery) of at least 60 min, and signed informed consent. Patients with one or more of the following characteristics were excluded: life expectancy <1 yr or evidence for (early) dementia as indicated by a score of 23 or less in the Mini-Mental State Examination.[12] This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[13]

Clinical assessment

Included patients were invited to the hospital for baseline measurements and clinical assessment by trained research staff. Preoperative alcohol use was estimated using the self-reported Alcohol Use Disorders Identification Test.[14] A cut-off value of 8 was used to define alcohol misuse.[15] Preoperative depressive symptoms were estimated with the self-reported Geriatric Depression Scale with 15 items,[16] with a score of 6 as a cut-off to define depression. Functional impairment before surgery was measured with the Barthel Index.[17] Preoperative physical status was scored by anaesthesiologists (in training) using the validated ASA physical status.[18] The diagnoses of preoperative hypertension and diabetes mellitus were extracted from patient medical records. Preoperative transient ischaemic attack or stroke was determined from patient medical records and scores from neuroradiologists on cortical, subcortical, and lacunar infarcts based on the Standards for Reporting Vascular changes on Neuroimaging (STRIVE) criteria.[19,20]

Cognitive assessment

The trail making test was administered at baseline and follow-up. We used the TMT-B in this study because lower TMT-B scores have been associated with delirium severity,[21] delirium duration,[22] and with decreased functional connectivity strength in dementia with Lewy bodies, a condition related to delirium.[8] A subject connects 25 dots randomly spread across the page, alternating between ascending letters (A–L) and numbers (1–13). Executive functioning is required, specifically working memory and task-switching ability. The score of the test is the number of seconds required for completion.[17]

Delirium assessment

Delirium was defined according to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders*.[23] Included patients were followed after surgery twice daily for delirium until the day of discharge, with a maximum of seven postoperative days. Delirium was assessed by trained research staff using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU),[24] the Nursing Delirium Screening Scale (Nu-DESC),[25] and chart review.[26] Patients were considered delirious if 2 or more cumulative points on the Nu-DESC or a positive CAM-ICU score or a chart review that showed clear descriptions of delirium (e.g. confused, agitated, drowsy, disorientated, delirious, and receiving delirium-related antipsychotic therapy) confirmed by a consulted delirium expert. In cases of uncertainty, a delirium expert was consulted to make the final determination. If a patient was delirious, we additionally registered the duration of delirium (in days).

Image processing

MRI scans

Magnetic resonance imaging (MRI) was performed before and 3 months after surgery using a 3T Achieva (Philips Medical Systems, Best, the Netherlands) scanner in Utrecht and a 3T TrioTim (Siemens Healthineers, Erlangen, Germany) scanner in Berlin. A T1-weighted 3D turbo field echo structural image was made in Utrecht or a T1-weighted magnetisation-prepared rapid gradient echo structural image was made in Berlin. A T2*-weighted gradient echo–echoplanar imaging image was used for the resting-state blood-oxygen-level-dependent (BOLD) fMRI scan with a duration of ~8 min.[27] Pre-processing of images and additional motion correction[28–30] were performed as described[27] and as in Supplementary digital content 1.

Connectivity and network analysis

Connectivity and network calculations were performed in MATLAB (version R2016b; MathWorks, Natick, MA, USA) using publicly available and personalised scripts to calculate minimum spanning tree (MST) metrics.[31,32] We selected 264 putative functional areas covering all cortical and subcortical brain regions (Supplementary digital content 2).[33] To estimate regional mean time series, voxel time series within each region were averaged. Using Pearson's correlations, functional connectivity was subsequently calculated between all-time series pairs, resulting in a 264 × 264 functional connectivity matrix for each patient.

Minimum spanning trees were calculated using Kruskal's algorithm.[34] The MST can be considered the backbone of the original network, connecting all regions without forming loops,[31,32,34] which allows a relatively unbiased comparison with another network with the same number of regions and connections.[31,32] The MST connections were based on positive correlation values, thus avoiding the problematic interpretation of negative BOLD correlations.[31,32] During delirium, altered global functional network connectivity strength, network efficiency (MST diameter), and network organisation (MST leaf fraction) have been shown[5,6,10]; therefore, these outcomes were also investigated in this study. A detailed description of the MST measures is available in Supplementary digital content 3.

