



Brain network disintegration as a final common pathway for delirium: a systematic review and qualitative meta-analysis



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ABSTRACT

Delirium is an acute neuropsychiatric syndrome characterized by altered levels of attention and awareness with cognitive deficits. It is most prevalent in elderly hospitalized patients and related to poor outcomes. Predisposing risk factors, such as older age, determine the baseline vulnerability for delirium, while precipitating factors, such as use of sedatives, trigger the syndrome. Risk factors are heterogeneous and the underlying biological mechanisms leading to vulnerability for delirium are poorly understood. We tested the hypothesis that delirium and its risk factors are associated with consistent brain network changes. We performed a systematic review and qualitative meta-analysis and included 126 brain network publications on delirium and its risk factors. Findings were evaluated after an assessment of methodological quality, providing N=99 studies of good or excellent quality on predisposing risk factors, N=10 on precipitation risk factors and N=7 on delirium. Delirium was consistently associated with functional network disruptions, including lower EEG connectivity strength and decreased fMRI network integration. Risk factors for delirium were associated with lower structural connectivity strength and less efficient structural network organization. Decreased connectivity strength and efficiency appear to characterize structural brain networks of patients at risk for delirium, possibly impairing the functional network, while functional network disintegration seems to be a final common pathway for the syndrome.

1. Introduction

Brain network organization is fundamentally related to cognitive functioning (Sporns, 2014) and disturbed in various neurological and psychiatric disorders (Stam, 2014). These impairments can even be a fingerprint of a specific disorder (Crossley et al., 2014) or a marker for vulnerability (Douw et al., 2010; van Diessen et al., 2013). Delirium is an acute neuropsychiatric syndrome characterized by an altered level of attention and awareness with other cognitive deficits, due to another medical condition (American Psychiatric Association, 2013). Delirium has several clinical manifestations: hypoactive, hyperactive and a

mixed type. Hypoactive delirium is characterized by lethargy and reduced psychomotor activity and speech. Patients with the hyperactive subtype, however, demonstrate features of restlessness, hyper vigilance and agitation. In the mixed type, hypoactive episodes alternate with periods with hyperactivity (Yang et al., 2009). Delirium is a common and serious clinical complication, affecting 10-50% of hospitalized elderly patients and related to poor outcomes, such as long-term cognitive impairment and death (Marcantonio, 2017). Delirium has been hypothesized to be a disconnection syndrome, caused by breakdown of brain networks (Sanders, 2011; van Dellen et al., 2014; Young, 2017).

Several risk factors for delirium have been recognized. However,

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known risk factors are heterogeneous and the underlying biological mechanisms leading to vulnerability for delirium are poorly understood. Risk factors for delirium can be distinguished into predisposing and precipitating factors (Inouye et al., 2014). Predisposing risk factors determine the baseline vulnerability for delirium, for example due to older age or cognitive impairment. Precipitating risk factors are acute changes that trigger the syndrome, for example sedation. Here, we evaluate if various predisposing risk factors induce similar brain network alterations, creating a more vulnerable (i.e. less connected and/or less integrated) brain network. Network vulnerability may lower the threshold for a transition from a healthy state towards disturbed brain activity and connectivity. Precipitating factors may then cause an acute alteration in brain dynamics, that results in a global loss of functional brain interactions as a final common pathway to delirium.

Graph theory provides tools to quantitatively analyze network organization from a whole brain perspective. A graph represents a network of nodes and connections between the nodes, i.e. the edges. On a macro level, structural brain networks can be reconstructed using anatomically defined regions as nodes and white matter tracts connecting these brain regions as edges. It is possible to map these brain networks with neuroimaging techniques such as magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI). The communication between brain regions (i.e. statistical relations or synchronization between time series of neural activity, recorded from different brain areas) is regarded as functional connectivity, which can be used to reconstruct a functional network. These functional brain networks can be characterized with imaging techniques such as functional MRI (fMRI) and positron emission tomography (PET), but also using neurophysiological measurements, such as near infrared spectroscopy (NIRS), magnetoencephalography (MEG) and electroencephalography (EEG) (Stam and Reijneveld, 2007). In the latter case, nodes are the electrodes of the EEG recording, and synchronized activities between brain regions are considered as edges. The EEG signal consists of different oscillations, i.e. delta (0.5-4Hz), theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz), and gamma (> 30Hz) band. All frequency bands show different functional network characteristics and can be analyzed separately. When the edges in a network are binary, i.e. a threshold is used to define if a connection is either present or absent, this is called an unweighted network (Biggs et al., 1986). A weighted network by contrast takes the connectivity strength or the weight of an edge into account (Biggs et al., 1986). Once a brain network is reconstructed, measures from graph theory can be used to further characterize network organization, which is illustrated in Fig. A.1.

The aim of this investigation was to compare graph theoretical studies on delirium and its risk factors to test the hypothesis that a disturbance in network organization is a final common pathway in the pathophysiology of delirium. The inclusion of risk factors was based on a recent landmark review on delirium (Inouye et al., 2014).

2. Methods

2.1. Systematic review

2.1.1. Risk factors for delirium

In this systematic review and qualitative meta-analysis, we based the inclusion of risk factors on a recent landmark review that described 29 recognized risk factors for delirium (Inouye et al., 2014). Dementia; cognitive impairment, i.e. cognitive problems without the clinical diagnosis of dementia; history of delirium; functional impairment; visual impairment; hearing impairment; comorbidity; severity of illness; depression; history of transient ischemic attack or stroke; alcohol misuse; and older age were considered as predisposing risk factors for delirium (Inouye et al., 2014). Polypharmacy; psychoactive drugs; use of sedatives or hypnotics; use of physical restraints; use of bladder catheter; acute kidney injury; decreased serum albumin; decreased sodium; hypoglycemia; hypokalemia; metabolic acidosis; infection; iatrogenic

disease; surgery; recent trauma; urgent admission; and previous coma were considered as precipitating risk factors for delirium (Inouye et al., 2014).

2.1.2. Delirium

As delirium is regarded as a manifestation of encephalopathy (Williams, 2013; Brown and Douglas, 2015; Maldonado, 2017), we included articles on either term, and grouped these into one category denoted as 'delirium'.

