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A systematic review of neuroimaging in delirium: predictors, correlates and consequences

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Objective: Neuroimaging advances our understanding of delirium pathophysiology and its consequences. A previous systematic review identified 12 studies (total participants $N = 764$, delirium cases $N = 194$; years 1989–2007) and found associations with white matter hyperintensities (WMH) and cerebral atrophy. Our objectives were to perform an updated systematic review of neuroimaging studies in delirium published since January 2006 and summarise the available literature on predictors, correlates or outcomes.

Methods: Studies were identified by keyword and MeSH-based electronic searches of EMBASE, MEDLINE and PsycINFO combining terms for neuroimaging, brain structure and delirium. We included neuroimaging studies of delirium in adults using validated delirium assessment methods.

Results: Thirty-two studies (total $N = 3187$, delirium $N = 1086$) met the inclusion criteria. Imaging included magnetic resonance imaging (MRI; $N = 9$), computed tomography ($N = 4$), diffusion tensor imaging ($N = 3$), transcranial Doppler ($N = 5$), near infrared spectroscopy ($N = 5$), functional-MRI ($N = 2$), single photon emission computed tomography ($N = 1$), proton MRI spectroscopy ($N = 1$), arterial spin-labelling MRI ($N = 1$) and 2-^{13}fluoro-2-deoxyglucose positron emission tomography ($N = 1$). Despite heterogeneity in study design, delirium was associated with WMH, lower brain volume, atrophy, dysconnectivity, impaired cerebral autoregulation, reduced blood flow and cerebral oxygenation and glucose hypometabolism. There was evidence of long-term brain changes following intensive care unit delirium.

Conclusions: Neuroimaging is now used more widely in delirium research due to advances in technology. However, imaging delirious patients presents challenges leading to methodological limitations and restricted generalisability. The findings that atrophy and WMH burden predict delirium replicates findings from the original review, while advanced techniques have identified other substrates and mechanisms that warrant further investigation. Copyright © 2017 John Wiley & Sons, Ltd.

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Introduction

Delirium is a neuropsychiatric syndrome characterised by acute and fluctuating disturbances in attention, awareness and cognitive processing (World.Health. Organization, 1993) affecting 10–42% of hospitalised adults (Siddiqi *et al.,* 2006), 50–80% of intensive care patients and 22–89% of inpatients with dementia (Fick *et al.,* 2002; Girard *et al.,* 2010).

Delirium is independently associated with adverse outcomes including admission to nursing home (McCusker *et al.,* 2001), long-term cognitive impairment (MacLullich *et al.,* 2009), accelerated dementia (Fong *et al.,* 2009) and death (McCusker *et al.,* 2002). However, delirium pathophysiology remains poorly understood. Neuroimaging provides a non-invasive means of advancing our understanding of the mechanisms underlying delirium.

A previous systematic review of neuroimaging studies of delirium found increased risk of delirium with cortical atrophy, white matter lesions and ventricular enlargement (Soiza *et al.,* 2008). Surprisingly for such a common condition, only 12 studies involving 194 patients were eligible for inclusion.

Since this review, several robust and noteworthy studies utilising recent advances in medical imaging technology have been published. We sought to systematically review the literature published after 1 January 2006 to consolidate information on neuroimaging in delirium and guide future work.

Objectives

The objectives of this review, much like that conducted in 2006, were as follows:

a) Summarise the available literature;
b) Determine whether conclusions regarding predictors, correlates or consequence of delirium could be drawn from structural and functional neuroimaging.

Methods

Protocol and registration

This review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.,* 2009) and registered with PROSPERO (CRD420160041562).

Search strategy

Studies published after 1 January 2006 were identified by searching EMBASE, MEDLINE, PsycINFO and the Cochrane databases. No language restrictions were applied. A forward citation search based on the original review article was conducted using SCOPUS. We used a search strategy combining keywords and MeSH terms relating to specific neuroimaging modalities, delirium and brain structure (Appendix A). As an updated search strategy was adopted, a 2-year overlap period with the previous review allowed assessment of article yield sensitivity.

Database search results were imported to EndNote. Two reviewers (A. N. and V. K.) independently screened article titles and abstracts for eligibility. Potentially eligible articles and relevant reviews were read in entirety; reference lists were manually searched for additional studies. Field experts were consulted for article suggestions.

Eligibility criteria

We evaluated all neuroimaging studies containing original data on delirium in adults (>18 years of age) using a validated diagnostic criteria for delirium, including but not limited to the following: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; *International Classification of Disease and Confusion Assessment Method* (Inouye *et al.,* 1990). All relevant studies published after January 2006 were included for review irrespective of their inclusion in the 2008 review. We excluded single case reports, conference abstracts and articles not published in English. Studies examining metabolic encephalopathies and delirium tremens were excluded because of their specific aetiologies and previously characterised features (Maes *et al.,* 2000; Sutter and Kaplan, 2015).

Article selection, data extraction and quality assessment

Article selection, data extraction and quality assessment were conducted independently by A. N. and V. K. Disagreement regarding eligibility was resolved by consensus and discussion with a third reviewer (G. C.).

Where available, data on study design, provenance, setting, recruitment process, presence of dementia, number of cases, average age, gender, method of assessing delirium, delirium cause, imaging modality and methods and use of comparator imaging were extracted. Data assessing structural, vascular and functional neuroimaging findings relating to predictors, correlates and consequences of delirium were recorded; most outcome measures were expressed as group difference between delirious and non-delirious cohorts. The probability (p values) and odds ratio (OR) with confidence intervals (CI) of observed differences were also noted.

Bias assessment was adapted from the validated Risk of Bias Assessment Tool for Nonrandomised Studies (Kim *et al.,* 2013) and quality criteria from the previous review (Soiza *et al.,* 2008) concerning participant selection, confounding variables, imaging methods, delirium assessment, blinding, incomplete data and selective outcome reporting. Individual biases were assessed as 'high', 'low' or 'unclear' risk (Appendix B).

Results

After removal of duplicates, database searches identified 4117 articles. Title and abstract review excluded 4039 leaving 78 articles; hand searching reference lists yielded five further papers. One article 'in-press' was added following discussion with a field expert. Of these 84, 32 met the inclusion criteria (Figure 1).

Overview

The 32 eligible articles are summarised in Tables 1 and 2. These comprised 26 prospective and one retrospective cohort studies, and three case–control studies. Sample sizes ranged from 10 to 527 totalling 3187 patients of whom 1086 had delirium (mean age: 70.3 years).

The imaging modalities captured included magnetic resonance imaging (MRI; $N = 9$), transcranial Doppler (TCD; $N = 5$), near infrared spectroscopy (NIRS; $N = 5$), computed tomography (CT; $N = 4$), diffusion tensor-MRI ($N = 3$), functional MRI (fMRI; $N = 2$), single-proton emission CT (SPECT; $N = 1$), arterial spin-labelled MRI (ASL-MRI; $N = 1$), 2-^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET; $N = 1$) and proton MRI spectroscopy (^{1}H-MRS; $N = 1$).

Participants were recruited from various populations: cardiothoracic surgery ($N = 10$), septic shock ($N = 5$), acute geriatrics ($N = 5$), other elective surgery ($N = 5$), stroke ($N = 3$), intensive care unit (ICU) patients ($N = 3$) and bone marrow transplant ($N = 1$).

The quality of included studies was variable. Table 3 and appendix C summarises the consensus bias assessment. The main sources of bias were participant recruitment (e.g. convenience sampling); inadequate consideration of confounding variables such as dementia or depression; and reliability of imaging analysis. Retrospective diagnosis of delirium using a validated chart review method also carries a high risk of bias from more false negatives (Inouye *et al.*, 2005). Attrition bias was low.

