Chapter 9
Neuroimaging Findings of Delirium

Robert Sanders and Paul Rowley

Introduction

The clinical significance of delirium may be contrasted with our limited understanding of its pathogenesis [1]. In particular, how the symptoms of delirium may arise so suddenly and severely, and yet then often dissipate days later, is perplexing. The lack of robust animal models that mimic the behavioral and cognitive changes in delirium further hampers our insights. This has led many groups to turn to neuroimaging as a tool to gain a greater understanding of the pathogenesis of delirium. Up front, it is important to acknowledge the limited gains that may be expected from this approach. Firstly, delirious patients are unlikely to cooperate with imaging (though hypoactive delirious patients may) [2]. Secondly, it is expensive, logistically complex, and occasionally unpleasant for the patient to undergo imaging, making this research hard to perform, often leading to limited sample sizes in imaging studies. Thirdly, delirium is a heterogeneous condition, and thus it is likely that it may be provoked by diverse pathological mechanisms, making imaging research more difficult again [3].

That said, providing insight into vulnerable brain regions in delirium or altered neuronal dynamics may illuminate the "black box" that is our understanding of delirium pathogenesis. Given the constraints above, research must proceed (at least initially) in a focused, hypothesis-driven manner. Recently the Cognitive Disintegration model [4] has been proposed wherein delirium is proposed to result from a breakdown in connectivity in higher order "cognitive" brain regions, such as

R. Sanders (✉) · P. Rowley
Department of Anesthesiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: robert.sanders@wisc.edu; prowley@wisc.edu

C. G. Hughes et al. (eds.), *Delirium*, https://doi.org/10.1007/978-3-030-25751-4_9

frontoparietal networks like the default mode network [4]. As such prior to delirium, weakened connectivity in these networks could bring someone closer to a "delirium threshold" in connectivity making them more vulnerable to any subsequent precipitant for delirium. Some predisposing factors for delirium, for example, have been associated with impaired functional and structural connectivity, and delirium has been associated with impaired functional connectivity on electroencephalogram (EEG) monitoring. While the literature to date is perhaps inconclusive, neuroimaging research in delirium certainly warrants further study, especially when combined with clear hypotheses about the nature of the pathogenesis of delirium.

Materials and Methods

Search Strategy

A PubMed search using the terms "delirium, imaging" was performed on 28 November 2018 (Fig. 9.1). This query returned 548 results which were initially screened based on their titles and abstracts. Five hundred twenty-two publications were excluded from further evaluation if they were editorials, commentaries, reviews, case reports, or irrelevant. Studies deemed irrelevant included those investigating disorders other than delirium defined as an acute confusional state. The full texts of 50 publications were read and included if quantitative analytic or reliable

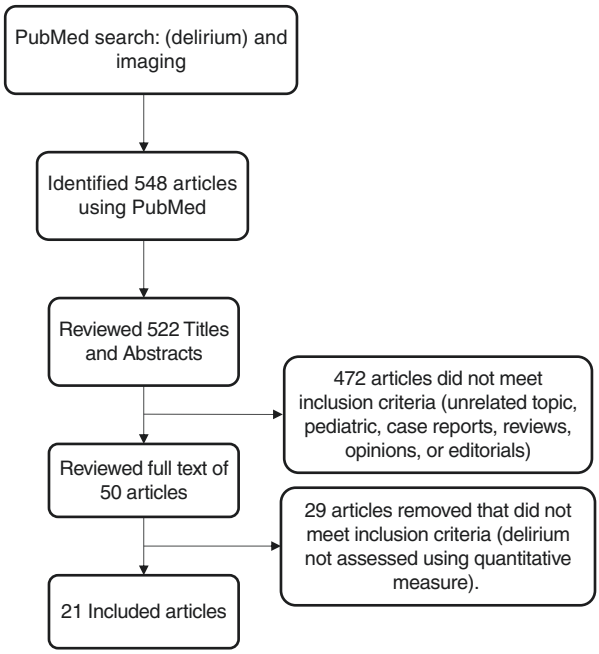

Fig. 9.1 Systematic review flow diagram

qualitative neuroimaging disease classification scales were reported. Twenty-one publications met all these criteria (Table 9.1).

Inclusion Criteria

Studies were considered for inclusion if (1) imaging modalities such as computerized tomography (CT), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), or positron emission tomography (PET) were used, and (2) the study reported quantitative measures such as cerebral blood flow (CBF), diffusion metrics (e.g., fractional anisotropy [FA]), volumetric analyses (e.g., gray matter volume), glucose metabolism (e.g., standardized uptake value ratios [SUVR]), or measured brain pathology using reliable disease classification scales (e.g., Fazekas scale for characterizing white matter lesions [29]).

Outcome Measures

Studies included described delirium incidence and severity using at least one of the following delirium assessment methods: Confusion Assessment Method (CAM), Confusion Assessment Method Short Form (CAM-S), Confusion Assessment Method for the ICU (CAM-ICU), Delirium Rating Scale-Revised-98 (DRS-98), and/or Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria. Studies were included if delirium diagnosis was based on prospective diagnosis and/or validated methods for retrospective diagnosis of delirium by chart review [30, 31].

Associations Between Delirium and Cerebrovascular Pathology

We identified 12 studies that investigated associations between cerebrovascular pathology (e.g., white matter hyperintensity burden [WMHB], brain atrophy) and delirium.

A prospective study of delirium in 47 intensive care unit (ICU) patients (median age = 58 years) involved baseline cognitive assessments (IQCOD-SF), 1-year follow-up cognitive testing, and volumetric MRIs at discharge and 3 months after discharge [8]. This study found greater brain atrophy (as measured by a larger ventricle-to-brain ratio [VBR]) associated with delirium duration at discharge ($p = 0.03$). Longer duration of delirium was also correlated with smaller superior frontal lobe ($p = 0.03$) and hippocampal volumes ($p < 0.001$). Furthermore, worse cognitive performance on the RBANS battery at 1 year after discharge was