2.1.3. Network outcomes

Since graph theory studies may include a variety of outcomes, we focused on the outcomes that are more commonly analyzed and have a straightforward interpretation, i.e. (connectivity) strength, global efficiency, local clustering and modularity (Fig. A.1).

2.1.4. Search term and search strategy

References for the systematic review were identified through searches of PubMed and EMBASE from inception to September 2018, by use of relevant terms "connectivity", "network", "graph", "disconnection", "dementia", "cognitive impairment", "history of delirium", "functional impairment", "visual impairment", "hearing impairment", "comorbidity or severity of illness", "depression", "(history of) transient ischemic attack or stroke", "alcohol misuse", "aging", "polypharmacy", "psychoactive drugs", "sedatives or hypnotics", "physical restraints", "bladder catheter", "acute kidney injury", "altered serum albumin level", "altered sodium, glucose or potassium level", "metabolic acidosis", "infection", "iatrogenic disease", "surgery", "trauma admission", "urgent admission", "coma", "delirium", "encephalopathy", "magnetic resonance imaging", "electroencephalography", "electrocorticography", "diffusion tensor imaging", "resting state", "magnetoencephalography", "brain", "neuroimaging", "functional neuroimaging", "positron-emission tomography", "staining", "neurophysiology", "diffusion tractography", "diffusion magnetic resonance imaging", and "near infrared spectroscopy" (for the exact search term see Tables A.1 and A.2). Articles resulting from these searches and relevant references cited in those publications were reviewed on the relevance of the title and the abstract by two authors (SVM and AA). The full text of potentially relevant articles were evaluated by two authors (SVM and AA).

2.1.5. Inclusion criteria

We included articles (a) published in English, (b) assessing whole brain graph analysis, (c) in humans (d) during delirium or during a state that is considered to be risk factor, (e) with use of a control group, (f) for functional imaging with measurements conducted during resting state without intervention, and (g) assessing one or more of the following outcomes: (normalized) connectivity strength of the global network, (normalized) global efficiency or (normalized) path length of the global network, (normalized) local clustering of the global network, and/or (normalized) modularity of the global network (Fig. A.1). If eligibility for inclusion was uncertain, we discussed the article with a third author (EVD) and included the paper by consensus of all three authors.

2.2. Quality criteria

Previous literature has indicated that network analyses may be subject to various methodological choices, for example the use of adequate connectivity measures (Zhang et al., 2015; van Diessen et al., 2015; Fornito et al., 2013; Rubinov and Sporns, 2010) and the definition of nodes and edges (Power et al., 2015; Pruim et al., 2015; van Dijk et al., 2012; van Wijk et al., 2010; van den Heuvel et al., 2017). These methodological choices can introduce bias and strongly influence the outcomes of graph analysis (van Diessen et al., 2015; Fornito et al., 2013; Alderson-Day et al., 2016; Tijms et al., 2013a). Therefore, we developed a priori quality criteria based on state-of-the-art

PART I		Score
1. Sample size		
a. Case-control study	N≤20	<input type="checkbox"/> 0
	N=21-50	<input type="checkbox"/> 1
	N≥51	<input type="checkbox"/> 2
b. Other study designs	N≤100	<input type="checkbox"/> 0
	N=101-200	<input type="checkbox"/> 1
	N≥201	<input type="checkbox"/> 2
2. Definition of patient population		
	No definition or non-validated screening- or diagnostic tool or opinion of one specialist	<input type="checkbox"/> 0
	Validated screening- or diagnostic tool or consensus of more than one specialist	<input type="checkbox"/> 1
3. Confounding		
	No adjusting for/matching on confounding reported	<input type="checkbox"/> 0
	Incomplete adjusting for/matching on confounding variables	<input type="checkbox"/> 1
	Full adjusting for/matching on confounding variables	<input type="checkbox"/> 2
		Total
PART II		
4. Network comparison		
Adequate network comparison corrected for confounders		
	Weighted network + regression of connection strength effects	<input type="checkbox"/> 1 out of 4
	Weighted network + comparison to null model	<input type="checkbox"/>
	Unweighted network with multiple different thresholds + multiple testing correction	<input type="checkbox"/>
	Minimum spanning tree	<input type="checkbox"/>
Statistics of connectivity analysis are reported and corrected for multiple comparisons when applicable		
		<input type="checkbox"/> 1
		Total
PART III		Score
5. Methodological quality		
a. DTI	Scanning procedure on 3T or higher	<input type="checkbox"/> 1
	Edge weight definitions applied leading to similar results	2 out of 4
	Streamline Density	<input type="checkbox"/>
	Streamline numbers/Fiber numbers	<input type="checkbox"/>
	Fractional Anisotropy	<input type="checkbox"/>
	1-Mean Diffusivity or 1/Mean Diffusivity	<input type="checkbox"/>
b. fMRI	EPI scans: scanning procedure is at least 9 minutes	<input type="checkbox"/> 1
	PRESTO scan	<input type="checkbox"/> 1
	Motion correction	1 out of 3
	Groups matched on motion correction parameters	<input type="checkbox"/>
	ICA aroma	<input type="checkbox"/>
	Data scrubbing or spike regression	<input type="checkbox"/>
c. EEG / MEG	Length and sample frequency of epochs are equal	<input type="checkbox"/> 1
	Connectivity measure with correction for field spread or common sources	1 out of 7
	Imaginary Coherence	<input type="checkbox"/>
	Phase Lag Index	<input type="checkbox"/>
	Phase Slope Index	<input type="checkbox"/>
	Phase Transfer Entropy	<input type="checkbox"/>
	Directed Transfer Function	<input type="checkbox"/>
	Partial Directed Coherence	<input type="checkbox"/>
	Amplitude Envelop Correlation	<input type="checkbox"/>
		Total
RESULTS		
	DTI / fMRI / EEG / MEG	PET / MRI
	0 – 4 points	0 – 3 points
	5 – 7 points	4 – 5 points
	8 – 9 points	6 – 7 points
		Outcome
		<input type="checkbox"/> Moderate Quality
		<input type="checkbox"/> Good Quality
		<input type="checkbox"/> Excellent Quality

Fig. 1. Criteria used in this qualitative meta-analysis to quantify the quality of the included studies.

methodological studies (van Diessen et al., 2015; Fornito et al., 2013; Ciric et al., 2017; Birn et al., 2013; Zaal et al., 2015). Consensus papers from experts in the field of interest (van Diessen et al., 2015; Fornito et al., 2013; Ciric et al., 2017) were used to assess the quality of the studies and quantify their impact (Fig. 1, Appendix text Section A.1). Based on these, two authors (CK and LM) evaluated each study independently and categorized the quality as excellent, good or moderate. If the scores differed between authors, a third author (EVD or SVM) evaluated the study, and the quality score was determined after consensus of all three authors.