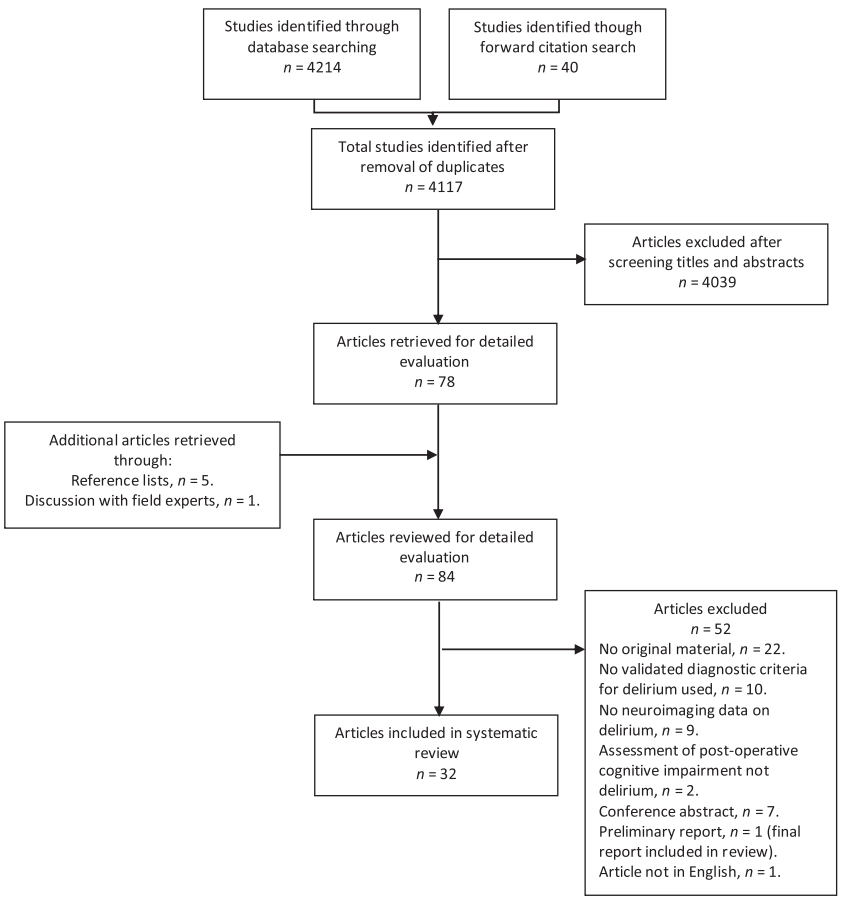

Figure 1 Flow chart of selection of studies for inclusion in this review.

Table 1 Studies assessing structural neuroimaging outcomes (MRI/CT/DTI)

Study/ provenance	Design/setting	Mean age (years)	Delirium assessment method and prevalence	Imaging modality and timing of scan.	Main findings with delirium
Shioiri *et al.* 2016 Japan	Prospective cohort; 116 patients, cardiothoracic surgery.	64	DSM IV, DRS-98. 19/119 (16%)	MRI Preoperative.	Reduced grey matter volume (delirium vs. no-delirium, expressed as a fraction [%] of total intracranial volume) in: Temporal lobe: 5.467 ± 0.665 vs. 6.116 ± 0.552 ($p < 0.0063$) Limbic lobe: 3.661 ± 0.340 vs. 3.973 ± 0.284 ($p < 0.0063$) Temporal transverse gyrus: 0.071 ± 0.018 vs. 0.381 ± 0.057 ($p < 0.0036$) Middle temporal gyrus: 1.664 ± 0.219 vs. 1.926 ± 0.219 ($p < 0.0036$) Fusiform gyrus: 1.144 ± 0.117 vs. 1.291 ± 0.113 ($p < 0.0036$) Hippocampus: 0.433 ± 0.092 vs. 0.502 ± 0.061 ($p < 0.0036$)
Brown *et al.* 2015 United States	Prospective cohort; 79 patients, cardiothoracic surgery with elevated risk of stroke.	70	Chart review method. 28/79 (35.4%)	MRI Median 6 days post-operatively.	Increased ventricular size ($p = 0.003$) (OR = 3.59, %95CI 1.59–8.12; $p = 0.002$). No statistical significance: Sulcal size ($p = 0.05$) WMH volume ($p = 0.05$)
Cavallari *et al*. 2015 United States	Prospective cohort; 146 patients, elective surgery (orthopaedic, vascular, abdominal).	76	CAM, chart review method. 32/146 (21.9%)	MRI <2 weeks prior to surgery.	No statistical significance: (delirium vs. no-delirium [cm^3]) WMH volume: 10.24 ± 7.59 vs.11.55 ± 9.94; $p = 0.710$. Brain Parenchymal volume: 996.79 ± 108.68 vs. 1018.71 ± 114.32; $p = 0.334$. Hippocampal volume: 3.23 ± 0.43 vs. 3.25 ± 0.47; $p = 0.862$.
Omiya *et al.* 2015 Japan	Prospective cohort; 88 patients, elective cardiothoracic surgery.	69	DRS-R98. Delirium: 7/88 (8%) Subclinical delirium: 48/88 (55%)	MRI <3 days prior to surgery. Repeat scanning: <2 weeks after removal of temporary pacing wires.	New ischaemic lesions (OR = 11.07, 95%CI 1.53–80.03; $p = 0.017$). Increased WMH burden (DWMH + PVH) (OR = 3.04, 95%CI: 1.14–8.12; $p = 0.027$).
Hatano *et al.* 2013 Japan	Retrospective cohort; 130 patients, cardiothoracic surgery.	67	Chart review method. 18/130 (13.8%)	MRI Preoperative.	Severe WMH. (OR = 3.9, 95%CI: 1.2–12.5; $p = 0.02$).

(*Continues*)

Table 1. (Continued)

Study/ provenance	Design/setting	Mean age (years)	Delirium assessment method and prevalence	Imaging modality and timing of scan.	Main findings with delirium
Polito *et al.* 2013 France	Prospective cohort; 71 patients, septic shock with acute brain dysfunction.	65	CAM-ICU. 35/71 (49.3%)	MRI During episode of delirium.	No statistical significance: Leukoencephalopathy, ischaemia ($p = 0.15$).
Otomo *et al.* 2013 Japan	Prospective cohort; 153 patients, elective cardiothoracic surgery.	72	DRS, DSMIV. 16/153 (10.5%)	MRI <2 weeks prior to surgery.	Higher prevalence of preoperative cerebral infarcts. (OR = 2.26, 95%CI: 1.10–4.77; $p = 0.027$). No statistical significance: Intracranial arterial stenosis, white matter lesions ($p > 0.05$).
Root *et al.* 2013 Unites States	Retrospective case–control; 47 patients, lung resection for NSCLCa.	73	Chart review method. 23/47 (49%)	MRI Preoperative (staging scan).	Increased WMH burden: Delirium vs. no-delirium (WMH: cranial volume ratio): (0.01 ± 0.01 vs. 0.005 ± 0.005; $p = 0.017$). No statistical significance: Cerebral atrophy (CSF: cranial volume ratio) (0.37 ± 0.05 vs. 0.35 ± 0.04; $p = 0.113$).
Gunther *et al.* 2012 United States	Prospective cohort; 47 patients, surviving ICU admission.	58	CAM-ICU. 33/47 (70%)	MRI Hospital discharge and 3 month follow up.	Longer duration of delirium associated with: Smaller brain volume at hospital discharge ($p = 0.03$) and at 3 months ($p = 0.05$). Smaller superior frontal lobe volume at discharge ($-2.11 cm^3$, 95%CI -3.89–-0.32; $p = 0.03$) and at 3 months ($-2.36\ cm^3$, 95%CI = -4.3–-0.41; $p = 0.02$). Smaller hippocampal volume at discharge ($-0.58 cm^3$, 95%CI-0.85–-0.31; $p < 0.001$) but not at 3 months ($p = 0.17$).
Naidech *et al.* 2016 United States	Prospective cohort; 89 patients, spontaneous intracerebral haemorrhage.	62	CAM-ICU. 25/89 (28.1%)	CT <48 h of admission.	Haematoma in: Right parahippoacampal gyrus (RR 7.8, 95%CI: 1.7–36.1; $p < 0.009$) Right posterior superior longitudinal fasciculus (RR 6.9, 95%CI: 2.0–24.1; $p = 0.002$) Right anterior superior longitudinal fasciculus (RR 6.5, 95%CI: 1.5–28.6; $p = 0.01$). Larger haematoma volumes not statistically significant.
Lai *et al*. 2012 Australia	Case–control; 200 patients admitted to delirium unit.	86	CAM. 200/200 (100%)	CT During hospital admission.	29/200 (14.5%) had true positive findings: 13 ischaemic strokes 7 Subdural haemorrhage 9 intracerebral haemorrhage.