Table 9.1 Associated neuroimaging findings of delirium

Reference	Sample size (D+/n)	Methods (scan time point)	Outcome measures	Quantitative metric/ analytic method	Study conclusions
Yokoto et al. [5]	10/10 (100%)	Xe-CT in ICU patients during and after delirium	Delirium incidence (delirium assessment test not listed)	Regional CBF	Regional (cortical and subcortical) and global CBF significantly lower during delirium compared to after delirium resolved
Shioiri et al. [6]	19/116 (16%)	Presurgical DTI, pre-, peri-, and postoperative factors collected	Delirium severity (DRS-98)	FA/voxel-based analysis	Incidence of POD correlated with significantly lower FA in bilaterally widespread deep white matter and bilateral thalamus on preoperative scan
Choi et al. [7]	22∗/44 (50%)	Resting-state fMRI during and after delirium ∗14/22 completed follow-up scans after delirium resolved	Incidence and severity of delirium (MDAS, DRS-98)	Cortical functional connectivity assessed using seed region of PCC and a priori subcortical regions related to Ach and DA	DLPFC activity and PCC activity were inversely related in control subjects but strongly correlated in delirious patients. Precuneus activity positively correlated with PCC in both groups, but more so in delirium, and the increment was associated with less severity and shorter duration of delirium
Gunther et al. [8]	33/47 (70%)	Baseline cognitive assessment (IQCODE-SF), volumetric brain MRI at discharge and 3-month follow-up	Delirium incidence (CAM-ICU), sedation level (RASS), cognitive performance (RBANS)	VBR, TBV, regional volumetric analysis based on a priori regional assignments	Increased duration of delirium associated with smaller brain volumes up to 3 months after discharge and smaller brain volumes associated with LTCI up to 12 months

Morandi et al. [9]	32/47 (68%)	DTI at discharge and 3 months follow-up	Delirium incidence and duration (CAM-ICU), pre-hospitalization cognitive assessment (IQCODE-SF), sedation level (RASS), cognitive performance (RBANS)	FA	Increased duration of delirium associated with decreased FA in the genu and splenium of corpus callosum and anterior limb of internal capsule at discharge
Root et al. [10]	23/47 (49%)	Retrospective analysis of preoperative structural MRI from 23 delirious patients to 24 age- and gender-matched control patients	Delirium assessments performed within 4 days postoperatively (delirium assessment test not listed)	Global WMHB, global CA	Delirium group exhibit greater WMHB, with advancing age being significantly associated with greater WMHB. (No significant difference in CA between groups)
Hatano et al. [11]	18/130 (14%)	Retrospective chart review of preoperative brain MRIs of patients undergoing cardiac surgery	Delirium incidence inferred by two psychiatrists reviewing medical charts using DSM-IV diagnostic criteria for delirium	WMH (Fazekas criteria)	WMH significantly higher in patients with delirium. Three independent predictors of delirium identified abnormal creatinine, severe WMH, and duration of surgery
Brown et al. [12]	28/79 (35%)	Postoperative brain MRI	Delirium assessed using a validated chart review method, preoperative neuropsychological testing	Validated method for grading WMH, ventricular size, and cerebral sulcal size; binary assessment of new ischemic lesions	In an unadjusted analysis, patients who developed POD had significantly higher ventricular size compared to patients without delirium
Omiya et al. [13]	55/80 (66%); 48/80 (60%) DRS between 1 and 7, 7/80 (9%) score DRS = 8	Preoperative (within 3 days) and postoperative (within 2 weeks) MRI and MR angiography (MRA)	Delirium incidence and severity (DRS-R98)	WMH (Fazekas criteria)	The presence of new deep subcortical white matter hyperintensities (DSWMH) following surgery was significantly associated with POD

(continued)

Table 9.1 (continued)

Reference	Sample size (D+/n)	Methods (scan time point)	Outcome measures	Quantitative metric/ analytic method	Study conclusions
Cavallari et al. [14]	32/146 (22%)	Preoperative brain MRI (1 month before surgery), baseline cognitive assessment (SF-12, 3MS, CAM, GDS, and multipart cognitive battery) 2 weeks before surgery	POD incidence (CAM and chart review) and delirium severity (CAM-S) during hospital stay	WMH volume (WM pathology), BPV (brain atrophy), hippocampal volume (regional atrophy)	No statistically significant differences in WMH, whole brain, or hippocampal volume between delirious and non-delirious groups. No statistically significant association between any MRI measure and delirium incidence or severity
Naidech et al. [15]	25/89 (28%)	CT	Delirium incidence (CAM-ICU)	Hematoma volume and location (voxel-wise analysis)	Patients with hematoma in the right parahippocampal gyrus, right anterior SLF, and right posterior SLF were significantly associated with the delirium group
Cavallari et al. [16]	29/136 (21%)	Presurgical DTI (median = 7 days before surgery)	POD incidence (CAM and chart review) and delirium severity (CAM-S long form) during hospital stay	DTI metrics (AD, FA, MD, RD)	Presurgical diffusion tensor imaging abnormalities of the cerebellum, cingulum, corpus callosum, internal capsule, thalamus, basal forebrain, occipital, parietal, and temporal lobes, including the hippocampus, were associated with delirium incidence and severity, after adjusting for covariates. After further controlling for general cognitive performance, diffusion tensor imaging abnormalities of the cerebellum, hippocampus, thalamus, and basal forebrain remained associated with delirium incidence and severity

Hshieh et al. [17]	32/146 (22%)	Preoperative brain MRI (1 month before surgery), baseline cognitive assessment (SF-12, 3MS, CAM, GDS, and multipart cognitive battery) 2 weeks before surgery	POD incidence (CAM and chart review) and delirium severity (CAM-S) during hospital stay	Whole-brain and globally normalized voxel-wise analysis of CBF	No significant association between CBF measures with delirium incidence or severity in both unadjusted and adjusted analyses. CBF globally and regionally (notably precuneus and posterior cingulate) was correlated with performance on several neuropsychological tests
Shioiri et al. [18]	19/116 (16%)	Presurgical MRI, pre-, peri-, and postoperative factors collected	Delirium severity (DRS-98)	Gray matter volume, evaluated as a fraction (%) of the total ICV	Delirium patients displayed a significant reduction in gray matter volume in the define gyri of the temporal and limbic lobes. A receiver operating characteristic curve revealed the gyri of the temporal lobe to display moderate value (>0.8) in predicting POD
Haggstrom et al. [19]	13/13 (100%)	FDG-PET during delirium (13/13) and post-delirium (6/13)	CAM	Cerebral glucose metabolism	Glucose metabolism was significantly higher post-delirium in the whole brain and bilateral PCC compared to during delirium
Cavallari et al. [20]	25/113 (22%)	Presurgical DTI (median = 7 days) and 1-year postoperative DTI (median = 378 days)	POD incidence (CAM and chart review) and delirium severity (CAM-S)	DTI metrics (FA, MD)	Positive association between GCP changes over 1 year and FA changes, and a negative association with MD changes, predominantly in the posterior temporal, parietal, and occipital white matter

(continued)

Table 9.1 (continued)