2.3. Qualitative meta-analysis

2.3.1. Case-specific results

Structural and functional brain network studies were separately analyzed for the different risk factors. As different imaging modalities measure various aspects of the structural and functional networks which should be interpreted differently, studies were grouped according to the imaging modality, i.e. white matter networks based on DTI, grey matter networks based on T1 structural MRI, functional networks based on fMRI and functional networks based on EEG or MEG. fMRI and EEG or MEG can be considered to give complementary information about functional interactions between brain areas, where the spatial resolution of fMRI provides more accurate anatomical information, whereas EEG and MEG provide a higher temporal resolution of functional connectivity. All good and excellent quality studies for each modality (DTI, MRI grey matter networks, fMRI/PET, EEG/MEG) were compared per risk factor and outcome measure (connectivity strength, global efficiency, local clustering and modularity). Results of the outcomes were selected from the articles by two authors (AA and SVM) independently and checked by two other authors independently (LM and CK). If comparison of the outcomes extracted by both authors produced contradictory results, the authors discussed this with a third author (EVD), and adapted the outcome after consensus of all three authors. If a publication explored more than one risk factor separately, we took the comparison of each risk factor as a separate result, referred to as case.

2.3.2. Composite scores

As methods used to perform graph analyses were not equal between the different included studies, a quantitative meta-analysis appeared not to be feasible. However, to study whether delirium and its risk factors are associated with consistent brain network changes we performed a qualitative meta-analysis, in which we summarized results of the different included studies in composite scores. A composite score for each modality (DTI, MRI grey matter networks, fMRI/PET, EEG/MEG) and each outcome measure (connectivity strength, global efficiency, local clustering and modularity) was calculated. After exclusion of the moderate quality studies, all studies were given an equal weight in the composite score of the risk factor. The result of the composite score was one of the following: (a) “no effect”, i.e. outcome was assessed, but the majority of studies found no effect of the risk factor on this outcome, (b) “higher” outcome value, i.e. the majority of investigations found an increase of this outcome measure associated with the risk factor, (c) “lower” outcome value, i.e. the majority of studies found a decrease of this outcome measure associated with the risk, (d) “inconclusive” outcome value, the more than 50% of the investigations reported contradictory results, (e) “not measured”, i.e. no studies assessing this outcome were available for this risk factor. The composite score was accompanied with the percentage of studies representing the score (i.e. “no effect”, “higher”, “lower”). For example, if 5 DTI studies on the risk factor aging assessed the outcome global efficiency, of which 4 studies found a decreased global efficiency in older subjects, the composite score was “lower: 4 out of 5”. Outcomes of moderate studies were qualitatively described in the results section if no good or excellent quality studies were available.

3. Results

Our literature search resulted in 24442 hits of which 126 studies met our inclusion criteria (Fig. A.2). These 126 publications described in total 151 cases on different predisposing risk factors, precipitating risk factors or delirium (i.e. if a publication explored more than one risk factor separately, we took the comparison of each risk factor as a separate case) (van Dellen et al., 2014; Zhu et al., 2012; Chen et al., 2011; Wu et al., 2013; Otte et al., 2015; Lim et al., 2015; Gong et al., 2009; Geerligs et al., 2015; Song et al., 2014; Ferreira et al., 2016; Cao et al., 2014; Chan et al., 2014; Onoda and Yamaguchi, 2013; Meunier et al., 2009; Liu et al., 2014a; Knyazev et al., 2015; Vecchio et al., 2014; Micheloyannis et al., 2009; Vysata et al., 2014; Smit et al., 2016; Yao et al., 2010; Phillips et al., 2015; Pereira et al., 2015; Li et al., 2012; Li et al., 2016; Wang et al., 2016a; Bai et al., 2012; Daianu et al., 2013; Morris et al., 2014; Shu et al., 2012; Vaessen et al., 2012; Tang et al., 2015; Zhao et al., 2017; Yi et al., 2015; Minati et al., 2014; Chang et al., 2016; Yu et al., 2015; Baggio et al., 2014; Wang et al., 2013; Xiang et al., 2013; Brier et al., 2013; Kim et al., 2015; Sun et al., 2014; Liu et al., 2012; Sang et al., 2018; Sanabria-Diaz et al., 2013; Seo et al., 2013; Zeng et al., 2015; Frantzidis et al., 2014; Koenig et al., 2005; Pineda-Pardo et al., 2014; Gomez et al., 2009; López-Sanz et al., 2017; Achard et al., 2012; Crone et al., 2014; van Montfort et al., 2018; Chen et al., 2018a; Brandt et al., 2019; Numan et al., 2017; He et al., 2008; Liu et al., 2014b; Tijms et al., 2013b; John et al., 2017; Wang et al., 2016b; Lo et al., 2010; Reijmer et al., 2013; Agosta et al., 2013; Sanz-Arigita et al., 2010; Zhao et al., 2012; Supekar et al., 2008; Qin et al., 2015; Peraza et al., 2015; Filippi et al., 2017; de Haan et al., 2009; Stam et al., 2007; van Dellen et al., 2015; Afshari and Jalili, 2017; Berendse et al., 2008; De Haan et al., 2012; Ajilore et al., 2014a; Lim et al., 2013; Singh et al., 2013; Lee et al., 2018; Chen et al., 2016a; Mak et al., 2016; Korgaonkar et al., 2014; Ajilore et al., 2014b; Qin et al., 2014; Charlton et al., 2015; Nigro et al., 2015; Long et al., 2015; Chen et al., 2016b; Bohr et al., 2013; Meng et al., 2014; Lord et al., 2012; Luo et al., 2015; Zhang et al., 2011; Jin et al., 2011; Ye et al., 2015; Wang et al., 2016c; Ye et al., 2016; Leuchter et al., 2012; Shim et al., 2018; Zhang et al., 2014; Jao et al., 2015; Li et al., 2014; Kim et al., 2014a; Xu et al., 2016; Zhang et al., 2018; Wang et al., 2015; Ma et al., 2015; Monti et al., 2013; Hashmi et al., 2017; Lee et al., 2013; Blain-Moraes et al., 2017; Shi et al., 2013; Guo et al., 2014; Kim et al., 2014b; Caeyenberghs et al., 2014; Messé et al., 2013; Han et al., 2014; van der Horn et al., 2017; Maestú et al., 2010; Shu et al., 2009; Bola et al., 2014; Wang et al., 2012). For a detailed overview of included studies, investigated risk factors, measurement techniques, outcomes and quality scores see Table A.3. After scoring, 118 cases were graded as qualitatively ‘good or excellent’, of which 99 on predisposing risk factors, 11 on precipitation risk factors and 7 on delirium, and included in our risk factor composite scores. Table 1 show findings for each modality: structural networks based on MRI grey matter similarity, structural networks based on DTI, functional networks based on fMRI, and functional networks based on EEG. Below we describe findings on risk factors with at least 2 good or excellent quality studies, if not otherwise specified.