(*Continues*)

Table 1. (Continued)

Study/ provenance	Design/setting	Mean age (years)	Delirium assessment method and prevalence	Imaging modality and timing of scan.	Main findings with delirium
Kostalova *et al.* 2012 Czech Republic	Prospective cohort; 100 patients, acute ischaemic and haemorrhagic stroke.	74	CAM-ICU, DSMIV. 43/100 (43%)	CT On admission. ±MRI 4–6 weeks post for ischaemic stroke with haemorrhage transformation.	Total anterior circulation infarction ($p = 0.001$). (OR = 6.66, 95%CI: 1.85–24.01; $p = 0.004$). Not statistical significance: Infarction or haematoma volume $>$ 40ccm ($p = 0.168$). Right hemispheric lesions ($p = 0.167$).
Oldenbeuving *et al.* 2011 The Netherlands	Prospective cohort; 527 patients, acute ischaemic and haemorrhagic stroke.	527	CAM, DRS. 62/527(11.8%)	CT On admission.	Total anterior and partial anterior circulation infarcts (OR = 3.1, 95%CI: 1.4–6.5; $p = 0.02$). Right cerebral hemisphere stroke (OR = 1.9, 95%CI: 1.1–3.6; $p = 0.02$). Cerebral atrophy ($p < 0.001$). Increased WMH burden (OR = 2.4, 95%CI: 1.2–9; $p = 0.005$).
Cavallari *et al.* 2016 United States	Prospective cohort; 136 patients, elective surgery (orthopaedic, vascular, GI).	76	CAM, chart review method. 29/136 (21.3%)	DTI $<$2 weeks prior to surgery	Delirium incidence and severity associated with pre-surgical DTI abnormalities (lower FA, higher mean, axial and radial diffusivity) in various regions including: Cerebellum, cingulum, thalamus, basal forebrain, occipital, parietal and temporal lobes and hippocampus ($p < 0.05$). FA delirium vs. non-delirium: Cingulum: 0.315 ± 0.026 vs. 0.333 ± 0.023; $p = 0.002$. Corpus callosum: 0.353 ± 0.025 vs. 0.370 ± 0.022; $p = 0.002$.
Morandi *et al.* 2012 United States	Prospective cohort; 47 patients, surviving ICU admission.	58	CAM-ICU. 32/47 (68.1%)	DTI Hospital discharge and 3 month follow up.	After adjusting for age and sepsis, longer duration of delirium was associated with lower FA at hospital discharge: Genu of Corpus callosum (-0.02, 95%CI: -0.04-0; $p = 0.04$) Splenium of corpus callosum (-0.01, 95%CI: -0.02-0; $p = 0.02$) Anterior limb of the internal capsule (-0.02, 95%CI: -0.03-20.01; $p = 0.01$) These associations persisted for 3 months in the genu (-0.02, $p = 0.02$) and splenium (-0.01, $p = 0.004$).

(*Continues*)

Table 1. (Continued)

Study/ provenance	Design/setting	Mean age (years)	Delirium assessment method and prevalence	Imaging modality and timing of scan.	Main findings with delirium
Shioiri *et al.* 2010 Japan	Prospective cohort; 116 patients, cardiothoracic surgery.	64	DSM IV, DRS-98. 19/119 (16%)	DTI Preoperative.	Lower FA after adjusting for age: Left subgyral of frontal lobe ($p < 0.001$) Right cingulate gyrus ($p < 0.001$) Left ventral anterior nucleus of thalamus ($p < 0.01$) Corpus callosum ($p < 0.01$).

Abbreviations: CAM = Confusion assessment method; CAM-ICU = Confusion assessment method for the intensive care unit; CSF = cerebrospinal fluid; CT = computed tomography; DRS = Delirium rating scale; DRS-R98 = Delirium rating scale revised 98; DSM IV = Diagnostic Statistical Manual Fourth Edition; DWMH = deep white matter hyperintensities; DTI = diffusion tensor imaging; FA = fractional Anisotropy;; ICU = Intensive Care Unit; MRI = magnetic resonance imaging; NSCLCa = non-small cell lung cancer; PVH = periventricular white matter intensities; WMH = white matter hyperintensities.

Structural neuroimaging

Structural neuroimaging outcomes were assessed using MRI, CT and diffusion tensor imaging (DTI). See Table 1.

Cerebral atrophy and brain volumes

Five studies assessed the relationship between cerebral atrophy and delirium involving 846 patients of whom 175 had delirium. One study (Brown *et al.,* 2015) used a validated 10-point rating scale for assessment of cerebral ventricular size and sulcal widening (Manolio *et al.,* 1994). A validated stroke-specific 4-point visual scale (Pasquier *et al.,* 1996) grading regional sulcal and ventricular atrophy was used in another study (Oldenbeuving *et al.,* 2011). Three studies quantified volumes using automated software (Gunther *et al.,* 2012; Root *et al.,* 2013; Cavallari *et al.,* 2015).

Patients with delirium post-cardiothoracic surgery had larger ventricular atrophy scores than non-delirium patients after surgery ($N = 79$; median 4 vs. 3; $p = 0.003$; Brown *et al.,* 2015) and severe sulcal atrophy and ventricular dilatation predicted delirium following stroke (N = 527; OR 2.7, 95%CI: 1.1–6.8; Oldenbeuving *et al.,* 2011).

In elective surgery, no differences were observed between patients with or without delirium in whole brain (996.79 vs. 1018.71 cm^3; $p = 0.334$) or hippocampal volumes (3.25 vs. 3.23cm^3; $p = 0.862$; Cavallari *et al.,* 2015). Similarly, a retrospective study of 47 patients post-lung resection for non-small cell lung cancer found no difference in cerebrospinal fluid (CSF) to cranial volume ratio (0.37 vs. 0.35; $p = 0.113$) between delirium and control groups (Root *et al.,* 2013).

Magnetic resonance imaging performed on discharge from hospital and at 3 months follow-up in 47 ICU survivors (average age 58 years) indicated longer duration of delirium was associated with greater ventricle-to-brain ratio at hospital discharge (0.76; $p = 0.03$) persisting at 3 months (0.62; $p = 0.05$). Superior frontal lobe volumes showed similar patterns ($-2.11cm^3$; $p = 0.03$ and $-2.36cm^3$; $p = 0.02$, respectively). Hippocampal volumes were smaller at discharge ($-0.58cm^3$; $p < 0.001$) but not at 3 months ($p = 0.17$; Gunther *et al.,* 2012). The strength of this study was repeated MRI scanning allowing within-subject analysis.

In summary, subjective scales indicated that ventricular enlargement was associated with delirium. Conversely, volumetric analysis suggested that lower baseline brain volumes are not a risk factor for post-operative delirium. The differences in these results may reflect the different methods used: rating scales provide information on change 'from baseline' whereas brain volumes differ greatly between individuals making comparison difficult (Ferguson *et al.,* 2010). One ICU study demonstrated that longer duration of delirium was associated with greater cerebral atrophy at discharge and 3 months follow up.

Grey matter volume

A single study used MRI and semi-automated software to assess the relationship between preoperative grey matter volume and delirium post-cardiothoracic surgery (age > 57 years; $N = 65$). The grey matter fraction (% of total intracranial volume) in the delirious group ($N = 19$) was significantly decreased in the temporal and limbic lobes (area under the curve

Table 2 Studies assessing functional neuroimaging outcomes (NIRS, SPECT, TCD, fMRI, ^{1}H-MRS)

Study/ provenance	Design/setting	Mean age (years)	Delirium assessment method and prevalence	Imaging modality and timing of scan.	Main findings with delirium
Lopez *et al.* 2017 United States	Prospective cohort; 310 patients, cardiothoracic surgery.	67	CAM-ICU. 90/310 (29%)	NIRS Every 5 s from induction for duration of surgery.	Hyperoxic cerebral reperfusion, 10%·h: (OR = 1.65, 95%CI: 1.12–2.44; p = 0.01). Cerebral hyperoxia, 10%·h: (OR = 1.10, 95%CI: 1.01–1.19; 0.02).
Wood *et al.* 2016 Canada	Prospective cohort; 10 patients, septic shock.	71	CAM-ICU. 3/10 (30%)	NIRS Every 2 s for first 72 h in ICU.	Lower ScO_2 (p = 0.0001).
Mailhot *et al.* 2016 Canada	Prospective cohort; 30 patients, post-operative cardiothoracic surgery.	75	CAM-ICU, delirium index. 30/30 (100%)	NIRS 20 s daily for 3 days.	Higher ScO_2 decreased the odd of delirium occurrence (OR 0.73; $p < 0.001$). Mean oximetry (% mean ± SD): Preoperatively 66.4 ± 6.7 Day one post-operatively 50.8 ± 6.8 Day three post-operatively 54.3 ± 5.4.
Schoen *et al.* 2011 Germany	Prospective cohort; 231 patients, cardiothoracic surgery.	67	CAM-ICU. 63/231 (27.2%)	NIRS Day 1 preoperatively and continuous monitoring intraoperatively.	Lower ScO_2 (delirium vs. control): Day 1 preoperatively: 58.1 ± 7.7 vs. 63.1 ± 7.2 ($p \leq 0.001$). On induction: 57.6 ± 7.5 vs. 63.1 ± 7.4 ($p \leq 0.001$). Intraoperatively: 48.6 ± 9.3 vs. 55.1 ± 8.6 ($p \leq 0.001$).
Morimoto *et al.* 2009 Japan	Prospective cohort; 20 patients, abdominal surgery.	76	DSM-IV, DRS 5/20 (25%)	NIRS One minute prior to induction and continuous monitoring intraoperatively.	Lower ScO_2 pre-induction (delirium vs. control): 60 ± 5 vs. 66 ± 7 ($p < 0.05$).
Fong *et al.* 2006 United States	Prospective cohort; 22 patients, delirium of varying aetiology.	82	CAM, DRS-98. 22/22 (100%)	SPECT During delirium. 6 patients underwent repeat imaging following resolution of delirium.	Reduction in regional cerebral blood ratio flow: (delirium vs. control) Pons: 0.63 ± 0.07 vs. 0.89 ± 0.20 (p = 0.001). Left inferior frontal lobe: 0.74 ± 0.14 vs. 0.99 ± 0.22 (p = 0.003). Right temporal lobe: 240.82 ± 0.06 vs. 1.04 ± 0. (p = 0.008)