Reference	Sample size (D+/n)	Methods (scan time point)	Outcome measures	Quantitative metric/ analytic method	Study conclusions
Rolandi et al. [21]	5/11 (45%)	Postoperative PET (^{18}F-Flutematamol), DTI and rs-fMRI	POD assessed daily for 3 days after surgery using CAM and chart review	GM atrophy, WMH volumes, DTI metrics (AD, FA, MD, RD), DMN functional connectivity	5/5 (100%) POD+ were amyloid negative, while 6/11 (54%) POD- were amyloid positive. POD+ compared to POD- displayed significantly lower gray matter volumes in amygdala, middle temporal gyrus, and ACC, increased diffusivity in the genu of corpus callosum and anterior corona radiata, and higher functional connectivity within the Default Mode Network (DMN) (i.e., R and L superior parietal cortex)
Detweiler et al. [22]	100/200 (50%)	CT	Delirium diagnosis (retrospective chart review for ICD-IX code for delirium during hospitalization, later verified using DSM-IV criteria)	White matter lesions (WML), atrophy, intracranial extravascular calcifications	Patients with delirium were found to have significantly more WMLs in the periventricular temporal lobe, subcortical temporal lobe, globus pallidus, putamen, and internal capsule. Atrophy in the parietal lobes and cerebellum was significantly associated with the delirium group
Kyeong et al. [23]	34/72 (47%)	rs-fMRI	Severity of delirium assessed using Korean version of the Delirium Rating Scale-Revised-98 (KDRS), KDRS sleep-wake cycle disturbances, and MMSE	Correlation analysis between SCN and regions associations between FC strengths	Resting-state functional connectivity between the suprachiasmatic nucleus (SCN) and right cerebellum was significantly decreased in delirious patients compared to non-delirium group

Matano et al. [24]	29/200 (13%)	MRI on admission to neuro ICU	Intensive care delirium screening checklist	Global WMH (Fazekas criteria)	Patients with severe white matter disease (per Fazekas criteria) were significantly more likely to become delirious than those without severe white matter disease
Racine et al. [25]	32/145 (22%)	Preoperative MRI	Delirium incidence (CAM), delirium severity (CAM-S), cognitive function (GCP)	Regional cortical thickness	Patients who developed delirium displayed significantly thinner superior parietal cortex than patients who did not develop delirium. Among patients who developed delirium, delirium severity was predicted by a significant reduction in cortical thickness of the middle frontal gyrus, superior frontal gyrus, supramarginal gyrus, and superior parietal cortex
van Montfort et al. [26]	∗22/44 (50%)	rs-fMRI ∗Of 22 patients in delirium cohort, only 16 imaging exams were acquired. Of these 16 patients, 9 were imaged while delirious and 7 imaged post-delirium	Diagnosis of delirium based on DSM-IV, delirium severity assessed by DRS-R-98, delirium duration based on days	Global and regional network analysis	Connectivity strength was significantly decreased in the post-delirium group compared to control and delirium group. Longer diameter and lower leaf fraction were found during delirium compared to control. Betweenness centrality of left anterior cingulum and right palladium was lower in the post-delirium group compared to control. Betweenness centrality of the orbital part of the right middle frontal gyrus, right medial orbitofrontal cortex, and left anterior cingulate was lower in the delirium group compared to the post-delirium group

(continued)

Table 9.1 (continued)

Reference	Sample size (D+/n)	Methods (scan time point)	Outcome measures	Quantitative metric/ analytic method	Study conclusions
Qu et al. [27]	38/261 (15%)	Neurologic deficit assessment (National Institutes of Health Stroke Scale (NIHSS)) on admission, MRI	Delirium incidence (CAM) and delirium severity (DRS-98) during 1st week after admission for acute ischemic stroke	Regional infarction (ROI area measurement), WML (Fazekas criteria), medial temporal lobe atrophy (MTLA) (Scheltens' scale)	Univariate analysis revealed patients with poststroke delirium (PSD) displayed significantly greater infarct volume and MTLA than patients without PSD. Multivariate logistic regression of risk factors for PSD found prior stroke and L-cortical infarction to be significantly associated with patients with PSD
Hijazi et al. [28]	1653/32,725 (5%)	CT, MRI −457/1653 (28%) D+ CT only −10/1653 (1%) D+ MRI only −71/1653 (4%) CT and MRI −1115 (75%) no imaging	Retrospective chart review (ICD-10)	Pathological changes on radiology report noting at least one finding from a set of 10 a priori selected diseases considered "positive" as possible delirium etiology	11% of CT brain scans from delirious patients were positive; diagnoses included hemorrhage ($n = 23$), infarct ($n = 18$), suspected neoplasm ($n = 15$), and posterior reversible encephalopathy syndrome ($n = 1$)

Postoperative delirium (POD), Xenon-enhanced computed tomography (Xe-CT), intensive care unit (ICU), cerebral blood flow (CBF), diffusion tensor imaging (DTI), Delirium Rating Scale-Revised-98 (DRS-R98), fractional anisotropy (FA), functional magnetic resonance imaging (fMRI), Memorial Delirium Assessment Scale (MDAS), posterior cingulate cortex (PCC), acetylcholine (ACh), dopamine (DA), dorsolateral prefrontal cortex (DFC), Short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-SF), Confusional Assessment Method (CAM), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), ventricle-to-brain ratio (VBR), total brain volume (TBV), long-term cognitive impairment (LTCI), white matter hyperintensity burden (WMHB), cerebral atrophy (CA), The Fourth Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), Short Form 12 (SF-12), Modified Mini-Mental State Examination (MMSE), Geriatrics Depression Scale (GDS), Cognitive Assessment Method Severity (CAM-S), general cognitive performance (GCP), brain parenchymal volume (BPV), axial diffusivity (AD), mean diffusivity (MD), radial diffusivity (RD), arterial spin labelling (ASL), intracranial volume (ICV), default mode network (DMN), resting-state functional MRI (rs-fMRI), MR angiography (MRA)

associated with greater brain atrophy (i.e., VBR) at 3 months after discharge ($p = 0.04$). Analysis of volumetric brain MRIs acquired 3 months after discharge compared to imaging at 1 year follow-up found smaller frontal lobe, thalamic, and cerebellar volumes at 3 months associated with worse performance on executive function and visual attention assessments at 12 months after discharge. Associations between brain volumes and cognitive outcomes (global RBANS score, memory, executive functioning, attention and concentration, visual spatial construction, and language) were adjusted for age at study enrollment and presence of sepsis at any time during ICU stay; however, analyses were not corrected for multiple comparisons.

A retrospective analysis of preoperative brain MRIs from 130 cardiac surgery patients (mean age = 66.9 years) found white matter hyperintensity burden (WMHB) in the 18 patients (14%) who developed delirium was significantly greater than in those without delirium ($p = 0.03$) [11]. Relative to patients without delirium, patients who developed postoperative delirium (POD) were also found to have a significantly greater proportion of severe periventricular white matter disease (Fazekas score 3) ($p = 0.04$). Multiple logistic regression analysis additionally identified severe deep WMH (Fazekas score 3) (odds ratio (OR) 3.9, $p = 0.02$), abnormal creatinine level (creatinine >1.1 mg/dL) (OR 4.5, $p = 0.01$), and duration of surgery (OR 1.4, $p = 0.02$) as independent predictors of delirium.