3.1. Predisposing delirium risk factors and structural networks

3.1.1. White matter networks

DTI-based structural network studies generally showed an association of predisposing risk factors for delirium with lower connectivity strength and lower network efficiency (Table 1, part 1A). Aging (2 out of 2 (2/2) studies), cognitive impairment (2/2 studies) and depression (2/3 studies) were associated with lower connectivity strength (Otte et al., 2015; Bai et al., 2012; Shu et al., 2012; Lim et al., 2013; Qin et al., 2014; Chen et al., 2016b). Aging (2/2 studies), cognitive impairment (5/7 studies), dementia (3/4 studies) and visual impairment (1 study) were all associated with lower network efficiency (Otte et al., 2015; Bai et al., 2012; Daianu et al., 2013; Morris et al., 2014; Shu et al., 2012;

Table 1

Overview of composite scores of graph studies on (I) predisposing risk factors for delirium, (II) precipitating risk factors for delirium and (III) delirium, grouped by modality.

Part I Predisposing risk factors								
Risk factor	Strength	N	Efficiency (global)	N	Local clustering	N	Modularity	N
1A. Predisposing DTI								
Aging	↓	2/2	↓	2/2	?	1/1	=	1/1
Cognitive imp	↓	2/2	↓	5/7	=	2/4	·	·
Dementia	·	·	↓	3/4	=	2/4	↑	1/1
Depression	↓	2/3	=	6/7	=	6/6	·	·
Stroke	=	1/1	?	2	=	1/1	·	·
Visual imp	·	·	↓	1/1	=	1/1	·	·
Total	↓	6/7	↓	13/23	=	12/17	?	2
1B. Predisposing GM								
Aging	·	·	↓	2/2	↑	1/1	=	1/1
Cognitive imp	?	2	=	3/4	=	3/5	·	·
Dementia	·	·	=	3/5	=	5/7	=	1/1
Depression	↑	1/1	=	3/6	?	5	↑	1/1
Hearing imp	·	·	·	·	?	2	·	·
Total	?	3	=	8/17	?	20	=	2/3
1C. Predisposing fMRI/PET								
Aging	↓	2/3	=	3/4	↑	1/1	↓	4/4
Cognitive imp	·	·	?	10	=	6/9	?	6
Dementia	↓	2/3	?	11	?	11	=	4/5
Depression	↑	1/1	=	4/7	=	5/6	↑	1/1
Hearing imp	·	·	?	2	?	2	·	·
Total	↓	4/7	?	34	?	29	?	16
1D. Predisposing EEG/MEG								
Delta								
Aging	=	2/2	?	2	=	2/2	=	1/1
Cognitive imp	?	3	=	4/4	=	3/4	·	·
Dementia	=	2/2	=	4/4	=	1/1	·	·
Depression	?	2	=	1/1	=	1/1	·	·
Stroke	·	·	·	·	·	·	·	·
Visual imp	·	·	·	·	·	·	·	·
Total	?	9	=	10/11	=	7/8	=	1/1
Theta								
Aging	?	2	?	2	=	2/2	=	1/1
Cognitive imp	?	3	=	4/4	=	3/4	·	·
Dementia	=	2/2	=	3/4	↑	1/1	·	·
Depression	?	2	=	1/1	↓	1/1	·	·
Stroke	·	·	·	·	·	·	·	·
Visual imp	·	·	·	·	·	·	·	·
Total	?	9	=	10/11	=	5/8	=	1/1
Alpha								
Aging	↓	2/2	?	2	?	2	=	1/1
Cognitive imp	↓	2/3	=	3/4	?	4	·	·
Dementia	?	2	?	4	↑	1/1	·	·
Depression	?	2	↓	1/1	↓	1/1	·	·
Stroke	↑	1/1	·	·	·	·	·	·
Visual imp	↑	1/1	·	·	·	·	·	·
Total	↓	6/11	?	11	?	8	=	1/1
Beta								
Aging	?	2	=	2/2	?	2	=	1/1
Cognitive imp	↓	3/5	=	3/4	=	2/4	·	·
Dementia	=	2/2	=	3/4	=	1/1	·	·
Depression	?	2	=	1/1	=	1/1	·	·
Stroke	·	·	·	·	·	·	·	·
Visual imp	·	·	·	·	·	·	·	·
Total	?	11	=	9/11	=	5/6	=	1/1
Part II Precipitating risk factors								
Risk factor	Strength	N	Efficiency (global)	N	Local clustering	N	Modularity	N
2A. Precipitating fMRI								
Coma	=	1/1	=	2/2	?	2	?	2
Renal failure	·	·	↓	1/1	·	·	·	·
Sedation	↓	1/1	↓	2/3	?	2	?	2
Neurotrauma	=	1/1	=	1/1	·	·	?	·
Total	=	2/3	?	7	?	4	?	4

(continued on next page)

Table 1 (continued)