Statistical analysis

Statistical analyses were performed in R statistics (version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria). Sample size was based on data availability in this exploratory study design. Based on previous findings of delirium showing fMRI connectivity differences in 13 patients and 22 controls, we expect that our sample is of sufficient size to find disease effects on outcomes, if present. Baseline characteristics were compared between patients who developed POD and patients who did not, using the χ^2 test for categorical variables and independent sample *t*-test or Mann–Whitney *U*-test for continuous variables, as appropriate.

We used generalised linear mixed models (GLMMs) to analyse the change in MST measures (global functional connectivity strength, MST diameter, and MST leaf fraction) derived from baseline or follow-up fMRI measurements.[35] This method allowed for inclusion of patients who were lost at follow-up or had only one fMRI with sufficient quality and could therefore forestall selection bias. Possible confounders included age, sex, surgical specialty, surgery duration, and study centre, which were entered into GLMMs as covariables. The selection of confounders was based on clinical reasoning and published literature.[2,36] GLMM was also used to compare the change in Trail Making Test B (TMT-B) score between the delirium and non-delirium groups.

As an exploratory analysis, we performed Spearman's correlation analyses to investigate the association between both TMT-B and MST measures (global functional connectivity strength, MST diameter, and MST leaf fraction) with duration of the delirium (in patients who developed POD only).

Lastly, GLMM was used to study if change over time in fMRI outcomes was related to change in executive function, as measured by TMT-B scores. The group that decreased in fMRI outcome measure was compared with the group that did not with regard to the TMT-B change from baseline to 3 months postoperatively. Two-sided tests were used for all analyses, and a *P*-value <0.05 was considered statistically significant. More detailed information on the modelling procedure is available in Supplementary digital content 4.

Results

The eligible cohort consisted of 554 patients with baseline measurements. In total, 246 patients with sufficient quality of the preoperative or postoperative fMRI scan and available postoperative data were included (Fig 1). Included patients were generally more often from Utrecht, younger, had less comorbidities, and scored higher on the TMT-B than excluded patients (Supplementary digital content 5). Of the 246 patients, 38 (16%) developed delirium within the first seven postoperative days. Patients who developed delirium were generally older, had a longer duration of surgery, and had a longer hospital stay compared with patients who remained delirium-free (Table 1).

Functional brain network at baseline

Preoperatively, the delirium group (POD+) did not differ from the group that remained delirium-free (POD−) when comparing the fMRI-based MST variable global functional connectivity strength (β=0.006; 95% confidence interval [CI]: −0.003 to 0.016; *P*=0.165), diameter (β=0.004; 95% CI: −0.004 to

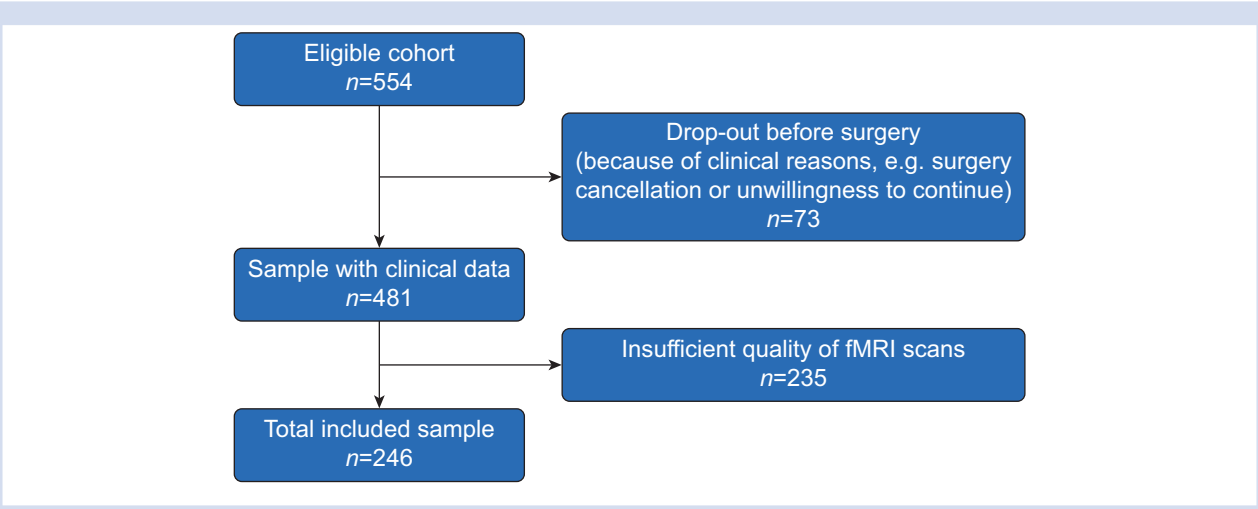

Fig 1. Flowchart of the inclusion of subjects. fMRI, functional MRI.