(*Continues*)

Table 2. (Continued)

Study/ provenance	Design/setting	Mean age (years)	Delirium assessment method and prevalence	Imaging modality and timing of scan.	Main findings with delirium
					Right occipital lobe: 0.83 ± 0.11 vs. 1.08 ± 0.27 (p = 0.008) Reversible abnormalities in parietal lobes of three participants ($p < 0.001$).
Hshieh *et al.* 2016 United States	Prospective cohort; 146 patients, elective surgery (orthopaedic, vascular, abdominal).	76	CAM, chart review method. 32/146 (21.9%)	ASL MRI <2 weeks prior to surgery	No significant association between global or regional cerebral blood flow with delirium incidence or severity.
Pierrakos *et al*. 2014 Belgium	Prospective cohort; 38 patients, sepsis admitted to ICU.	68	CAM-ICU. 21/38 (55.3%)	TCD 10 s on day 1 and day 3 of sepsis.	PI >1.3 on day 1 predicted delirium ($p < 0.01$). PI on day 3 was not predictive of delirium (p = 0.24).
Caplan *et al.* 2014 Australia	Prospective cohort; 44 patients, acute geriatric unit and geriatric outpatients.	81	CAM, delirium index. 20/44 (45%)	TCD Second daily for hospitalisation. One-off reading for outpatients.	Lower FV in delirium superimposed on dementia (28.3 ± 4.7) compared to: Acute illness (43.0 ± 8.3; $p < 0.001$) Delirium alone (37.7 ± 8.2; p = 0.009) Alzheimer's disease only (41.3 ± 15.7; p = 0.04). Resolution of delirium improves FV (p = 0.005). FV correlates with delirium severity (p = 0.009).
Schramm *et al.* 2012 Germany	Prospective cohort; 29 patients, severe sepsis in ICU.	64	CAM-ICU. 23/29 (79.3%)	TCD 60 min daily for first 4 days in ICU.	Impaired cerebral AR at day 1 associated with delirium (p = 0.035).
Rudolph *et al.* 2009 United States	Prospective cohort; 68 patients, elective cardiothoracic surgery.	71	CAM. 33/68 (48.5%)	TCD Opening of pericardium to closure of chest cavity.	Post-operative delirium not associated with increase microemboli intraoperatively: (299 ± 350 vs. 303 ± 449; p = 0.97).
Pfister *et al.* 2008 Switzerland	Prospective cohort; 16 patients, Severe sepsis in ICU.	75	CAM-ICU. 12/16 (75%).	TCD Over a 60 min period. (Near-infrared spectroscopy also conducted).	Disturbed AR (p = 0.015). No significant difference in cerebral perfusion. FV (p = 0.3). ScO_2 (p = 0.2).

(*Continues*)

Table 2. (Continued)

Study/ provenance	Design/setting	Mean age (years)	Delirium assessment method and prevalence	Imaging modality and timing of scan.	Main findings with delirium
Jackson *et al.* 2015 United States	Prospective cohort; 47 patients, surviving ICU admission.	58	CAM-ICU. 32/47 (68.1%)	fMRI At hospital discharge and 3 months follow up.	No significant association observed delirium duration and activation of specific brain regions at discharge or 3 months ($p > 0.25$ across all regions of interest).
Choi *et al.* 2012 South Korea	Case–control; 42 patients, delirium of varying aetiologies and matched controls.	73	MDAS, DRS-98. 20/42 (47.6%)	fMRI During delirium. 13 patients underwent repeat imaging following resolution of delirium (mean 5.8 days).	Increased functional connectivity in dorsolateral prefrontal cortex and posterior cingulate cortex ($p < 0.05$). Increased connectivity in precuneus and posterior cingulate cortex ($p < 0.05$). Reversible reduction in intralaminar thalamic and caudate nuclei with subcortical regional activity ($p < 0.05$).
Yager *et al*. 2010 United States	Prospective cohort; 23 patients, bone marrow transplant recipients and healthy controls.	58	MDAS, DRS-98. 5/23 (22%)	^{1}H-MRS Mean 15.6 days post-bone marrow transplant.	In white matter superior to the corpus callosum: Higher tCho/tCre ($p = 0.049$). Lower NAA/tCho ($p < 0.05$).
Haggstrom *et al.* 2017 Australia	Prospective cohort; 13 patients, acute geriatric unit.	84	CAM, delirium index. 13/13 (100%)	FDG-PET During delirium. 6 patients underwent repeat imaging following resolution of delirium (mean 73.5 days).	Cortical hypometabolism (13/13) of varying severity and extent which improved with delirium resolution (6/6). Hypermetabolic sensorimotor cortex (11/13) which resolved with delirium resolution (5/6). Whole brain metabolism 1.4% higher post-recovery from delirium ($p = 0.03$).

Abbreviations: ^{1}H-MRS = proton magnetic resonance spectroscopy; AR = autoregulation; ASL = arterial spin labelling (ASL); CAM = Confusion assessment method; CAM-ICU = Confusion assessment method for the intensive care unit; DRS = Delirium rating scale; DRS-R98 = Delirium rating scale revised 98; DSM IV = Diagnostic Statistical Manual Fourth Edition; FDG-PET =2-^{18}F-fluoro-2-deoxyglucose positron emission tomography; fMRI = functional magnetic resonance imaging; FV = flow velocity; ICU = Intensive Care Unit; MDAS = memorial delirium assessment scale; NAA/tCho = N-acetyl aspartate to total choline ratio; NIRS = Near infrared spectroscopy; OR = odds ratio; ScO_2 = cerebral oxygenation saturation; SD = standard deviation; SPECT = single-photon emission computed tomography; TCD = trans-cranial Doppler, PI = pulsatility index; tCho/tCre = total choline to total creatine ratio.

(AUC) = 0.777, 95%CI 0.66–0.89; $p < 0.001$ and AUC = 0.764, 95%CI 0.647–0.882; $p < 0.001$, respectively; Shioiri *et al.*, 2016).

White matter hyperintensity burden

Six studies used MRI to evaluate the relationship between white matter hyperintensity (WMH) burden and post-operative delirium in 643 patients of whom 158 had delirium. Five studies used subjective rating scales; four of these (Hatano *et al.*, 2013; Otomo *et al.*, 2013; Cavallari *et al.*, 2015; Omiya *et al.*, 2015) used the Fazekas scale, which separates periventricular WMH and deep WMH (Fazekas *et al.*, 1993). The other (Brown *et al.*, 2015) applied a 10-point validated rating scale (Manolio *et al.*, 1994). Two studies used semi-automated volumetric analysis (Root *et al.*, 2013; Cavallari *et al.*, 2015).