Part II Precipitating risk factors								
Risk factor	Strength	N	Efficiency (global)	N	Local clustering	N	Modularity	N
2B. Precipitating EEG								
<i>Delta</i>								
Sedation	?	2	?	2	=	1/1	=	1/1
<i>Theta</i>								
Sedation	=	2/2	=	2	=	1/1	=	1/1
<i>Alpha</i>								
Sedation	=	2/3	↓	2/3	↑	2/2	=	1/1
<i>Beta</i>								
Sedation	=	2/2	=	2/2	↑	1/1	↑	1/1
Part III Delirium								
Syndrome	Strength	N	Efficiency (global)	N	Local clustering	N	Modularity	N
3A. Delirium fMRI								
Delirium	=	1/1	?	3	↓	2/2	↓	1/1
3B. Delirium EEG								
<i>Delta</i>								
Delirium	=	3/3	=	2/2	=	1/1	·	·
<i>Theta</i>								
Delirium	=	3/3	=	2/2	=	1/1	·	·
<i>Alpha</i>								
Delirium	↓	3/3	?	2/2	=	1/1	·	·
<i>Beta</i>								
Delirium	=	3/3	=	2/2	=	1/1	·	·

= equal outcome value (the majority of studies found no effect of the risk factor on this outcome).

↑ higher outcome value (the majority of studies found an increase of this outcome measure associated with the risk factor).

↓ “lower” outcome value (the majority of studies found a decrease of this outcome measure associated with the risk).

? “inconclusive” outcome value (the studies found contradictory results).

· “not measured” (no studies assessing this outcome were available for this risk factor).

Abbreviations: DTI = diffusion tensor imaging, EEG = encephalography, fMRI = functional magnetic resonance imaging, GM = grey matter, MEG = magnetoencephalography, PET = positron emission tomography

Vaessen et al., 2012; Tang et al., 2015; Zhao et al., 2017; Wang et al., 2016b; Lo et al., 2010; Reijmer et al., 2013; Lim et al., 2013; Shu et al., 2009). Depression (6/7 studies) showed however no effect on efficiency and stroke (N=2) showed contradictory findings on efficiency (Bai et al., 2012; Tang et al., 2015; Korgaonkar et al., 2014; Ajilore et al., 2014b; Qin et al., 2014; Charlton et al., 2015; Nigro et al., 2015; Chen et al., 2016b; Shi et al., 2013). The majority of risk factors showed no effect on local clustering (Otte et al., 2015; Bai et al., 2012; Dainu et al., 2013; Morris et al., 2014; Shu et al., 2012; Vaessen et al., 2012; Tang et al., 2015; Wang et al., 2016b; Lo et al., 2010; Reijmer et al., 2013; Ajilore et al., 2014a; Lim et al., 2013; Korgaonkar et al., 2014; Qin et al., 2014; Charlton et al., 2015; Nigro et al., 2015; Chen et al., 2016b; Shi et al., 2013; Shu et al., 2009). Mixed results were found for different risk factors for modularity: while one study on aging showed no effect (Lim et al., 2013), a study on dementia showed increased modularity (Wang et al., 2016b).

3.1.2. Grey matter networks

Evidence for grey matter network alterations due to delirium predisposing risk factors was scarce (Table 1, part 1B). The two studies on aging both showed an association between aging and loss of efficiency (Zhu et al., 2012; Wu et al., 2013). However, no effect on grey matter network efficiency was found for cognitive impairment (N=5), dementia (N=6) and depression (N=6) in at least 50% of studies (Yao et al., 2010; Phillips et al., 2015; Pereira et al., 2015; Li et al., 2016; He et al., 2008; Liu et al., 2014b; Tijms et al., 2013b; John et al., 2017; Lim et al., 2013; Singh et al., 2013; Lee et al., 2018; Chen et al., 2016a; Mak et al., 2016; Ajilore et al., 2014b). Inconsistent results were found for various delirium risk factors on strength, local clustering and modularity (Zhu et al., 2012; Chen et al., 2011; Wu et al., 2013; Liu et al., 2014a; Yao et al., 2010; Phillips et al., 2015; Pereira et al., 2015; Li

et al., 2012; Li et al., 2016; He et al., 2008; Tijms et al., 2013b; John et al., 2017; Lim et al., 2013; Singh et al., 2013; Lee et al., 2018; Chen et al., 2016a; Mak et al., 2016; Ajilore et al., 2014b; Kim et al., 2014a).

3.2. Predisposing delirium risk factors and functional networks

3.2.1. fMRI and PET

fMRI-based functional network studies generally showed an association of predisposing risk factors for delirium and lower connectivity strength (Table 1, part 1C). Aging (2/3 studies) and dementia (2/3 studies) were associated with lower fMRI connectivity strength (Geerligts et al., 2015; Song et al., 2014; Ferreira et al., 2016; Peraza et al., 2015; Filippi et al., 2017). The same effect was found for cognitive impairment (2/2 studies) (Minati et al., 2014; Chang et al., 2016), but these studies were of moderate quality. Regarding efficiency, most of the risk factors reported conflicting results on fMRI and PET networks (cognitive impairment: N=10, dementia: N=11 and hearing loss: N=2) (Brier et al., 2013; Kim et al., 2015; Sun et al., 2014; Sang et al., 2018; Sanabria-Diaz et al., 2013; Seo et al., 2013; Sanz-Arigitia et al., 2010; Zhao et al., 2012; Peraza et al., 2015; Filippi et al., 2017; Xu et al., 2016; Zhang et al., 2018). Aging (3/4 studies) and depression (4/7 studies) were associated with no effect on efficiency in fMRI and PET studies (Geerligts et al., 2015; Song et al., 2014; Cao et al., 2014; Liu et al., 2014a; Yi et al., 2015; Yu et al., 2015; Baggio et al., 2014; Wang et al., 2013; Brier et al., 2013; Kim et al., 2015; Sun et al., 2014; Sang et al., 2018; Sanabria-Diaz et al., 2013; Seo et al., 2013; Meng et al., 2014; Lord et al., 2012; Luo et al., 2015; Jin et al., 2011; Ye et al., 2015; Wang et al., 2016c; Zhang et al., 2011). For local clustering, fMRI and PET studies on dementia (N=11) and hearing impairment (N=2) showed conflicting results as well (Brier et al., 2013; Kim et al., 2015; Sun et al., 2014; Sanabria-Diaz et al., 2013; Seo et al., 2013; Sanz-