A retrospective analysis of preoperative brain MRIs from 47 age- and gender-matched patients (23 delirious, 23 not delirious, mean = 74 years) who had surgical resection of non-small cell cancer found patients who developed POD displayed greater presurgical global WMHB ($p = 0.017$) than patients without delirium [10]. WMHB was calculated as the ratio of WMH to total intracranial volume, whereas cerebral atrophy was calculated by percent cerebrospinal fluid (CSF) as a fraction of intracranial volume (ICV). While this study found greater WMHB associated with advanced aging ($p = 0.002$), it did not find a significant difference in cerebral atrophy between delirious patients and those without delirium. Advanced aging for all patients was significantly associated with cerebral atrophy ($p = 0.007$).

A prospective study involving 116 cardiac surgical patients (mean age = 64.3 years) reported a significant reduction in temporal and limbic gray matter volume in the 16% (19/116) of patients who developed POD relative to 65 age-controlled non-delirium patients [18]. Delirium was diagnosed using DSM-IV criteria. Delirium severity was quantified using the DRS-98 score. Brain volumes were calculated using automatic atlas-based and voxel-based morphometry. Relative to patients without delirium, the delirium cohort demonstrated significant reductions in gray matter volume in the temporal transverse gyrus ($F = 13.615$, $p < 0.0036$), middle temporal gyrus ($F = 14.033$, $p < 0.0036$), fusiform gyrus ($F = 18.424$, $p < 0.0036$), and hippocampus ($F = 9.539$, $p < 0.0036$). There was no significant decrease in global white matter volume among patients with delirium. A receiver operating characteristic (ROC) analysis revealed atrophy of the fusiform gyrus, middle temporal gyrus, and limbic lobe to be moderately predictive of POD ([AUC = 0.824, $p < 0.001$], [AUC = 0.813, $p < 0.001$], [AUC = 0.764. $p < 0.001$], respectively). Linear regression analysis found weak, albeit statistically significant

correlations between age of the non-delirium group and associated gray matter volumes for the fusiform gyrus ($r = 0.316$, $p = 0.010$) and middle temporal gyrus ($r = 0.378$, $p = 0.002$). In a similar analysis for the delirium group, linear regression analysis found a statistically significant correlation between age and middle temporal gyrus volume reduction ($r = 0.516$, $p = 0.024$).

A prospective cohort study of 88 patients undergoing elective off-pump coronary artery bypass (OPCAB) reported 66% (55/80) of patients developed POD [13]. Postoperative brain MRI revealed 7.9% (7/88) of patients had new ischemic lesions that were not present on preoperative brain MRI. Multivariate logistic regression analysis found new ischemic lesions (OR 11.07, 95% confidence interval [CI] = 1.53–80.03; $p = 0.017$) and deep subcortical WMH (OR 3.04, 95% CI = 1.14–8.12; $p = 0.027$) were significantly associated with POD.

A retrospective chart review study examining the association of brain MRI characteristics and POD in cardiac surgery patients reported a delirium prevalence of 35.4% (28/79) [12]. An unadjusted analysis found patients who developed POD had significantly higher ventricular size compared to patients who did not develop delirium ($p = 0.002$).

An analysis from a subsample of the Successful Aging after Elective Surgery (SAGES) study found that in 146 elderly patients (≥70 years) without dementia, there was no statistically significant difference in WMHB ($p = 0.710$), brain atrophy ($p = 0.334$), and hippocampal atrophy ($p = 0.862$) between the 22% (32/146) of patients who developed POD and those who did not (114/146) [14]. All patients completed baseline cognitive testing within 2 weeks prior to surgery. Incidence and severity of delirium were measured by either CAM alone (0/32), a validated chart review method (9/32), or both (23/32). Presurgical MRI indices of brain damage, which included WMHB (by proxy of white matter hyperintensity volume), brain atrophy (by proxy of brain parenchymal volume [BPV]), and hippocampal volume, were found to have no significant impact on POD incidence; this lack of effect was robust in both an unadjusted and adjusted regression model which included the following covariates: intracranial cavity volume (ICV), age, gender, global cognitive performance (GCP), and vascular comorbidity. However, there was an effect of presurgical MRI indices (WMH volume, brain atrophy, and hippocampal) on delirium severity (as measured by CAM-S test Long Form); in the fully adjusted model, white matter hyperintensity volume was found to be significantly reduced in the delirium group ($p = 0.045$).

A prospective study of 90 patients with intracerebral hemorrhage used voxel-based lesion-symptom mapping with acute CT to identify hematoma locations associated with delirium symptoms ($N = 89$ patients included in analysis) [15]. Delirium was assessed using CAM-ICU and occurred in 28% (25/89) of patients. Patients with hematoma in the right parahippocampal gyrus, right anterior superior longitudinal fasciculus (SLF), and right posterior SLF were significantly associated with the delirium group. Based on the results of voxel-based lesion-symptom mapping analysis, hematoma locations were treated as regions of interest (ROI) to assess the increased likelihood of delirium symptoms given hematoma location. The investigators found hematoma within the ROI increased relative risk for delirium by 6.8

(95% CI = 2.7–17.0, $Z = 4.1$, $P < 0.0001$; OR 13.0, 95% CI = 3.9–43.3, $Z = 4.2$, $P < 0.0001$). Relative risk for hematoma within separate ROIs was calculated and found statistically significant associations for each region: parahippocampal gyrus relative risk = 7.8, 95% CI = 1.7–36.1, $Z = 2.6$, $P = 0.009$; posterior white matter relative risk = 6.9, 95% CI = 2.0–24.1, $Z = 3.1$, $P = 0.002$; and anterior white matter relative risk = 6.5, 95% CI = 1.5–28.6, $Z = 2.5$, $P = 0.01$.

A case-control retrospective chart review of $n = 200$ military veterans (100 delirious, 100 age-, sex-, race-matched controls) examined the association of white matter lesions (WML), cerebral atrophy, intracranial extravascular calcifications, and ventricular-communicating hydrocephalus discovered on CT with delirium [22]. Patients with delirium were found to have significantly more WMLs in the periventricular temporal lobe, subcortical temporal lobe, globus pallidus, putamen, and internal capsule ($p = 0.001$, $p = 0.038$, $p = 0.036$, $p = 0.005$, $p = 0.019$, respectively). Logistic regression for various sizes of WML in brain areas in military veterans with and without delirium revealed significant associations between temporal periventricular WML of <1 cm, 1–2 cm, and >2 cm and delirium occurrence ([OR 20.1, $p = 0.024$], [OR 30.7, $p = 0.009$], [OR 120.9, $p = 0.018$], respectively). Military veterans with WML less than 1 cm in the globus pallidus, putamen, and internal capsule were also significantly associated with the delirium group ([OR 0.005, $p = 0.039$], [OR 00.3, $p = 0.002$], [OR 00.4, $p = 0.010$]). There was also a significant association between parietal and cerebellar atrophy and delirium occurrence among military veterans ($p = 0.044$, $p = 0.041$, respectively).