0.012; P=0.339), and leaf fraction (β=0.000; 95% CI: −0.009 to 0.008; P=0.843) (Supplementary digital content 6).

Change in functional brain network over time

Overall, postoperative global functional connectivity strength was increased compared with baseline (β=0.006; 95% CI: 0.001–0.011; P=0.013). However, a significant interaction between delirium and measurement (i.e. baseline and follow-up) was found, showing a decline in global functional connectivity strength for POD+ (β=−0.015; 95% CI: −0.028 to −0.002; P=0.023) (Fig 2; Table 2).

No significant change was found at 3 months follow-up compared with baseline in MST diameter (β=0.000; 95% CI: −0.004 to 0.005; P=0.977) and MST leaf fraction (β=−0.004; 95% CI: −0.008 to 0.000; P=0.122). In addition, no interaction was found for delirium comparing 3 months follow-up with baseline in MST diameter or leaf fraction, respectively (β=0.000; 95% CI: −0.013 to 0.013; P=0.932) (β=0.002; 95% CI: −0.011 to −0.015; P=0.751) (Table 2).

No significant correlations were found between duration of delirium and brain network connectivity and duration of delirium and TMT-B (Supplementary digital content 7). A sensitivity analysis in a group of non-surgical controls indicated that all fMRI outcomes remained stable during the 3–5 months time interval (Supplementary digital contents 8 and 9).

Global functional connectivity strength and executive function

Clinical consequences of the significant postoperative change in global functional connectivity strength were explored by investigating their relationship to changes in TMT-B scores. The POD+ and POD− groups did not differ in TMT-B scores at 3 months follow-up compared with preoperatively (β=−0.43; 95% CI: −12.39 to 11.54; P=0.944) (Table 1). The relation between change in global functional connectivity strength and TMT-B was performed in a subpopulation for which fMRI scans of sufficient quality for both baseline and follow-up measurements were available (n=130). Patients who had two fMRI scans of sufficient quality were more often from Utrecht and were younger, and 18 patients (14%) were diagnosed with delirium in this group (Supplementary digital content 10). A sensitivity analysis of our main findings was performed on this subpopulation (Supplementary digital content 11).

There were 52 patients (40%) who showed a decrease in global functional connectivity strength at follow-up compared with baseline. The remaining patients (60%) showed stable or increased connectivity strength at follow-up compared with baseline. The frequency of POD was 15.4% in patients with reduced connectivity and 10.3% in patients with stable or increased connectivity strength (P=0.549). Patients with reduced global functional connectivity strength had significant declines in TMT-B score (β=11.04; 95% CI: 0.85–21.2; P=0.034) compared with patients with equal or increased global functional connectivity strength. No interaction with delirium was found (scatterplot is shown in Supplementary digital content 12).

Discussion

This longitudinal study investigated the impact of major surgery and delirium on fMRI functional brain networks in a population of older patients, specifically those network outcomes known to be disturbed during delirium. At 3 months after surgery and relative to the preoperative measurements, global functional connectivity strength was decreased in patients who suffered POD but increased in the total postoperative population. Patients who showed reduced global functional connectivity strength at follow-up had a decline in executive function (TMT-B score) compared with those with increased or unchanged global functional connectivity strength, irrespective of delirium.

No baseline preoperative differences in functional brain networks were found between patients who developed POD and those who remained delirium-free. The current study focused on brain network characteristics altered during delirium (global functional connectivity strength, diameter, and leaf fraction).[4–6] These characteristics do not apparently reflect delirium vulnerability, in line with previous studies.[5,27] The onset of delirium appears to be accompanied by new functional network impairments. This was recently confirmed by an EEG

Table 1 Characteristics of the study population. *P-values of comparisons between the no delirium and delirium groups. Missing values: three Trail Making Test A baseline, eight Trail Making Test B baseline, four hypertension, one diabetes mellitus, 34 Geriatric Depression Scale, 17 Alcohol Use Disorders Identification Test, two surgical specialty, one surgery duration, 41 Trail Making Test A follow-up, and 43 Trail Making Test B follow-up.