Table 3 – Summary of Neuroimaging Outcomes and Bias Assessment

Neuroimaging Outcomes	Studies (N)	Total Participants	Studies	Risk of bias					Association
				A	B	C	D	E	
PREDICTORS									
Cerebral atrophy & Brain Volumes.	4	799	Brown 2015	-	+	-	+	+	Yes
			Cavallari 2015	+	+	+	+	+	No
			Root 2013	-	-	-	-	-	No
			Oldenbeuving 2011	+	+	-	?	+	Yes
Reduced Grey Matter Volume.	1	116	Shioiri 2016	+	+	+	?	-	Yes
White Matter Hyperintensity Burden.	6	643	Brown 2015	-	+	-	+	+	Yes
			Cavallari 2015	+	+	+	+	+	No
			Omiya 2015	+	+	+	+	+	Yes
			Hatano 2013	+	?	-	+	+	Yes
			Otomo 2013	+	+	+	+	+	No
			Root 2013	-	-	-	-	-	Yes
Pre-operative and new post-operative ischaemic lesions.	3	320	Brown 2015	-	+	-	+	+	No
			Omiya 2015	+	+	+	+	+	Yes
			Otomo 2013	+	+	+	+	+	Yes
Stroke characteristics: haemorrhagic, right cerebral hemisphere, total anterior circulation infarcts.	3	716	Naidech 2016	-	-	+	-	+	Yes
			Kostalova 2012	+	+	+	?	-	Yes
			Oldenbeuving 2011	+	+	-	?	+	Yes
White matter tract abnormalities: corpus callosum, fronto-thalamic, cerebello-thalamic and limbic systems.	2	255	Cavallari 2016	+	+	+	+	+	Yes
			Shioiri 2010	+	+	+	?	-	Yes
Reduced preoperative cerebral oxygenation.	3	561	Lopez 2017	+	+	+	?	+	No
			Schoen 2011	+	+	+	+	+	Yes
			Morimoto 2009	-	+	?	+	?	Yes
Hyperoxic cerebral reperfusion post-intraoperative ischaemic events.	1	310	Lopez 2017	+	+	+	?	+	Yes
Higher pulsatility index.	1	38	Pierrakos 2014	-	-	+	-	+	Yes
Intraoperative microemboli.	1	68	Rudolph 2009	?	+	+	+	+	No
CORRELATES									
Reduced cerebral oxygenation saturation.	2	40	Mailhot 2016	+	+	-	+	+	Yes
			Wood 2016	?	-	+	+	+	Yes
Reduced cerebral blood flow.	4	228	Hshieh 2016	+	+	+	+	+	No
			Caplan 2014	+	+	?	?	+	Yes
			Fong 2006	-	-	?	+	+	Yes
			Pfister 2008	+	-	-	+	?	No
Impaired autoregulation.	2	46	Schramm 2012	-	-	-	+	+	Yes
			Pfister 2008	+	-	-	+	?	Yes
Abnormal connectivity within the default mode network.	1	22	Choi 2012	?	-	+	?	+	Yes
Metabolites suggesting reduced neuronal integrity or glial proliferation.	1	13	Yager 2011	-	-	+	?	?	Yes
Reversible cortical glucose hypometabolism.	1	13	Haggstrom 2017	+	+	?	+	?	Yes
CONSEQUENCES									
Smaller cerebral and superior fontal lobe volumes.	1	47	Gunther 2012	-	+	+	+	+	Yes
White matter tract abnormalities of corpus callosum.	1	47	Morandi 2012	-	+	+	?	+	Yes
Activity in specific brain regions during a working memory task.	1	47	Jackson 2015	-	+	+	?	-	No

Risk of Bias: A = selection of participants; B = confounding variables; C = assessment of delirium; D = method of imaging; E = Blinding of Imaging Assessments (also see Appendix C).

Two similar prospective cohort trials demonstrated no relationship between preoperative WMHs and post-operative delirium: one in different elective surgical procedures ($N = 146$; age > 70 years; WMH volume [delirium vs. control]: 10.24 vs. 11.55 cm^3; $p = 0.710$; Cavallari *et al.,* 2015) and one in elective coronary artery bypass grafting patients ($N = 153$; age > 60 years; $p = 0.549$; Otomo *et al.,* 2013).

Another study assessed WMHs after cardiothoracic surgery and demonstrated a trend towards association with post-operative delirium ($N = 79$; WMH 10-point scale: 3 vs. 2; $p = 0.05$; Brown *et al.,* 2015).

Three studies showed significant associations between WMHs and delirium. New WMH following cardiothoracic surgery were associated with delirium ($N = 88$; OR 3.04, 95%CI: 1.14–8.12; $p = 0.027$; Omiya *et al.,* 2015), and severe baseline WMH were more prevalent in cardiothoracic surgery patients who developed delirium ($N = 130$; OR 3.9, 95%CI: 1.12–12.5; $p = 0.02$; Hatano *et al.,* 2013). Non-small cell lung cancer patients who experienced delirium post-lung resection exhibited significantly greater baseline WMH than the non-delirium group ($N = 47$; WMH volume to total brain volume ratio: 0.01 vs. 0.005; $p = 0.017$; Root *et al.,* 2013).

In total, six studies, all in surgical populations, demonstrated mixed relationships between WMHs and delirium. These were predominantly cardiothoracic surgical populations, an at-risk population for WMHs therefore affecting generalisability.

Ischaemic lesions

Three MRI studies examined ischaemic lesions in post-operative delirium in 320 cardiothoracic patients (92 with delirium).

One study found no difference in the prevalence of new post-operative lesions between patient groups ($N = 79$; percentage with new lesions delirium vs. no-delirium: 64.3% vs. 51%; $p = 0.26$; Brown *et al.,* 2015).

One prospective cohort study observed that post-operative delirium was associated with more preoperative cerebral infarcts ($N = 153$; OR 2.26, 95%CI: 1.10–4.77; $p = 0.027$; Otomo *et al.,* 2013). Another found a strong association between new ischaemic lesions and post-operative delirium ($N = 88$; OR 11.07, 95%CI: 1.53–80.03; $p = 0.017$; Omiya *et al.,* 2015).

Therefore, two out of three studies in cardiothoracic surgery patients found links between ischaemic lesions and post-operative delirium. These results may not be generalisable to other populations.

Stroke characteristics

Three studies evaluated the relationship between stroke characteristics and delirium in 716 patients of whom 130 had delirium. Two studies used semi-automated software for volumetric analysis (Kostalova *et al.,* 2012; Naidech *et al.,* 2016), one assessed stroke locations visually (Oldenbeuving *et al.,* 2011) using published criteria (Mead *et al.,* 2000; Oldenbeuving *et al.,* 2011).

In acute intracerebral haemorrhage ($N = 89$), CT at hospital discharge indicated an increased risk of delirium with haematoma of the right subcortical white matter, specifically the right parahippocampal gyrus (Relative Risk (RR) 7.8, 95%CI:1.7–36.1; $p < 0.009$), right posterior superior longitudinal fasciculus (RR 6.9, 95%CI: 2.0–24.1; $p = 0.002$) and right anterior superior longitudinal fasciculus (RR 6.5, 95%CI 1.5–28.6; $p = 0.01$; Naidech *et al.,* 2016).

The second study used admission CT and MRI 4–6 weeks later (for haemorrhagic transformation) in ischaemic and haemorrhagic stroke ($N = 100$). Higher incidence of delirium was associated with intracerebral haemorrhage (OR 6.11, 95%CI 1.62–22.98) and total anterior circulation infarction (OR 6.66, 95%CI 1.85–24.01; Kostalova *et al.,* 2012).

The final study examined admission CT in patients presenting with ischaemic and haemorrhagic stroke ($N = 527$). Right-sided hemispheric stroke (OR 2.0, 95%CI 1.0–3.0) and anterior circulation large-vessel stroke (OR 3.4, 95%CI 1.1–10.2) increased the risk of delirium (Oldenbeuving *et al.,* 2011).

In summary, right hemispheric, total anterior circulation and haemorrhagic strokes may increase risk of delirium but study heterogeneity and methodological limitations prevent firm conclusions from being drawn.

Aetiology of delirium and yield of neuroimaging

The pattern of brain injury in delirium due to sepsis in ICU patients was assessed with MRI ($N = 71$; Polito *et al.,* 2013). MRI findings of the 31 chart review method-positive patients were as follows: 19 normal, 7 leukoencephalopathy and 5 ischaemia. The relationship between delirium and radiological findings was not statistically significant ($p = 0.15$).

Intracranial pathology accounting for delirium was demonstrated on CT in 29 out of 200 geriatric patients from a delirium ward: 13 ischaemic stroke, 7 subdural haemorrhage and 9 intracerebral haemorrhage. New focal neurological deficit (OR 18.17, 95%CI: 5.99–55.15; $p < 0.001$), deterioration in conscious level (OR 4.58, 95%CI: 1.33–15.79; $p < 0.05$) and recent fall (OR 5.58, 95%CI: 1.90–16.42; $p < 0.005$) were the best predictors of clinically significant radiological findings (Lai and Wong Tin Niam, 2012).

Diffusion tensor imaging

Diffusion tensor imaging is used to derive mean diffusivity (MD) and fractional anisotropy (FA),

quantitative measures of the magnitude and direction of water diffusion (Basser *et al.,* 1994; Basser *et al.,* 2000). The architecture of white matter produces restricted but highly directional diffusion and consequently low MD and high FA values. Changes in MD and FA are useful indicators of WM microintegrity.

Three studies assessed 299 patients (80 with delirium) using DTI.