A prospective study examining environmental and clinical risk factors for delirium in a neurosurgical center reported a delirium incidence of 13.2% (29/200) [24]. MRI on admission to the neurological intensive care unit and global WMH was assessed using Fazekas criteria; univariate analysis revealed patients with severe white matter disease were significantly more likely to become delirious than those without severe white matter disease (OR 7.826, $p = 0.0001$). Additionally, the univariate analysis showed patients diagnosed with subarachnoid hemorrhage on admission were also significantly more likely to become delirious than patients without subarachnoid hemorrhage (OR 4.933, $p = 0.0293$).

As a sub-analysis of the Successful Aging after Elective Surgery (SAGES) study, an investigation into the association between Alzheimer's-related cortical atrophy and POD reported a delirium incidence of 22% (32/145) in a population of elderly patients without dementia who underwent elective surgery [25]. There was no significant association between preoperative MRI estimates of cortical thickness within a set of nine regions associated with Alzheimer's disease (termed the "AD signature") and delirium incidence. However patients who developed delirium were found to have significantly thinner superior parietal cortex than patients without delirium ($p = 0.018$) at baseline. Among patients who developed delirium, delirium severity was predicted by a significant reduction in cortical thickness of the middle frontal gyrus, superior frontal gyrus, supra marginal gyrus, and superior parietal cortex ($p = 0.028$, $p = 0.011$, $p = 0.012$, $p = 0.004$, respectively).

Delirium occurred in 14.6% (38/261) of patients enrolled in a prospective cohort study assessing the incidence of and risk factors for delirium following acute

ischemic stroke [27]. A univariate analysis of MRI data acquired within 7 days of admission revealed patients with poststroke delirium (PSD) displayed significantly greater infarct volume and medial temporal lobe atrophy than patients without PSD ($p < 0.001$, $p < 0.001$, respectively). Furthermore, multivariate logistic regression analysis of risk factors for PSD revealed patients with previous stroke and left cortical infarct were significantly more likely to develop delirium than patients without either risk factor ($p = 0.006$, $p = 0.001$).

Cerebrovascular pathology, such as age-related atrophy, white matter disease, and ischemic lesions, is common among patients with delirium and seem to cluster in regions critical to memory and attention. However, the evidence does not point to a discrete pattern of vascular brain lesions to reliably predict or retrospectively explain delirium.

Association Between Delirium and Cerebral Blood Flow

In a study of ten ICU patients (mean age = 47.5 years) diagnosed with hypoactive delirium [2], regional cerebral blood flow (rCBF) was measured using xenon-enhanced computer tomography (Xe-CT) during delirium and after delirium resolved [5]. Global cerebral blood flow (CBF) was significantly decreased during delirium compared to after delirium resolved ($p = 0.0056$). Cortical CBF was also significantly decreased during delirium across all reported regions. The most significant decreases in cortical CBF occurred in bilateral frontal ($p = 0.0010$) and right frontal regions ($p = 0.007$). Subcortical CBF was also significantly diminished during delirium with the most significant decreases observed in the left lenticular nucleus ($p = 0.0038$), left thalamus ($p = 0.0044$), and bilateral thalami ($p = 0.0045$).

A study demonstrated cerebral blood flow MRI in the nondemented elderly is not predictive of POD but is correlated with cognitive performance [17]. Preoperative brain MRIs from 146 patients (ages ≥70 years) were acquired within 1 month of surgery, and baseline cognitive assessments were performed within 2 weeks prior to surgery. Twenty-two percent (32/146) of patients were prospectively diagnosed with delirium based on confusional assessment method (CAM) alone (0/32), retrospectively based on chart review (9/32), or both (23/32). Delirium severity was prospectively measured during hospital stay using the CAM short form (CAM-S). This study found no significant association between voxel-wise cerebral blood flow measures with delirium incidence or severity. This negative finding was robust in follow-up analyses which included other covariates such as vascular comorbidities and years of education. Positive associations were however found between CBF of the posterior cingulate and precuneus and baseline performance on cognitive tests such as the Hopkins Verbal Learning Test Total Recall (HVLT-R Total Recall), Visual Search and Attention Test (VSAT), and the general cognitive performance measure (GCP). Thus, differences in cerebral blood flow before delirium do not seem to predispose to delirium, but studies suggest that CBF may be reduced during delirium.

Associations Between Delirium and Impaired Functional Connectivity

We identified several studies which investigated impaired functional connectivity (FC) in delirium.

In a case-control functional MRI (fMRI) study, 22 actively delirious patients (mean age = 73.6 years) and 22 age-matched comparison patients received resting-state fMRI scans [7]. Of the 22 delirious patients, 14 completed follow-up scans after delirium resolved. Functional connectivity was assessed by seeding the posterior cingulate cortex (PCC) and measuring FC between the PCC seed and "a priori subcortical regions related to acetylcholine and dopamine." Differences in FC were assessed between 18 of the 20 initial scans (2 excluded due to head movement) and 13 follow-up scans in the delirium group. Follow-up scans were acquired an average of 5.8 days after the initial scan. FC differences between the 18/20 of the delirious and 20 comparison patient scans were also evaluated. The investigators reported that fMRI data from comparison subjects revealed inversely correlated activity between the PCC and the dorsolateral prefrontal cortex bilaterally. Actively delirious patients (also referred to as "during-episode patients") showed a positive correlation between these two regions as well as the left inferior frontal gyrus and precuneus bilaterally. Data acquired from actively delirious patients also showed significantly decreased connectivity between the PCC and left cerebellum compared to the comparison group ($T_{max} = -5.333$). Patients who had previously been delirious showed no correlation with any dorsolateral prefrontal cortex region on fMRI scans acquired after delirium resolved.

Analyses of FC strengths between subcortical regions revealed similar patterns of positively correlated activity between regions in control patients and post-resolution delirium patients. Actively delirious patients, however, lacked significantly correlated FC between several pairs of regions. These pairs of regions include the intralaminar thalamic nuclei and nucleus basalis ($p = 0.888$), the intralaminar thalamic nuclei and ventral tegmental area ($p = 0.103$), the caudate and mesencephalic tegmentum ($p = 0.225$), and the caudate and nucleus basalis ($p = 0.065$). Relative to comparison subjects, during-episode patients had reduced correlation between the intralaminar thalamic nuclei and the mesencephalic tegmentum, nucleus basalis, and ventral tegmental area. Decreased correlation coefficients for connections of the mesencephalic tegmentum with the ventral tegmentum area were also detected ($p = 0.049$) in during-episode patients relative to comparison subjects.