	Total (*n*=246)	No delirium (*n*=208)	Delirium (*n*=38)	*P*-value*
Baseline characteristics				
Centre Utrecht, *n* (%)	126 (51.2)	107 (51.4)	19 (50.0)	1
Female, *n* (%)	85 (34.6)	68 (32.7)	17 (44.7)	0.211
Age (yr), median [25th–75th percentile]	71 [68–74]	70.5 [68–74]	73 [69.25–75]	0.050
Mini-Mental State Examination, median [25th–75th percentile]	29 [28–30]	29 [28–30]	28.50 [27–30]	0.063
Trail Making Test B (s), median [25th–75th percentile]	90 [73–120]	89 [72–117]	104 [74–127]	0.215
Hypertension, *n* (%)	134 (55.4)	114 (55.6)	20 (54.1)	1
Transient ischaemic attack or stroke, *n* (%)	89 (36.2)	74 (35.6)	15 (39.5)	0.782
Diabetes mellitus, *n* (%)	42 (17.1)	32 (15.4)	10 (27.0)	0.135
Barthel Index, median [25th–75th percentile]	100 [100–100]	100 [100–100]	100 [100–100]	0.783
Geriatric Depression Scale, median [25th–75th percentile]	1 [0–2]	1 [0–2]	1 [0–2]	0.739
Depression, *n* (%)	10 (4)	8 (4)	2 (5)	1
Alcohol Use Disorders Identification Test, median [25th–75th percentile]	3 [1–4]	3 [1–4]	2 [1–4]	0.379
Alcohol misuse, *n* (%)	14 (6)	10 (5)	4 (11)	0.27
ASA physical status, *n* (%)				0.772
1	19 (7.7)	17 (8.2)	2 (5.3)	
2	151 (61.4)	128 (61.5)	23 (60.5)	
3	76 (30.9)	63 (30.3)	13 (34.2)	
Surgery characteristics				
Surgical specialty, *n* (%)				0.117
Cardiothoracic	34 (13.9)	25 (12.1)	9 (23.7)	
Intra-abdominal	88 (36.1)	72 (35.0)	16 (42.1)	
Orthopaedic	59 (24.2)	52 (25.2)	7 (18.4)	
Other	63 (25.8)	57 (27.7)	6 (15.8)	
Surgery duration (min), median [25th–75th percentile]	153 [94–247]	139 [89–224]	248 [160–335]	<0.001
Length of hospital stay (days), median [25th–75th percentile]	5 [3–8]	4 [2–7]	9.50 [6–15]	<0.001
Hospital mortality, *n* (%)	2 (0.8)	2 (1.0)	0 (0.0)	1
Three months follow-up characteristics				
Mortality before follow-up, *n* (%)	5 (2.0)	5 (2.4)	0 (0.0)	0.733
Trail Making Test B (s), median [25th–75th percentile]	85 [70–112]	83 [69–110]	95 [81–117]	0.123

study that showed a decrease in functional connectivity strength associated with the transition into delirium.[37] Structural network dysconnectivity, expressed as loss of white matter integrity (e.g. of the cerebellum, hippocampus, thalamus, and basal forebrain),[38] has been described as a predisposing factor for delirium.[39] The dynamic nature of the functional brain network and the complex interactions between brain network structure and function might imply that other characteristics predispose patients to delirium than those observed during delirium. Another explanation could be that exclusion of patients with pre-existing cognitive impairment in the current study might have caused an underestimation of differences in the functional network predisposing to delirium, especially because we found that decline in TMT-B was associated with decreased global functional connectivity strength.

In a pilot study, we previously found that global functional connectivity strength was lower in patients 1 week after delirium compared with healthy controls,[5] but no fMRI data were available before onset of delirium. In the current study, the decrease in global functional connectivity strength is evident even after 3 months. A decrease in global functional connectivity strength was associated with deteriorated executive function, as measured with TMT-B. As this decrease was also observed in patients with severe cognitive impairment and dementia,[7–9] we speculate that the long-term decrease in global functional connectivity strength could be related to poor cognitive outcomes in some patients after recovery from surgery. As we found no decline in TMT-B test scores at follow-up between patients with and without POD, we could not test if delirium-related cognitive decline was mediated by decreased global functional connectivity strength.