Arigita et al., 2010; Zhao et al., 2012; Peraza et al., 2015; Filippi et al., 2017; Xu et al., 2016; Zhang et al., 2018), while most fMRI and PET studies on cognitive impairment (6/9 studies) and depression (5/6 studies) showed no effect (Wang et al., 2013; Brier et al., 2013; Kim et al., 2015; Sun et al., 2014; Sanabria-Diaz et al., 2013; Seo et al., 2013; Meng et al., 2014; Lord et al., 2012; Luo et al., 2015; Jin et al., 2011; Zhang et al., 2011). Although all studies on aging (4/4 studies) showed decreased modularity (Geerligs et al., 2015; Song et al., 2014; Cao et al., 2014; Chan et al., 2014), studies on other risk factors showed inconclusive findings (cognitive impairment: N=6) or no effect on modularity (4/5 studies) (Yi et al., 2015; Baggio et al., 2014; Wang et al., 2013; Brier et al., 2013; Kim et al., 2015; Sun et al., 2014; Peraza et al., 2015).

3.2.2. EEG and MEG

EEG and MEG-based functional network studies showed mixed results with a tendency towards lower connectivity strength in the alpha band (Table 1, part 1D). Specifically, aging (2/2 studies) and cognitive impairment (2/3 studies) were associated with a decreased EEG connectivity strength in the alpha band (Vysata et al., 2014; Smit et al., 2016; Zeng et al., 2015; Frantzidis et al., 2014; Pineda-Pardo et al., 2014). Studies on alpha band connectivity strength in dementia showed mixed results of decreased connectivity strength (1/2 studies) and no effect (1/2 studies). However, two moderate quality studies also showed decreased alpha band connectivity strength (Koenig et al., 2005; Berendse et al., 2008). No effects were found for other frequency bands. Mixed results for different risk factors were found on efficiency, local clustering and modularity (Knyazev et al., 2015; Vecchio et al., 2014; Smit et al., 2016; Zeng et al., 2015; Frantzidis et al., 2014; Pineda-Pardo et al., 2014; van Dellen et al., 2015; Afshari and Jalili, 2017; Leuchter et al., 2012; Shim et al., 2018; Guo et al., 2014).

3.3. Precipitating delirium risk factors and functional networks

3.3.1. fMRI

Evidence for fMRI network alterations due to delirium-precipitating risk factors was scarce (Table 1, part 2A). Sedation (2/3 studies) and renal failure (N=1) were associated with decreased efficiency (Ma et al., 2015; Monti et al., 2013; Hashmi et al., 2017), but coma (N=2) and neurotrauma (N=1) showed no effect on efficiency (Achard et al., 2012; Crone et al., 2014; Messé et al., 2013). Mixed results for different risk factors were found for strength, local clustering and modularity (Achard et al., 2012; Crone et al., 2014; Monti et al., 2013; Hashmi et al., 2017; Messé et al., 2013; Han et al., 2014).

3.3.2. EEG and MEG

EEG and MEG-based functional network studies generally showed an association of precipitating risk factors for delirium with lower efficiency and a higher local clustering in the alpha band (Table 1, part 2B). Sedation (2/3 studies) and neurotrauma (N=1 of moderate quality) were associated with a decreased efficiency in the alpha band (Numan et al., 2017; Lee et al., 2013; Blain-Moraes et al., 2017; Maestú et al., 2010). Sedation (2/2 studies) and neurotrauma (N=1 of moderate quality) were further associated with increased local clustering in the alpha band (Lee et al., 2013; Blain-Moraes et al., 2017; Maestú et al., 2010). No effect was found in these two risk factors on connectivity strength (Numan et al., 2017; Lee et al., 2013; Blain-Moraes et al., 2017; Maestú et al., 2010).

3.4. Delirium and functional networks

3.4.1. fMRI

Evidence for fMRI network alterations in delirium was scarce (Table 1, part 3A). Only one fMRI study during delirium was detected, showing a loss in efficiency and local clustering (van Montfort et al., 2018). Modularity was not assessed in this study. Three fMRI studies on

hepatic encephalopathy (Chen et al., 2018a; Zhang et al., 2014; Jao et al., 2015) (of which one of moderate quality (Jao et al., 2015)) did not show loss of efficiency, and reported decreased local clustering (Chen et al., 2018a; Zhang et al., 2014; Jao et al., 2015). Two fMRI studies on hepatic encephalopathy (of which one of moderate quality (Jao et al., 2015)) showed decreased modularity (Li et al., 2014).

3.4.2. EEG

EEG-based functional network studies showed an association of delirium with lower connectivity strength in the alpha band (Table 1, part 3B). A decreased connectivity strength in the alpha band was reported in the available EEG publications (3/3 studies) (van Dellen et al., 2014; Brandt et al., 2019; Numan et al., 2017), but two of these were based on the same dataset. No effect on local clustering (van Dellen et al., 2014; Numan et al., 2017) was found (2/2 studies). An inconclusive effect on alpha band efficiency was found due to methodological differences between studies (Sanders, 2011; van Montfort et al., 2018). Using the minimum spanning tree (MST) diameter, a less biased measure of efficiency than the path length of a weighted network (Tewarie et al., 2015; Stam et al., 2014), a decreased alpha band efficiency was observed.

4. Discussion

We evaluated the evidence for alterations in the structural and functional brain network related to delirium and its risk factors (Fig. 2). On a structural level, predisposing risk factors were generally associated with lower connectivity strength and less efficient organization of white matter connections. On a functional level, a decrease of functional connectivity strength was found in most fMRI- and some EEG studies related to predisposing risk factors. The limited fMRI and EEG data available on precipitating factors generally indicated less efficiency of functional networks. During delirium, functional brain networks were characterized by decreased alpha band EEG connectivity and lower fMRI network integration. Taken together, we found evidence that a less connected and less integrated brain network is a common mechanism in the pathophysiology of delirium.