Greater FC between the bilateral precuneus and PCC in during-episode patients was correlated with delirium severity, as measured by Memorial Delirium Assessment Scale (MDAS) (left precuneus $r = -0.47$, $p < 0.05$; right precuneus $r = -0.58$, $p < 0.01$). This FC association with delirium was also detected when delirium severity was measured by the Delirium Rating Scale-Revised-98 (left precuneus = -0.58, $p < 0.01$; right precuneus $r = -0.62$, $p < 0.01$). Delirium duration

was negatively correlated with the increased FC between PCC and bilateral precuneus (left precuneus $r = -0.80$, $p < 0.01$; right precuneus $r = -0.66$, $p < 0.05$).

Resting-state functional MRI was collected from 34 delirious patients and 38 non-delirious controls to assess differences in FC of the circadian clock and neural substrates of sleep-wake disturbances in delirium [23]. Seed-based connectivity of the suprachiasmatic nucleus (SCN) was compared between groups. Analysis of the FC data found connectivity between the SCN and right cerebellum was significantly decreased in delirious patients compared to controls without delirium ($p = 0.02$).

In a study investigating network disintegration during delirium, resting-state functional MRI were collected from 22 delirious and 22 age- and sex-matched non-delirious controls [26]. Controls were also matched on degree of white matter hyperintensity burden. Of the 22 patients in the delirium cohort, imaging exams were acquired from 16 patients. Of these 16 imaging exams, 9 were acquired from delirious patients, whereas 7 were collected from patients after delirium resolution. Global network analysis revealed connectivity strength was significantly reduced in the post-delirium group (M 0.16, SD 0.01) compared to the control group (M 0.19, SD 0.02) with a difference of −0.04 (95% CI −0.05, −0.02, corrected $p = 0.001$) and compared to the delirium group (M 0.17, SD 0.03) with a difference of −0.02 (95% CI −0.02–0.00, corrected $p = 0.027$). Diameter, a measure of the efficiency of global network organization, was significantly increased during delirium (M 0.03, SD 0.05) compared to the control group (M 0.28, SD 0.04) with a difference of 0.04 (95% CI −0.01–0.08, corrected $p = 0.024$). Leaf fraction reflects the extent to which the network has central, integrated organization and was found to be significantly decreased during delirium (M 0.32, SD 0.03) compared to control group (M 0.35, SD 0.03), with a difference of −0.02 (95% CI −0.04–0.02, corrected $p = 0.027$). There were significant negative correlations between delirium duration and leaf fraction (rho = −0.73, $p = 0.039$) and between delirium duration and tree hierarchy (rho = −0.92, $p = 0.001$). Analysis of regional measures by degree, an indication of the importance of a node in the network, found the degree of right posterior cingulate cortex was lower in the delirium group compared to the control group (corrected $p = 0.039$). Betweenness centrality is defined as the fraction of shortest paths that pass through a particular node and was found to be lower in the right inferior temporal gyrus in the delirium group compared to the control group (corrected $p = 0.004$). There was decreased betweenness centrality of the orbital part of the right middle frontal gyrus, right medial orbitofrontal cortex, and left anterior cingulate in the delirium group compared to the post-delirium group (corrected $p = 0.030$, corrected $p = 0.016$, corrected $p = 0.031$, respectively).

Disturbances in functional connectivity during and after episodes of delirium are observed in the limited set of functional imaging studies on delirium. In particular, breakdown in short- and long-range connections, especially those involving the posterior cingulate cortex (PCC), appears to be a common feature of delirium.

Associations Between Delirium and White Matter Integrity

Five studies used diffusion tensor imaging (DTI) to examine white matter tract characteristics associated with delirium. A study of 116 surgical patients (mean age 64.3 years) reported 19 of the 116 patients (16.4%) were delirious [6]. Of these 19 patients with delirium, 18 (94.7%) were older than 60 years. Voxel-wise analysis of preoperative DTI brain scans revealed a significantly increased incidence of POD in individuals with lower fractional anisotropy (FA) in widespread deep white matter structures bilaterally, bilateral thalamus, and corpus callosum compared to non-delirious patients ($p < 0.001$ uncorrected). When the analysis was adjusted for age, a significant decrease in FA was only detected in the left frontal lobe white matter and left thalamus when compared to the non-delirium group.

A two-center, prospective cohort study used DTI to examine the relationship between delirium duration, white matter integrity, and cognitive impairment in 47 ICU survivors (median age 58 years) [9]. Patients were scanned at discharge and at 3 months follow-up. Increased duration of delirium (3 vs 0 days) was associated with decreased FA in the genu (−0.02; $p = 0.04$) and splenium (−0.01; $p = 0.02$) of corpus callosum and anterior limb of internal capsule (−0.02; $p = 0.01$) at discharge. Neuroimaging at 3 months after discharge demonstrated persistent reductions for the genu (−0.02; $p = 0.02$) and splenium (−0.01; $p = 0.004$).

In another DTI study, presurgical diffusion MRIs were collected from 136 elderly patients (≥70 years). Twenty-one percent (29/136) of these patients developed POD [16]. POD diagnosis was made prospectively using the confusional assessment method (CAM) (24/29) or retrospectively based on chart review (5/29). After adjusting for variables such as age, gender, and vascular comorbidity, abnormalities in white matter tracts (as indicated by decreased fractional anisotropy (FA), increased axial diffusivity (AD), increased mean diffusivity (MD), and increased radial diffusivity (RD)) were positively associated with delirium incidence and severity across several brain regions. FA in the cingulum and corpus callosum was significantly decreased in the delirious group compared to patients without delirium ($p = 0.002$, $p = 0.002$, respectively). Delirious patients were found to have significantly greater AD in corpus callosum ($p = 0.004$) and right temporal lobe ($p = 0.015$) compared to patients without delirium. MD was significantly increased in delirious patients in the cingulum ($p = 0.008$), left frontal lobe ($p = 0.013$), left cerebellum ($p = 0.002$), and right parietal lobe ($p = 0.001$). Compared to patients without delirium, delirious patients were found to have significantly increased RD in the cingulum ($p = 0.001$), frontal lobe ($p = 0.006$), and left and right cerebellum ($p = 0.001$, $p = 0.001$).

An additional analysis of a subset of the Successful Aging after Elective Surgery (SAGES) study examined longitudinal diffusion changes in a cohort of older adults (≥70 years) without dementia who underwent elective surgery [20]. Postoperative delirium occurred in 22% (25/113) of participants who had DTI before and 1 year after surgery. Multiple linear regression analysis adjusted for age, sex, education,

and baseline general cognitive performance (GCP) found a positive association between changes in GCP over 1 year and reductions in FA and increases in MD, predominantly in the posterior temporal, parietal, and occipital white matter ($p = 0.02$).