The absence of long-term executive dysfunction, as shown by TMT-B impairment in the delirium group, could reflect a lack of impact of delirium on long-term executive function. However, we cannot rule out that patients who had more severe cognitive problems were lost to follow-up or were excluded because of strict motion correction.[11] Included patients could have had higher cognitive reserves and strong brain plasticity, possibly resulting in the ability to recover from delirium cognitively.[40]

An interesting observation is that major surgery was associated with an overall increase in global functional connectivity strength over time. However, it is known that surgery alone can increase the risk of long-term cognitive dysfunction.[41] Interpretation of general alterations in connectivity strength is not straightforward. A simulation study of activity-dependent neural degeneration indicated that at an early stage, increased functional connectivity strength might reflect high neural activity levels, which can result in neural damage and could therefore be considered an early state of vulnerability.[42] As major surgery can produce neuro-inflammation and reduced oxygen supply, the increase of global functional

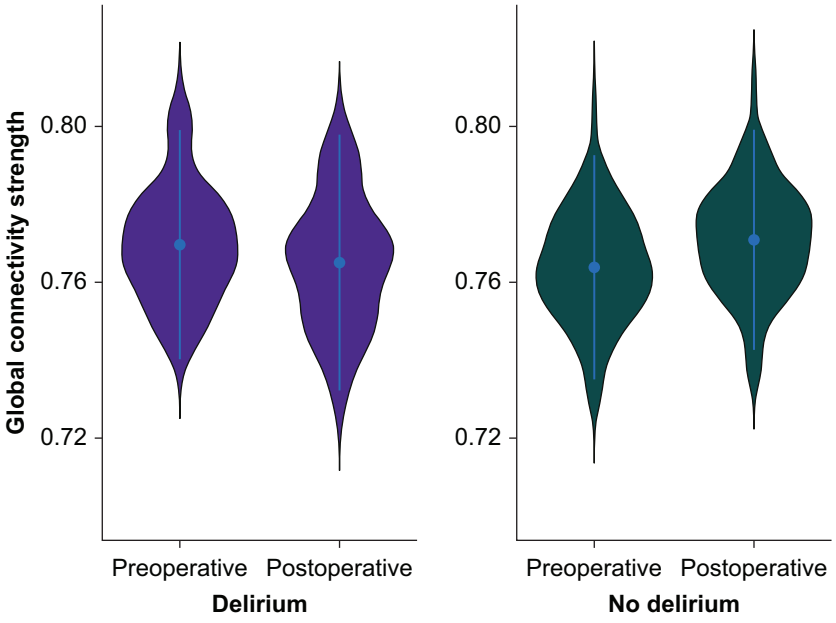

Fig 2. Violin plots of global functional connectivity strength. Global functional connectivity strength preoperatively *vs* 3 months postoperatively for the delirium (n=38) and non-delirium groups (n=208). Global functional connectivity strength was evaluated with a generalised mixed model in an older patient population undergoing major elective surgery. Global functional connectivity strength was significantly increased after surgery (β=0.006; 95% CI: 0.001–0.010; P=0.021) but decreased in patients that developed postoperative delirium 3 months after surgery (β=−0.015; 95% CI: −0.028 to −0.002; P=0.026). CI, confidence interval.

Table 2 Mixed-model analyses of delirium and functional network characteristics. *The β coefficients with 95% CI represent the differences in functional network outcomes. For example, within the global functional connectivity strength column, the β for delirium indicates a 0.007 stronger global functional connectivity at the preoperative measurement compared with non-delirious patients. The β for time reveals an increase of 0.006 at the postoperative measurement compared with the preoperative measurement for global functional connectivity strength. The interaction between time and delirium presents the change over time (i.e. postoperative *vs* preoperative measurement) for delirious patients (e.g. −0.015 for global functional connectivity strength). This means that patients who developed delirium had a decreased global functional connectivity strength of −0.002 at the postoperative measurement (i.e. 0.007+0.006−0.015=−0.002). A random intercept was used for each individual. CI, confidence interval; MMSE, Mini-Mental State Examination; MST, minimum spanning tree; Ref, reference.