4.1. Effects of predisposing delirium risk factors on brain networks

Although all studied risk factors were generally associated with decreased strength and loss of efficiency, most conclusive evidence for brain network alterations was found for aging, dementia and cognitive impairment. However, depression showed an aberrant effect in global efficiency of structural networks. A possible explanation is that depression is a more heterogeneous disorder with a largely unknown biological substrate (Fried et al., 2014), making it difficult to compare studies within this risk factor. The risk factor age showed a stronger risk factor-specific pattern compared to other risk factors. Investigations on aging showed decreased efficiency in grey matter MRI studies and loss of modularity in fMRI studies, while findings on other risk factors were inconclusive or absent. Aging is known as a key risk factor for delirium (Inouye et al., 2014; Zaal et al., 2015), which may be related to its extensive impact on brain network topology.

4.2. Effects of precipitating delirium risk factors on brain networks

The small number of available studies on precipitating factors for delirium generally showed loss of efficiency of the functional network. Sedation and renal failure were associated with loss of efficiency, but coma and neurotrauma did not show this effect. A possible explanation is that sedation and renal failure are manifestations of acute brain changes, whereas coma and neurotrauma were studied in the subacute phase. Loss of network efficiency could initially have been present in the acute phase of coma or neurotrauma, but this may have normalized thereafter (Kraft et al., 2012). However, the evidence was limited, so

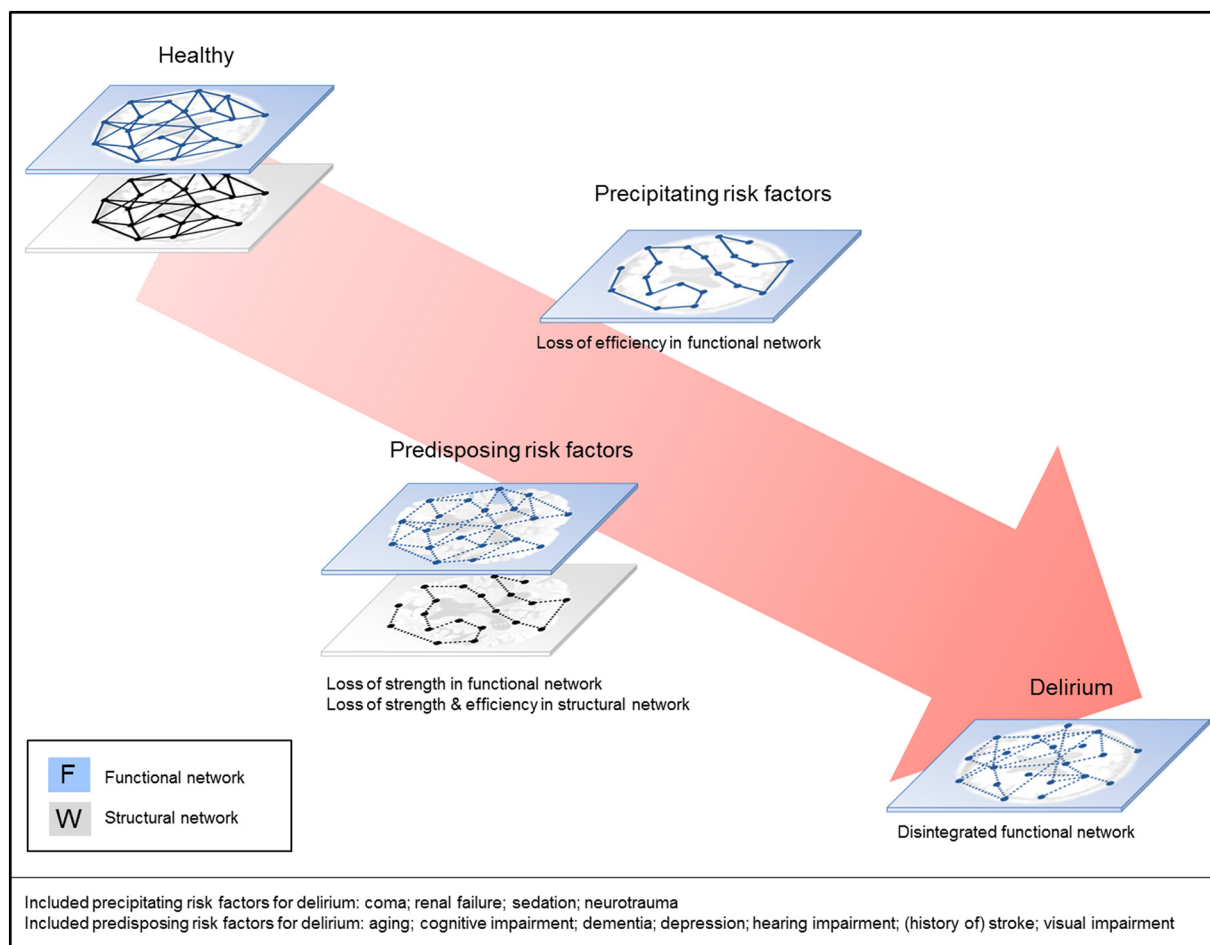


Fig. 2. Brain network disintegration as a final common pathway for delirium. During the healthy state the structural white matter network and the functional network show an integrated and efficient organization. Predisposing risk factors were found to be associated with loss of connectivity strength and loss of efficiency of the white matter network and some evidence was found for a loss of connectivity strength in the functional network. Little evidence was available on precipitating risk factors, but sedation was associated with a loss of efficiency in the functional network. During delirium the functional network was found to be weakened and less integrated.

more studies are needed to unravel the exact mechanism.

4.3. Effects of delirium on brain networks

During delirium, a variety of network changes have been observed, i.e. reduced connectivity strength, reduced global efficiency, reduced local clustering and reduced modularity, although the number of investigations was small. In general, the strongest evidence was found for a less connected and disintegrated network during the syndrome. Due to the limited number of studies, we are currently unable to distinguish specific network alterations to the different clinical subtypes of delirium.

4.4. Strengths and limitations

The framework of graph theory provides new opportunities to study the development of neuropsychiatric diseases. Our rigorous systematic review and qualitative meta-analysis revealed new insights on the pathophysiology of delirium. The development and use of the quality criteria for network studies, largely based on recent consensus papers on methodological approaches, allowed us to assess the robustness of findings (van Diessen et al., 2015; Fornito et al., 2013; Alderson-Day et al., 2016; Tijms et al., 2013a). These quality criteria can be used and adapted for future investigations on other topics.