A retrospective chart review investigating CT and MRI findings among hospitalized patients identified delirium occurrence in 5% (1653/32,725, median age = 80 years, IQR 71–86, 54% male) of the study population [28]. Within the cohort of delirious patients who had cerebral imaging (538/1653, 33%), 11% ($n = 57$) of CT brain scans most commonly showed evidence of hemorrhage ($n = 23$), followed by infarct ($n = 18$), suspected neoplasm ($n = 15$), and posterior reversible encephalopathy ($n = 1$). Brain MRI was completed in 17 delirious patients with evidence of pathologic changes on brain CT (17/57); in two cases of suspected neoplasm based on CT, diagnoses were changed after brain MRI to an abscess and an infarct.

Diffusion tensor imaging studies of delirium have shown patients with delirium often demonstrate decreased white matter integrity within the prefrontal cortex, cingulum, and corpus callosum. Nevertheless, future studies are needed to clarify the relationship between DTI measures and delirium pathogenesis.

Associations Between Delirium and Amyloid Positron Emission Tomography

We identified two studies that center on positron emission tomography (PET) imaging findings associated with delirium.

A multimodal imaging study used ^{18}F-Flutemetamol PET, DTI, and resting state functional MRI to investigate the association of POD with markers of neurodegeneration and brain amyloidosis [21]. The study found 45% (5/11) of patients developed POD. All delirious patients in this study were amyloid negative, and 54% (6/11) patients without delirium displayed brain amyloid positivity. Compared to patients without delirium, patients who developed POD displayed significantly lower gray matter volumes in the amygdala ($p = 0.003$) and in the middle temporal gyrus and in the anterior cingulate cortex ($p < 0.001$) and increased diffusivity in the genu of the corpus callosum and in the anterior corona radiata ($p < 0.05$). Analysis of functional connectivity data revealed high functional connectivity within the default mode network, particularly in the right and left superior parietal cortex, in the patients without delirium compared to those with delirium. Voxel-wise tract-based analysis showed no significant difference between groups in FA; however, POD patients were found to have higher mean, axial, and radial diffusivity in the genu of corpus callosum and anterior corona radiata compared to patients without delirium.

One study investigated disturbances in cerebral glucose metabolism in elderly inpatients (median age = 84 years) during delirium ($N = 13/13$) and after delirium

resolution (N = 6/6) using 2-^{18}F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) [19]. All participants (N = 13) showed evidence of cortical hypometabolism during delirium that improved upon delirium resolution (N = 6/6). The authors report glucose metabolism was higher post-delirium in the whole brain and bilateral posterior cingulate cortex (PCC) compared to during delirium ($p < 0.05$).

Despite constituting the smallest category of imaging studies on delirium, PET is already proving to be a promising approach for tracing disturbances in brain glucose metabolism to cognitive changes during and after delirium.

Discussion

In general, these studies demonstrate that delirious patients have sicker brains prior to a stimulus than non-delirious subjects, but these associations are slightly fragile as there is little consideration for the precipitating event that actually induces the delirium. Nonetheless, they provide important preliminary insights about what makes a delirious subject's brain vulnerable to delirium. It seems consistent that both gray and white matter degeneration may predispose to delirium. In particular, differences in structural connectivity appear to be associated with subsequent delirium; whether this can be meaningfully used to predict delirium in other cohorts should be tested. These changes are broadly consistent with our Cognitive Disintegration model, but the role of degenerating gray matter was not covered in our model and may be critically important, especially if specific cell types or synaptic loss can be identified to be selectively degenerating. Perhaps most intriguing is the recent paper suggesting that amyloid beta deposition is not associated with delirium, contrasting with strong evidence that dementia predisposes to delirium. While this study was very small and prone to selection bias, it seems to oppose the view that dementia pathology is associated with delirium based on studies of cerebrospinal fluid markers of dementia [32]. A large amyloid PET study is required to resolve this ambiguity.

In contrast, differences in cerebral blood flow before delirium do not seem to predispose to delirium. Studies of the critical dynamic phase of delirium (i.e., during delirium) are rare. Studies suggest that CBF may be reduced during delirium, and functional connectivity may shift from baseline patterns to a new network orientation with greater connectivity in posterior cortex and impaired connectivity of subcortical regions. These latter studies are remarkably difficult due to motion artifact, and this makes reproducing these results of particular importance. Nonetheless the fact there are changes in CBF and connectivity during delirium is an important insight. Of course, decreases in CBF may also make interpretation of changes in fMRI connectivity (a measure that is dependent on blood flow) more complicated, and this confound requires that other imaging modalities are considered when assessing the pathophysiology of delirium. While CBF studies suggest frontal cortical involvement, fMRI studies suggest that the most relevant connectivity changes

may occur posteriorly in cortex or at a subcortical level in delirium. This discordance is intriguing and may yield important clues about the pathophysiology of delirium. However, a key issue is to understand the direction of causality (if any) between these findings. Assuming causation from observational imaging studies is clearly dangerous and warrants cautious interpretation. Nonetheless it appears biologically plausible that changes in blood flow (presumably indicating changes in neuronal activity) and functional connectivity (presumably reflecting integration of information across neurons) may be associated with delirium.

Future Directions

Future studies must concentrate on reproducing prior findings and consideration of both imaging and confounding factors including the severity of the precipitating event. Ideally, longitudinal scanning designs will be adopted to improve the likelihood that any factor identified changed contemporaneously with delirium symptoms. In particular, resolving the role of amyloid pathology and delirium seems a key issue for the field.

References

1. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, Serafim RB, Stevens RD. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ. 2015;350:h2538.
2. Hosker C, Ward D. Hypoactive delirium. BMJ. 2017;357:j2047.
3. Sanders RD, Pandharipande PP, Davidson AJ, Ma D, Maze M. Anticipating and managing postoperative delirium and cognitive decline in adults. BMJ. 2011;343:d4331.
4. Sanders RD. Hypothesis for the pathophysiology of delirium: role of baseline brain network connectivity and changes in inhibitory tone. Med Hypotheses. 2011;77(1):140–3.
5. Yokota H, Ogawa S, Kurokawa A, Yamamoto Y. Regional cerebral blood flow in delirium patients. Psychiatry Clin Neurosci. 2003;57(3):337–9.
6. Shioiri A, Kurumaji A, Takeuchi T, Matsuda H, Arai H, Nishikawa T. White matter abnormalities as a risk factor for postoperative delirium revealed by diffusion tensor imaging. Am J Geriatr Psychiatry. 2010;18(8):743–53.
7. Choi SH, Lee H, Chung TS, Park KM, Jung YC, Kim SI, Kim JJ. Neural network functional connectivity during and after an episode of delirium. Am J Psychiatr. 2012;169(5):498–507.
8. Gunther ML, Morandi A, Krauskopf E, Pandharipande P, Girard TD, Jackson JC, Thompson J, Shintani AK, Geevarghese S, Miller RR III, Canonico A. The association between brain volumes, delirium duration and cognitive outcomes in intensive care unit survivors: a prospective exploratory cohort magnetic resonance imaging study. Crit Care Med. 2012;40(7):2022.
9. Morandi A, Rogers BP, Gunther ML, Merkle K, Pandharipande P, Girard TD, Jackson JC, Thompson J, Shintani AK, Geevarghese S, Miller RR III. The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging. Crit Care Med. 2012;40(7):2182.
10. Root JC, Pryor KO, Downey R, Alici Y, Davis ML, Holodny A, Korc-Grodzicki B, Ahles T. Association of pre-operative brain pathology with post-operative delirium in a cohort