	Global functional connectivity strength			Functional network efficiency (MST diameter)			Functional network integration (MST leaf fraction)		
	β	95% CI	P -value	β	95% CI	P -value	β	95% CI	P -value
Baseline									
Age (yr)	0.001	(0.000–0.001)	0.008	0.000	(0.000–0.001)	0.849	0.000	(−0.001 to 0.000)	0.200
Sex	−0.009	(−0.015 to 0.003)	0.004	0.000	(−0.005 to 0.004)	0.895	0.005	(0.000–0.010)	0.035
MMSE	0.001	(−0.001 to 0.003)	0.424	0.001	(−0.001 to 0.002)	0.481	0.001	(−0.001 to 0.003)	0.444
Surgical specialty									
Cardiac surgery	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Intra-abdominal	0.015	(0.005–0.025)	0.003	0.000	(−0.008 to 0.007)	0.911	0.000	(−0.008 to 0.008)	0.958
Orthopaedic	0.004	(−0.007 to 0.015)	0.500	−0.002	(−0.011 to 0.006)	0.563	0.001	(−0.008 to 0.010)	0.854
Other specialties	0.01	(0.000–0.023)	0.042	−0.005	(−0.014 to 0.003)	0.232	0.002	(−0.007 to 0.011)	0.712
Duration of surgery (min)	0.000	(0.000–0.000)	0.907	0.000	(0.000–0.000)	0.273	0.000	(0.000–0.000)	0.917
Centre (Utrecht)	0.011	(0.005–0.017)	0.001	0.007	(0.002–0.012)	0.004	−0.010	(−0.015 to 0.004)	0.000
Delirium	0.007	(−0.003 to 0.016)	0.165	0.004	(−0.004 to 0.012)	0.339	−0.001	(−0.009 to 0.008)	0.844
Postoperative vs preoperative measurement									
Time	0.006	(0.001–0.010)	0.021	0.000	(−0.004 to 0.005)	0.871	−0.004	(−0.008 to 0.001)	0.135
Time–delirium interaction	−0.015	(−0.028 to 0.002)	0.026	0.000	(−0.013 to 0.013)	0.977	0.002	(−0.011 to 0.015)	0.771

connectivity strength in most patients without POD might reflect the resilient initial brain response to the complex interaction of these (and possibly other) factors.[42,43] Computational modelling of brain plasticity after acute events, such as surgery, could bring more insight into the complex phenomena of increased global functional connectivity strength at an early stage and a decrease in more heavily affected patients.

At 3 months follow-up, we found that POD was not associated with changes in functional network efficiency or functional network integration. This finding is consistent with a previous study on functional brain networks that showed that there were no lasting changes in functional network efficiency or network integration 7 days after delirium was clinically resolved.[5] Alterations in functional network efficiency and functional network integration thus seem to be related to the clinical syndrome of delirium and can recover when delirium resolves.

This study evaluated changes in macroscale functional brain network preoperatively compared with 3 months postoperatively in relation to the presence of POD, and linked changes in the functional brain network to postoperative cognitive performance. An important strength of this study is that we obtained measurements before onset of delirium by studying patients undergoing surgery preoperatively. We used robust methods, and a large number of patients were included in this multicentre study. However, there are also important limitations. Our stringent methods, together with the extensive study protocol, including multiple visits to the hospital,[11] might have selected a relatively healthy population with a relatively low incidence of delirium and minimal cognitive burden. Secondly, we focused on the TMT-B, as reduced TMT-B test scores have been associated with delirium severity[21] and duration,[22] and with decreased global functional connectivity strength in dementia with Lewy bodies.[8] However, long-term cognitive impairment after delirium based on functional network changes could be reflected in other cognitive tasks. Another limitation is that information on medication use by patients was not stored. Therefore, we cannot exclude drug-related effects on fMRI measurements (e.g. psychotropic medication). However, all patients were non-hospitalised during the fMRI measurements, which would limited such drug-related effects, and recent studies have shown no fMRI disturbances by chronic use of anti-psychotics.[44,45] Further, we solely focused on fMRI network characteristics altered during delirium; functional brain impairments related to surgery or delirium might be represented in other fMRI outcomes.

Conclusions

Postoperative delirium was associated with a decrease in global functional connectivity strength after 3 months. Reduced global functional connectivity strength was associated with cognitive decline irrespective of postoperative delirium. These findings provide new insights into the biological substrate of long-term brain changes after surgery and postoperative delirium.

Authors' contributions

Data collection: SJTvM, IMJK, EA, CDS, JH, AJCS
Data preparation: FLD, SJTvM, LMV, IMJK, EA, JH, AJCS, EvD
Data analysis: FLD, LMV, SJTvM, EvD
Preparation of article: FLD, SJTvM, LMV, CDS, JH
Revision of article: IMJK, EA, CDS, JH, AJCS, EvD
All authors contributed to the intellectual content of this article and gave final approval of the version to be published.

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Declaration of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.07.054.

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