Baseline DTI-MRI in various elective surgeries ($N = 136$) suggested that DTI abnormalities of the cerebellum, cingulum, corpus callosum, internal capsule, thalamus, basal forebrain, occipital, parietal and temporal lobes (including hippocampus) were associated with delirium incidence and severity ($p < 0.05$). These effects persisted in the cerebellum, hippocampus, thalamus and basal forebrain after controlling for general cognitive performance ($p < 0.05$; Cavallari *et al.,* 2016).

In 116 cardiothoracic cases, delirious patients demonstrated significant reduction in FA values in four clusters: left subgyral of frontal lobe, right cingulate gyrus, left ventral anterior nucleus of the thalamus and corpus callosum ($p \leq 0.01$; Shioiri *et al.,* 2010).

In the final study using diffusion tensor-MRI, ICU-delirium survivors scanned at hospital discharge exhibited lower FA of the genu ($p = 0.04$), splenium of corpus callosum ($p = 0.02$) and anterior limb of the internal capsule ($p = 0.01$) in association with delirium duration. After adjusting for age and sepsis, these associations persisted for 3 months in the genu ($p = 0.02$) and splenium ($p = 0.04$) of the corpus callosum (Morandi *et al.,* 2012).

Diffusion tensor imaging abnormalities demonstrate consistent associations with post-operative and ICU-related delirium and suggest loss of white matter integrity in the corpus callosum, fronto-thalamic-cerebellar and limbic systems. Again, the specific populations studied affects generalisability.

Functional neuroimaging outcomes

Functional neuroimaging outcomes were assessed using NIRS, TCD, ASL-MRI, SPECT, fMRI, ^{1}H-MRS and FDG-PET. See Table 2.

Cerebral oxygenation

Near infrared spectroscopy measures regional cerebral oxygenation transcranially via NIR light signals. (Owen-Reece *et al.,* 1999; Scott and Hoffman, 2014) allowing assessment of oxygenation within local arterial, venous and capillary compartments (Owen-Reece *et al.,* 1999). Five articles assessed cerebral oxygenation using NIRS in 601 participants (190 with delirium).

Cerebral oxygenation saturation (ScO_2) was significantly lower during the first 72 h of ICU admission in sepsis patients with delirium for the majority of their ICU stay ($N = 10$, $p < 0.0001$; Wood *et al.,* 2016). Oximetry measurements in delirious patients following cardiothoracic surgery ($N = 30$) suggested that higher ScO_2 decreased the odd of delirium occurrence over time (OR 0.73; $p < 0.001$) whilst peripheral oxygen saturations did not (OR 1.01; $p = 0.871$). In addition, higher ScO_2 inversely correlated with delirium severity ($p < 0.001$; Mailhot *et al.,* 2016).

Two studies assessed the relationship between perioperative cerebral oxygenation and post-operative delirium. After abdominal surgery ($N = 20$), delirious patients demonstrated significantly lower ScO_2 prior to surgery (60% vs. 66%; $p < 0.05$), but not during surgery (Morimoto *et al.,* 2009). In 231 cardiothoracic surgery patients, delirium was associated with lower ScO_2 the day before surgery (58.1% vs. 63.1%), during anaesthetic induction (57.6% vs. 63.1%) and during surgery ($p \leq 0.001$). Low preoperative ScO_2 was reported to be an important predictor of post-operative delirium (OR 3.27, 95%CI: 1.14–9.37; $p = 0.027$; Schoen *et al.,* 2011).

One study assessed the relationship between hyperoxic cerebral reperfusion (defined as cerebral oxygenation greater than baseline) following ischaemic events during cardiothoracic surgery and post-operative delirium ($N = 310$). The duration of intraoperative hyperoxic cerebral reperfusion was associated with increasing odds of delirium (OR 1.65, 95%CI, 112–2.44; $p = 0.01$). Hyperoxia prior to ischaemia was associated with delirium (OR 1.10, 95%CI, 1.01–1.19; $p = 0.02$). Intraoperative hypoxia was not associated with delirium (OR 1.12, 95%CI, 0.97–1.29; $p = 0.11$; Lopez *et al.,* 2017).

These studies demonstrate that reduced ScO_2 during an episode of delirium and low ScO_2 preoperatively may predict post-operative delirium. Sample sizes and NIRS imaging methods were variable.

Cerebral perfusion and autoregulation

Single-proton emission CT assesses regional cerebral blood flow (CBF) via intravenous gamma-emitting

radioisotopes (Kuhl *et al.,* 1982). Reduced blood flow was demonstrated in the pons, left inferior frontal, right temporal and right occipital lobes of 22 delirious patients from a general medical unit ($p < 0.01$). Repeat scanning in three patients following delirium resolution showed that these deficits had resolved ($p < 0.001$; Fong *et al.,* 2006).

Arterial spin-labelling MRI uses radiofrequency irradiation to magnetically label arterial blood water allowing quantitative measurement of CBF (Detre *et al.,* 2012). Preoperative ASL-MRI conducted in 146 cognitively intact patients undergoing various elective surgical procedures demonstrated no association between global and voxel-wise CBF and post-operative delirium incidence or severity (Hshieh *et al.,* 2016).

Transcranial Doppler enables monitoring of blood flow through major arteries using ultrasound (Aaslid *et al.,* 1982). Measurements from TCD include flow velocity (FV), pulsatility index (PI—cerebral vascular resistance), autoregulation index (Mx) and microemboli detection.

Five studies assessed delirium using TCD; involving 195 patients of whom 109 had delirium.

The use of TCD as a diagnostic tool was examined in 44 participants with either Alzheimer's dementia, delirium without dementia, delirium superimposed on dementia (DSD) or acute illness (no delirium) recruited from the geriatric ward or outpatient clinic. The DSD group demonstrated lower FV (28.2 cm/s) compared with Alzheimer's dementia (41.3 cm/s; $p = 0.04$), delirium alone (37.7 cm/s; $p = 0.009$) or acute illness (43.0 cm/s; $p < 0.001$). Mean FV increased post-delirium resolution ($p = 0.006$), and a mean middle cerebral artery FV of 32.25 cm/s accurately diagnosed DSD from the other groups (sensitivity 0.875 specificity 0.788, $p = 0.001$; Caplan *et al.,* 2014).

In an ICU study, TCD was performed on day one of sepsis and repeated 3 days later in delirious patients ($N = 38$). Using a cut-off of PI > 1.3, PI on the first and not the third day was a predictor of the presence of delirium (AUC = 0.908, 95%CI 0.80–0.98; $p < 0.01$ and AUC = 0.618 95%CI 044–0.791, $p = 0.24$ respectively; Pierrakos et al., 2014).

Two further ICU studies assessed the relationship between sepsis-associated delirium and Mx. Both studies performed TCD for 1 h daily and used a cut-off of Mx > 0.3 to imply impaired autoregulation. Mx > 0.3 on day one was associated with delirium on day four in a cohort of 30 patients ($p = 0.035$; Schramm *et al.,* 2012). In the other cohort of 16 patients, Mx was significantly higher in delirious compared with non-delirious patients ($p = 0.015$; Pfister *et al.,* 2008).

Microemboli counts did not differ between delirium and non-delirium groups (303 ± 449 vs. 299 ± 350, respectively; $p = 0.97$) in 68 coronary artery bypass grafting patients who underwent continuous TCD monitoring throughout surgery (Rudolph *et al.,* 2009). In addition, patients with longer duration of delirium did not have higher microemboli burden ($p = 0.93$).

These studies suggest that delirium is associated with reduced blood flow, which is at least partially reversible with resolution of delirium. High PI early in sepsis can predict delirium, and there may be impaired cerebral autoregulation in sepsis-associated delirium. Reduced CBF did not predict the incidence and severity of post-operative delirium. Only half of the studies assessed for pre-existing dementia, which is an important confounder in assessing cerebral perfusion. No relationship between microemboli burden during cardiothoracic surgery and delirium was demonstrated.

Functional connectivity

Functional MRI uses blood-oxygenation level-dependent images to map neuronal activity based on changes in regional blood flow (Matthews and Jezzard, 2004). Functional connectivity is the temporal correlation between spatially remote neuro-physiological events and provides characterisation of regional functional interactions (Friston, 1994). fMRI imaging can be conducted at rest, to assess the default-mode network or during goal-direct tasks to determine specific brain activation patterns.

Two studies used fMRI in 89 patients of whom 54 had delirium.

Functional MRI was conducted at resting state in 22 delirious patients; 14 of whom underwent repeat fMRI following resolution of delirium (median 5.8 days). Control patients ($N = 22$, recruited from a pre-existing database) demonstrated inverse correlation in functional connectivity between the dorsolateral prefrontal cortex and posterior cingulate cortex (PCC), whilst in delirious patients, these were strongly correlated ($p < 0.05$) and this persisted following resolution of delirium (Choi *et al.,* 2012).