We studied a variety of presumed delirium risk factors in relation to

brain network alterations. As there is no general consensus which factors increase the risk of delirium, it could be argued that inclusion of some of these factors may have biased our analyses. In the absence of strong epidemiological evidence on the exact risk profile of delirium, we included delirium risk factors based on a recent landmark article published in a high-impact medical journal (Inouye et al., 2014).

Comparing brain network outcomes of different studies in a qualitative way may be unconventional. The outcomes of the studies were similar, but some studies differed in study design and exact calculations of the outcomes. Moreover, efficiency estimates may be biased by connection strength (van Wijk et al., 2010; van den Heuvel et al., 2017; Tijms et al., 2013a), which may be relevant for our qualitative analysis. A qualitative assessment suggested that efficiency loss due to delirium risk factors may at least partially be explained by lower connectivity strength, but average connectivity was not reported as outcome measure in the majority of cases (results in Appendix text Section A.2). Future work, implementing recently introduced corrections for this possible confounder (van den Heuvel et al., 2017; Stam et al., 2014), is needed to show if efficiency loss is present independent of connectivity strength effects. Observations of decreased connectivity strength and loss of network efficiency have been associated to other disorders as well, and may therefore not be specific for the pathophysiology of delirium (Stam, 2014; Crossley et al., 2014; Mashour and Hudetz, 2018).

As positive and negative results are not equally reported in the literature (Easterbrook et al., 1991; Rothstein et al., 2006), our review

may have been influenced by publication bias. We have attempted to reduce this bias by defining the risk factors for delirium on a previously published landmark paper (Inouye et al., 2014), by using a predefined systematic search term and by conducting our search in two different libraries, i.e. PubMed and EMBASE. However, like in other systematic reviews and meta-analyses, unpublished negative studies could not be included.

Delirious patients can be restless or agitated (American Psychiatric Association, 2013), which may have influenced the quality of EEG and fMRI measurements (Power et al., 2015; Ciric et al., 2017). Although in EEG analyses artifact-free epochs were used and usage of fMRI motion correction was part of our quality criteria, the results shown in this study may still have been (partly) effected by motion. Future studies on delirium may benefit from strict motion correction. In addition, patients with delirium always suffer from an underlying physical condition and may use a variety of medication, which may have influenced the functional network status. However, the included studies on delirium all used a clinically matched control group to minimize medication (and other hospitalization) effects, and in some studies patients were even matched on (specific types of) medication use. Furthermore, antipsychotics such as haloperidol may not particularly influence measures of brain function (Roder et al., 2010). Likewise, delirious patients could suffer from brain damage, which might have led to differences in brain function (Stam, 2014; Kant et al., 2017). This may however not be the essential factor for network disruptions during delirium as studies that strictly corrected for brain lesions in their study sample report similar results as studies that did not (van Montfort et al., 2018; Brandt et al., 2019).

Neuropsychiatric disorders may be associated with alterations of hubs in the network (Stam, 2014; Crossley et al., 2014). Hubs were not considered in the current study because of the lack of a formal definition of hubs, together with the small number of studies using hubs as a comparable outcome measure. Not all factors influencing vulnerability for delirium have been studied in relation to brain network alterations. Future work is needed to validate our hypothesis for other delirium risk factors and to integrate the framework of graph theory and brain networks with other biological processes underlying delirium.

5. A network model of delirium

Our findings suggest that delirium predisposition is associated with a less connected and less efficient structural network, and a less connected functional network. Structural and functional network organization are closely related (Honey et al., 2009), and this relation may be of particular relevance for the pathophysiology of delirium. Computational studies have shown that reduced structural connectivity strength as characterized by reduced white matter volume, can cause decreased functional connectivity strength and efficiency (Cabral et al., 2012a; Cabral et al., 2012b). Moreover, weakening of structural network efficiency may decrease global spreading of information in the functional networks, disabling cooperative effects between network components (Mišić et al., 2015). Precipitating delirium risk factors may cause further loss of functional brain network efficiency towards a critical transition (Honey et al., 2009; Cabral et al., 2012a), consequently inducing an acute global loss of functional interactions and network integration, as seen in functional connectivity studies in delirium patients (van Dellen et al., 2014; van Montfort et al., 2018; Numan et al., 2017). Accordingly, white matter network studies on delirious patients or patients at risk for delirium, specifically show disturbances in white matter network strength and efficiency (Kyeong et al., 2018; Chen et al., 2018b), strengthening the evidence for our proposed network model of delirium.

The theory of alterations of brain networks does not have to replace other hypotheses on the pathophysiology of delirium. Important theories on the etiology of delirium include persistent neuroinflammation, an aberrant stress response and alterations of neurotransmission

(Maldonado, 2018). It remains to be studied to what extent these are associated with brain network alterations. A recent modeling study showed that EEG phenomena associated with delirium, including connectivity and network alterations, may be the result of imbalance between excitatory and inhibitory activity, as well as increased fluctuations in subcortical information (Ponten et al., 2013). Particularly an altered balance between glutamatergic and GABAergic neurotransmission may contribute to network vulnerability (Sanders, 2011). Previous studies have shown GABAergic medication, including benzodiazepines, as precipitant of delirium (Zaal et al., 2015) and reduced network connectivity (Ferrarelli et al., 2010).

At present, management of delirium consists of symptomatic treatment and treatment of underlying conditions, while there is no proven intervention that directly improves the underlying brain dysfunction. There is therefore a need for targeted interventions focused on the pathophysiology of the disorder. Non-invasive targeted brain stimulation, such as transcranial direct current stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS), may normalize the functional brain network and can have beneficial therapeutic effects in several groups of (neuro)psychiatric patients (Cocchi, 2018; Kuo et al., 2014). Based on the proposed model for delirium, we suggest that these network-based interventions, such as targeted brain stimulation, will be studied for delirium treatment.

6. Conclusion

Decreased connectivity strength and efficiency seem to characterize structural brain networks of patients at risk for delirium, while functional network disintegration appears to be the final common pathway for the syndrome.

Disclosures

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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