of non-small cell lung cancer patients undergoing surgical resection. Psycho-Oncology. 2013;22(9):2087–94.
11. Hatano Y, Narumoto J, Shibata K, Matsuoka T, Taniguchi S, Hata Y, Yamada K, Yaku H, Fukui K. White-matter hyperintensities predict delirium after cardiac surgery. Am J Geriatr Psychiatry. 2013;21(10):938–45.
12. Brown CH IV, Faigle R, Klinker L, Bahouth M, Max L, LaFlam A, Neufeld KJ, Mandal K, Gottesman RF, Hogue CW Jr. The association of brain MRI characteristics and postoperative delirium in cardiac surgery patients. Clin Ther. 2015;37(12):2686–99.
13. Omiya H, Yoshitani K, Yamada N, Kubota Y, Takahashi K, Kobayashi J, Ohnishi Y. Preoperative brain magnetic resonance imaging and postoperative delirium after off-pump coronary artery bypass grafting: a prospective cohort study. Can J Anesth/J C d'anesthésie. 2015;62(6):595–602.
14. Cavallari M, Hshieh TT, Guttmann CR, Ngo LH, Meier DS, Schmitt EM, Marcantonio ER, Jones RN, Kosar CM, Fong TG, Press D. Brain atrophy and white-matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons without dementia. Neurobiol Aging. 2015;36(6):2122–9.
15. Naidech AM, Polnaszek KL, Berman MD, Voss JL. Hematoma locations predicting delirium symptoms after intracerebral hemorrhage. Neurocrit Care. 2016;24(3):397–403.
16. Cavallari M, Dai W, Guttmann CR, Meier DS, Ngo LH, Hshieh TT, Callahan AE, Fong TG, Schmitt E, Dickerson BC, Press DZ. Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. Brain. 2016;139(4):1282–94.
17. Hshieh TT, Dai W, Cavallari M, Guttmann CR, Meier DS, Schmitt EM, Dickerson BC, Press DZ, Marcantonio ER, Jones RN, Gou YR. Cerebral blood flow MRI in the nondemented elderly is not predictive of post-operative delirium but is correlated with cognitive performance. J Cereb Blood Flow Metab. 2017;37(4):1386–97.
18. Shioiri A, Kurumaji A, Takeuchi T, Nemoto K, Arai H, Nishikawa T. A decrease in the volume of gray matter as a risk factor for postoperative delirium revealed by an atlas-based method. Am J Geriatr Psychiatry. 2016;24(7):528–36.
19. Haggstrom LR, Nelson JA, Wegner EA, Caplan GA. 2-18F-fluoro-2-deoxyglucose positron emission tomography in delirium. J Cereb Blood Flow Metab. 2017;37(11):3556–67.
20. Cavallari M, Dai W, Guttmann CR, Meier DS, Ngo LH, Hshieh TT, Fong TG, Schmitt E, Press DZ, Travison TG, Marcantonio ER. Longitudinal diffusion changes following postoperative delirium in older people without dementia. Neurology. 2017;89(10):1020–7.
21. Rolandi E, Cavedo E, Pievani M, Galluzzi S, Ribaldi F, Buckley C, Cunningham C, Guerra UP, Musarra M, Morzenti S, Magnaldi S. Association of postoperative delirium with markers of neurodegeneration and brain amyloidosis: a pilot study. Neurobiol Aging. 2018;61:93–101.
22. Detweiler MB, Sherigar RM, Bader G, Sullivan K, Kenneth A, Kalafat N, Reddy P, Lutgens B. Association of white matter lesions, cerebral atrophy, intracranial extravascular calcifications, and ventricular-communicating hydrocephalus with delirium among veterans. South Med J. 2017;110(6):432–9.
23. Kyeong S, Choi SH, Shin JE, Lee WS, Yang KH, Chung TS, Kim JJ. Functional connectivity of the circadian clock and neural substrates of sleep-wake disturbance in delirium. Psychiatry Res Neuroimaging. 2017;264:10–2.
24. Matano F, Mizunari T, Yamada K, Kobayashi S, Murai Y, Morita A. Environmental and clinical risk factors for delirium in a neurosurgical center: a prospective study. World Neurosurg. 2017;103:424–30.
25. Racine AM, Fong TG, Travison TG, Jones RN, Gou Y, Vasunilashorn SM, Marcantonio ER, Alsop DC, Inouye SK, Dickerson BC. Alzheimer's-related cortical atrophy is associated with postoperative delirium severity in persons without dementia. Neurobiol Aging. 2017;59:55–63.
26. van Montfort SJ, van Dellen E, van den Bosch AM, Otte WM, Schutte MJ, Choi SH, Chung TS, Kyeong S, Slooter AJ, Kim JJ. Resting-state fMRI reveals network disintegration during delirium. NeuroImage: Clinical. 2018;20:35–41.

27. Qu J, Chen Y, Luo G, Zhong H, Xiao W, Yin H. Delirium in the acute phase of ischemic stroke: incidence, risk factors, and effects on functional outcome. J Stroke Cerebrovasc Dis. 2018;27(10):2641–7.
28. Hijazi Z, Lange P, Watson R, Maier AB. The use of cerebral imaging for investigating delirium aetiology. Eur J Intern Med. 2018;52:35–9.
29. Helenius J, Henninger N. Leukoaraiosis burden significantly modulates the association between infarct volume and National Institutes of Health Stroke Scale in ischemic stroke. Stroke. 2015;46(7):1857–63.
30. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST Jr, Leslie DL, Agostini JV. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. J Am Geriatr Soc. 2005;53(2):312–8.
31. Saczynski JS, Kosar CM, Xu G, Puelle MR, Schmitt E, Jones RN, Marcantonio ER, Wong B, Isaza I, Inouye SK. A tale of two methods: chart and interview methods for identifying delirium. J Am Geriatr Soc. 2014;62(3):518–24.
32. Cunningham EL, McGuinness B, McAuley DF, Toombs J, Mawhinney T, O'Brien S, Beverland D, Schott JM, Lunn MP, Zetterberg H, Passmore AP. CSF beta-amyloid 1–42 concentration predicts delirium following elective arthroplasty surgery in an observational cohort study. Annals of surgery. 2019;269(6):1200–5.