Patients with reduced delirium severity and duration also demonstrated strong correlation between precuneus and PCC activity. Delirious patients demonstrated reversible reduction in significant functional connections across intralaminar thalamic and caudate nuclei with other subcortical regions (Choi *et al.,* 2012).

In survivors of critical illness with delirium (N = 47), no association was observed between delirium duration and activation of any brain region during a working memory task at discharge or 3-month follow up ($p > 0.25$ across 11 regions of interest; Jackson *et al.,* 2015).

Therefore, delirious patients exhibit abnormal connectivity among dorsal prefrontal and subcortical regions at resting state. This abnormal connectivity may contribute to clinical features of delirium including inattention and disorientation, sleep–wake disturbances and low arousal.

Proton magnetic resonance spectroscopy

Proton MRI spectroscopy allows non-invasive quantification of relatively abundant brain metabolites (Frahm *et al.,* 1989), commonly *N*-acetyle aspartate (NAA), a marker of neuronal integrity, choline (tCho) representing phospholipid membrane turnover and demyelination and creatine (tCre), involved in energy metabolism, higher levels of which may reflect increased cell density and inflammation (Ferguson and MacLullich, 2011; Yager *et al.,* 2011).

One case control study used single-voxel ^{1}H-MRS in the cetrum semiovale to investigate delirium in 13 patients (five delirious) post bone marrow transplant (BMT, median 15.6 days after transplant; Yager *et al.,* 2011). The BMT-delirium group demonstrated significant elevation of tCho/tCre compared with BMT no delirium (p = 0.049) and lower NAA/tCho compared with BMT no delirium (p = 0.037) and healthy age-matched controls (N = 10; p = 0.012). The results indicate lower NAA, reflecting reduced neuronal integrity, or increased Cho, suggesting a catabolic process or glial proliferation. However, outcomes are expressed as ratios (to avoid the partial volume effects of CSF in voxels), which makes interpretation of changes in individual metabolites problematic.

Cerebral metabolic activity

2-^{18}F-Fluoro-2-deoxyglucose-PET measures cerebral metabolic activity by providing quantitative and qualitative estimates of the rate of glucose uptake by cells (Mosconi, 2013). One study conducted FDG-PET in 13 delirious acute geriatric patients with six undergoing repeated scanning following delirium resolution (mean 73.5 days). Visual analysis demonstrated cortical hypometabolism in all patients, which improved on repeat scanning. The sensorimotor cortex was hypermetabolic in 11/13 patients with delirium; this increased metabolism resolved in 5/6 patients after they recovered from delirium. Semi-quantitative analysis demonstrated higher glucose metabolism in the whole brain, bilateral frontal, occipital and PCC, left parietal and temporal lobes and right cerebellum following delirium resolution ($p < 0.05$; Haggstrom *et al.,* 2017).

Discussion

This updated systematic review demonstrates significant progress in the use of neuroimaging in delirium since 2006.

Firstly, more studies were eligible for inclusion, and these were methodologically more sophisticated with larger sample sizes (average 93.7 [10–527] vs. 63.6 [5–235] participants), prospective recruitment and better consideration of potential confounders. Secondly, we captured more imaging modalities (10 vs. 4), particularly functional imaging. Thirdly, there was a diversity of study outcomes including predictors (N = 18), correlates (N = 11) and consequences (N = 3) of delirium. Finally, almost all studies used validated methods of scan assessment or semi-automated software allowing more objective analysis.

However, significant variation in study design affected the comparability of results. Increased application of advanced MRI and functional imaging techniques introduces selection bias as patient recruitment is restricted to those able to tolerate scanning, especially for functional imaging during delirium. Furthermore, obtaining baseline imaging places an emphasis on elective surgery patients and excludes acute medical or hip fracture cases in patients that there is a high prevalence of delirium.

In addition, focus on cardiovascular or ICU patients affects the generalisability of results. As delirium results from the interaction between predisposing vulnerabilities and precipitating insults, patient selection may influence imaging outcomes. For example, younger ICU-delirium patients with severe illness may have fewer predisposing factors compared with frail older patients who can become delirious after a relatively mild illness. This raises the issue of appropriate controls because cohort studies of surgical patients often show significant baseline differences such as age and comorbidities between delirious and non-delirious patients. Better matching of patient demographics would strengthen imaging findings.

This systematic review furthers our understanding of the pathophysiology of delirium. Although there was heterogeneity of study design, relatively small sample sizes and variable quality, there are commonalities worthy of consideration. See Table 3 for a summary of significant outcomes.

Although most studies focus on a specific aspect of pathophysiology, some of these may be related. For example, WMHs are correlated with atrophy (Appelman *et al.,* 2009) and inversely related to CBF (O'Sullivan *et al.,* 2002).

Many of the results implicate white matter pathology, such as ventricular enlargement (indicating depletion of subcortical white matter), WMHs, changes in diffusion characteristics, metabolites and connectivity. However, it should be noted that many techniques concentrate only on white matter, and grey matter pathology may be underrepresented.

The mixed outcomes regarding cerebral atrophy and WMH as predictors of delirium may result from the varying methods of imaging analysis. Whilst the use of quantitative methods is less subjective than validated visual scales, they give less information regarding change overtime. This may partially explain differences in atrophy and WMH rating scores compared with volumes in relation to delirium. Studies examining changes overtime (visual ratings) demonstrated stronger relationships with delirium than cross-sectional volumetric studies.

The included studies can be linked to several existing hypotheses regarding delirium pathogenesis. Delirium is more prevalent in dementia, indicating that pre-existing damage is a strong predictor of delirium. The studies included in this review strengthen this by implicating cerebral atrophy, ischaemic lesions and white matter lesions as risk factors for delirium. More specifically, hippocampal damage may also contribute to the aberrant stress response and higher cortisol production observed in delirious patients through loss of inhibition of the hypothalamus-pituitary–adrenal axis. Changes in diffusion characteristics and metabolites reflect microscopic tissue damage and also glial activity, a key focus of animal studies of delirium pathophysiology.

Common regions identified by neuroimaging as putative substrates for delirium include the fronto-thalamic and limbic systems and corpus callosum, which support functions that include executive functioning, sensory processing, attention, emotional regulation, memory formation and orientation. Many of these functions are typically disturbed during delirium and findings from neuroimaging strengthen delirium neuropsychology work. In particular, abnormal connectivity demonstrated within the default-mode network is an intriguing outcome warranting of further investigation (Choi *et al.,* 2012; Mantini and Vanduffel, 2013).

Functional neuroimaging outcomes highlight cerebral haemodynamic abnormalities. Microvascular abnormalities indicated by NIRS and TCD may reflect the cerebrovascular deficits underpinning WMHs and ischaemic lesions. More work is required to determine the impact of small vessel disease on delirium in older patients, but microcirculatory changes resulting in cytokine release are involved in the development of delirium during sepsis (Sonneville *et al.,* 2013), which may suggest common neuroinflammatory mechanisms.

Opportunities for future research are vast. Larger sample sizes would enable more definitive conclusions to be drawn. Studies involving more vulnerable patients such as those with acute illness and dementia would be more representative. Novel research opportunities include assessing micro-circulatory changes using dynamic susceptibility contrast MR perfusion and blood–brain-barrier integrity using contrast-enhanced MRI (Alsop *et al.,* 2006, Wang *et al.,* 2006). The application of NIRS using units with multiple detectors offers opportunities to assess variations in oxygenation beyond the frontal lobe as well as multi-modality integration with MRI.

This review has some limitations. We did not seek unpublished data, only included full text published articles for quality assessment, and utilised strict inclusion criteria regarding the use of validated diagnostic tools. It is possible that articles were missed despite screening 4117 articles and hand searching their reference lists. The heterogeneity of study design and imaging modalities also precluded meta-analysis.

Neuroimaging offers a means of understanding brain-specific predisposing factors as well as functional and molecular changes during delirium. It also enables investigation of long-term brain changes associated with delirium, an area that is neglected despite evidence of accelerated cognitive impairment following delirium. So far, the application of neuroimaging in delirium has been limited, but with expanding interest, advances in technology and wider scanning availability, this field will grow and provide valuable insights into delirium pathophysiology.

Conflict of interest

None declared.

Key points

- Neuroimaging can provide useful information about predictors, correlates and consequences of delirium.
- Neuroimaging studies offer useful information pertaining to structural risk factors which make an individual more vulnerable to developing delirium.
- Functional neuroimaging studies demonstrate abnormalities in cerebral perfusion, oxygenation, glucose metabolism and neural connectivity during an episode of delirium, however, small sample sizes prevent firm conclusions from being drawn.
- There are limited studies examining structural and functional neuroimaging consequences following an episode of delirium.
- Despite the inherent challenges of performing neuroimaging studies in delirious patients, future research is paramount to further our understanding of the pathophysiology and neural outcomes of this common and serious condition.

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Appendix A: search strategy

Database	MEDLINE	EMBASE	PsycINFO
1	Exp delirium/ or delirium.tw.	Exp delirium/ or delirium.tw.	Delirium/ or delirium.tw.
2	Exp confusion/ or Acute confusion.tw.	Acute confusion/ or acute confusion.tw.	Mental confusion/ or acute confusion.tw.
3	1 or 2	1 or 2	1 or 2
4	Exp Tomography, X-Ray Computed	Exp computer assisted tomography/	Exp tomography/ or neuroimaging/ or magnetic resonance imaging/ or positron emission tomography/ or single photon emission computed tomography/
5	Exp Magnetic Resonance Imaging/	Exp nuclear magnetic resonance imaging/	Functional magnetic resonance imaging/
6	Exp Magnetic Resonance Spectroscopy/	Exp nuclear magnetic resonance spectroscopy/	Magnetic resonance spectroscopy.mp.
7	Functional MRI.mp.	Functional magnetic resonance imaging/	Transcranial Doppler.mp.
8	Positron-emission tomography/ or tomography, emission-computed, single-photon/	Positron emission tomography/ or single photon emission computer tomography/	4 or 5 or 6 or 7
9	Ultrasonography, Doppler, Transcranial/	Transcranial Doppler/	3 and 8
10	Exp neuroimaging/ or neuroimaging.mp.	Exp neuroimaging/ or neuroimaging.mp.	Exp BRAIN/
11	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10	3 and 10
12	3 and 11	3 and 11	9 and 11
13	Exp Brain/	Exp brain/ or brain.mp.	Limit 12 to yr='2006-Current'
14	3 and 13	3 and 13	
15	12 or 14	12 or 14	
16	Limit 15 to yr='2006-Current'	Limit 15 to yr='2006-Current'	
Total	647	3440	124

Appendix B: bias criteria

Adapted from Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS; Kim *et al.*, 2013) and quality criteria from previous systematic review on Neuroimaging in Delirium (Soiza *et al.*, 2008).

Bias type	Low-risk bias	Unclear	High-risk bias
Selection of participants	Method of recruitment and participant selection is clearly described. Study participants were consecutively recruited. Case–control studies: Delirious and non-delirious groups are the same population group (identical institution and period) OR they are selected from a comparable population group. Cohort studies: The absence of delirium was confirmed at the starting point of the study.	It is uncertain whether the selection of participants results in a 'high risk' or a 'low risk' bias.	It is unclear or not documented how participants were selected. Study participants were recruited using convenience sampling. Case–control studies: Delirious and non-delirious groups are selected from different population groups (e.g. differing study centre or historical control groups were used). Cohort studies: The absence of delirium was not confirmed at the starting point.
Confounding Variables	Study reports appropriate information on participant background characteristics. In particular, prevalence and previous diagnosis of dementia, depression, medications, vascular risk factors. Confounding variables are considered during analysis of results. For prospective studies, baseline cognitive testing was performed or collateral history was obtained to determine possible cognitive impairment or dementia. In surgical studies, standardised operating and anaesthetic procedures were adopted.	It is unclear is confounding variables were adequately considered.	Major confounding variables are not considered. Major confounding variables are reported, however, these variables were not adequately considered during the design and analysis phases. No exploration of possible cognitive impairment or mood disorder.
Assessment of Delirium (Performance and Measurement Bias)	Delirium was assessed prospectively. Assessment conducted by a dedicated trained clinician. Delirium assessment was standardised. Diagnosis of delirium was blinded i.e. without prior knowledge of scan results.	It is uncertain whether delirium assessment results in a 'high risk' or 'low risk' of bias.	Delirium was identified retrospectively. It is unclear who conducted delirium assessment. Several clinicians of varying expertise assessed for delirium and interrater reliability was not assessed. Delirium was diagnosed based on one brief clinical encounter.
Method of Imaging (Performance and Measurement Bias)	Scans conducted for research on dedicated scanners. Use of validated methods of measuring scan outcomes. E.g. validated scales measuring white matter disease or brain volumes.	It is uncertain whether the method of imaging results in a 'high risk' or a 'low risk' of bias.	Scans conducted for non-research purposes and retrospectively evaluated. Low scan report detail. No validated scales utilised. Inadequate quality control of scan results. E.g. no documentation of who

(*Continues*)

(Continued)

Bias type	Low-risk bias	Unclear	High-risk bias
	Adequate quality control of scan results. E.g. use of two independent radiology reporters OR reporting interreporter reliability in two reporters OR use of quantitative analysis e.g. voxel based mapping and single trained reporter interpreted all scans. For Transcranial Doppler (TCD): Scanning conducted by single trained investigator. TCD and delirium assessments occurred within a defined time period. For Near-infrared Spectroscopy (NIRS): A clear protocol exists for placement of sensors.		interpreted scans, single reporter without the use of a predefined scales or semi-quantitative analysis. For TCD: Scanning conducted by several investigators (not standardised). For NIRS: No documented protocol for placement of sensors.
Blinding of imaging assessments	Scan reporters were blinded (i.e., no subject information available to the reporter). Although blinding was not present its absence was judged to have no effect on the outcome of measurements.	It is uncertain whether the exposure measurement results in a 'high risk' or a 'low risk' of bias.	No documentation regarding blinding. Scan reporters not blinded, this lack of appropriate blinding appears likely to have affected the outcome measures.
Incomplete data and selective outcome reporting	There is no missing data. All participants accounted for at conclusion of study. The experimental protocol is available and the pre-defined primary and secondary outcomes were described as planned. All of the expected outcomes were included in the study descriptions (even in the absence of the experimental protocols).	It is uncertain whether the incomplete outcome data or selective outcome reporting resulted in a 'high risk' or a 'low risk' of bias.	Missing data could affect study outcomes. Participants lost to follow up and not accounted for at end of study. The pre-defined primary outcomes were not fully reported. The outcomes were not reported in accordance with the previously defined standards Primary outcomes that were not pre-specified in the study existed. The existence of incomplete reporting regarding the primary outcome of interest. The absence of reports on important outcomes that would be expected to be reported for studies in related fields.

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Appendix C: consensus bias assessment

	Selection of Participants	Confounding Variables	Assessment of Delirium	Method of Imaging	Blinding of Imaging Assessments	Incomplete data and Selective Outcome Reporting
Haggstrom *et al.,* 2017	+	+	?	+	?	+
Lopez *et al.,* 2017	+	+	+	?	+	+
Shioiri *et al.,* 2016	+	+	+	?	-	+
Hshieh *et al.,* 2016	+	+	+	+	+	-
Wood *et al.,* 2016	?	-	+	+	+	?
Naidech *et al.,* 2016	-	-	+	-	+	+
Mailhot *et al.,* 2016	+	+	-	+	+	+
Cavallari *et al.,* 2016	+	+	+	+	+	+
Omiya *et al.,* 2015	+	+	+	+	+	+
Jackson *et al.,* 2015	-	+	+	?	-	+
Cavallari *et al.,* 2015	+	+	+	+	+	+
Brown *et al.,* 2015	-	+	-	+	+	+
Pierrakos *et al.,* 2014	-	-	+	-	+	?
Caplan *et al.,* 2014	+	+	?	?	+	+
Root *et al.,* 2013	-	-	-	-	-	+
Otomo *et al.,* 2013	+	+	+	+	+	+
Hatano *et al.,* 2013	+	?	-	+	+	+
Polito *et al.,* 2013	-	-	+	-	-	+
Schramm *et al.,* 2012	-	-	-	+	+	+
Morandi *et al.,* 2012	-	+	+	?	+	+
Lai *et al.*, 2012	+	+	-	-	+	+
Kostalova *et al.*, 2012	+	+	+	?	-	+
Gunther *et al.,* 2012	-	+	+	+	+	+
Choi *et al.,* 2012	?	-	+	?	+	+
Yager *et al.,* 2011	-	-	+	?	?	+
Schoen *et al.,* 2011	+	+	+	+	+	+
Oldenbeuving *et al.,* 2011	+	+	-	?	+	-
Shioiri *et al.,* 2010	+	+	+	?	-	+
Rudolph *et al.,* 2009	?	+	+	+	+	+
Morimoto *et al.,* 2009	-	+	?	+	?	?
Pfister *et al.,* 2008	+	-	-	+	?	+
Fong *et al.,* 2006	-	-	?	+	+	?

+ = Low risk bias

? = Unclear risk

- = High risk bias