Clinical Neurophysiology 131 (2020) 1051–1058

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Predisposition for delirium and EEG characteristics ☆

S.J.T. van Montfort [a,*], E. van Dellen [a,b], L.L. Wattel [a,c], I.M.J. Kant [a], T. Numan [d], C.J. Stam [e], A.J.C. Slooter [a]

[a] Department of Intensive Care Medicine and UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, the Netherlands
[b] Department of Psychiatry and UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, the Netherlands
[c] Faculty of Science, University of Amsterdam, the Netherlands
[d] Department of Anatomy and Neurosciences, Amsterdam UMC, VU University Medical Center, Amsterdam, the Netherlands
[e] Department of Clinical Neurophysiology and MEG Center, Neuroscience Campus Amsterdam, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Accepted 27 January 2020
Available online 21 February 2020

Keywords:
Delirium
Risk factors
Functional impairment
EEG
Functional connectivity
Graph analysis

HIGHLIGHTS

- Functional impairment is related to decreased connectivity of the alpha frequency band.
- Other EEG characteristics of delirium were not associated with predisposition to delirium.
- The onset of delirium may reflect new neurophysiological alterations.

ABSTRACT

Objective: Delirium is associated with increased electroencephalography (EEG) delta activity, decreased connectivity strength and decreased network integration. To improve our understanding of development of delirium, we studied whether non-delirious individuals with a predisposition for delirium also show these EEG abnormalities.
Methods: Elderly subjects (N = 206) underwent resting-state EEG measurements and were assessed on predisposing delirium risk factors, i.e. older age, alcohol misuse, cognitive impairment, depression, functional impairment, history of stroke and physical status. Delirium-related EEG characteristics of interest were relative delta power, alpha connectivity strength (phase lag index) and network integration (minimum spanning tree leaf fraction). Linear regression analyses were used to investigate the relation between predisposing delirium risk factors and EEG characteristics that are associated with delirium, adjusting for confounding and multiple testing.
Results: Functional impairment was related to a decrease in connectivity strength (adjusted R^2 = 0.071, β = 0.201, $p < 0.05$). None of the other risk factors had significant influence on EEG delta power, connectivity strength or network integration.
Conclusions: Functional impairment seems to be associated with decreased alpha connectivity strength. Other predisposing risk factors for delirium had no effect on the studied EEG characteristics.
Significance: Predisposition for delirium is not consistently related to EEG characteristics that can be found during delirium.

1. Introduction

Delirium is an acute neuropsychiatric syndrome, predominantly characterized by a disturbance of attention and awareness with additional cognitive dysfunction (American Psychiatric Association, 2013). It is a common and serious clinical complication of another medical condition, affecting over 10% of hospitalized elderly patients (Marcantonio 2017). Delirium is related to poor outcomes, such as long-term cognitive impairment and death (Marcantonio 2017). The development of delirium is often not the result of one factor, but rather of an interaction of various risk factors (Inouye et al. 2014; Zaal et al. 2015; Marcantonio 2017). Risk factors for delirium can be distinguished into predisposing and precipitating factors (Inouye et al. 2014). Predisposing risk factors

☆ On behalf of the BioCog Consortium, clinicaltrials.gov identifier: NCT02265263, ethical approval number EA2/092/14 (Berlin), 14-469 (Utrecht).

* Corresponding author at: Department of Intensive Care Medicine, University Medical Center Utrecht, HP F.06.149, Postbus 85500, 3508 GA Utrecht, the Netherlands.
E-mail address: s.j.t.vanmontfort-2@umcutrecht.nl (S.J.T. van Montfort).

https://doi.org/10.1016/j.clinph.2020.01.023
1388-2457/

determine the baseline vulnerability to delirium, for example due to older age. Precipitating risk factors for delirium are acute changes that trigger the syndrome, for example sedation. A variety of risk factors have been recognized, but the underlying biological mechanisms leading to vulnerability to delirium remain poorly understood.

Delirium appears to be related to global neurophysiological disturbances, which can be measured on three different levels (van Dellen et al. 2014; Numan et al. 2017b; van Montfort et al. 2018; Brandt et al. 2019) (Fig. 1). Focusing on the frequency spectrum of the neurophysiological signal, previous studies have shown slowing of resting state electroencephalography (EEG) activity during delirium, most accurately characterized by an increase in relative delta power (van Dellen et al. 2014; Numan et al. 2017b). In addition, focusing on functional connectivity (i.e. statistical interdependencies between activity of remote brain regions which are assumed to reflect communication between these regions (Aertsen et al. 1989)), delirium has been characterized by decreased functional connectivity strength in the alpha frequency band (van Dellen et al. 2014; Numan et al. 2017b; van Montfort et al. 2019). Patterns of functional connectivity can be represented as networks, which can subsequently be analyzed with methods derived from network theory (Stam and van Straaten 2012; van Straaten and Stam 2013). Global organizational patterns, such as network efficiency and network integration, can be calculated from these functional networks (Bullmore and Sporns 2009; Stam and van Straaten 2012; van Straaten and Stam 2013). Focusing on functional network characteristics, delirium has been associated with impaired network integration (Numan et al. 2017b; van Montfort et al. 2018, 2019). Therefore, it is hypothesized that delirium is a disconnection syndrome, reflecting a breakdown of functional brain networks (Sanders 2011; van Dellen et al. 2014; Young 2017).

However, it is unknown if these neurophysiological alterations coincide with the onset of delirium, or reflect vulnerability to the disorder. The aim of this study was to test the hypothesis that predisposing delirium risk factors induce similar neurophysiological alterations as during delirium. In this way, vulnerability may lower the threshold for a transition from a healthy state towards disturbed brain activity that manifests as delirium. More specifically, we hypothesized that predisposing risk factors for delirium are associated with increased delta power, decreased connectivity strength and decreased network integration in the alpha frequency band (Fig. 1). To gain more insight in the multifactorial nature of the disorder, we additionally evaluated the cumulative effect of the predisposing risk factors on these EEG characteristics.

2. Methods

2.1. Design and study population

The subjects for this study derive from the *Biomarker Development for Postoperative Cognitive Impairment in the Elderly* (BioCog) project at the University Medical Center (UMC) Utrecht (Winterer et al. 2018). In this cross-sectional sub-study, elderly individuals were included, consisting of non-hospitalized participants that were on the waiting list for elective surgery, recruited via the University Medical Center (UMC) Utrecht (i.e. orthopedic-, cardiac-, gastro-intestinal-, maxillofacial- or otorhinolaryngologic surgery), as well as participants that were recruited via a local general practitioner. Inclusion criteria were a European ancestry, age of 65 year or above, and a signed informed consent for the study. Participants with one or more of the following characteristics were excluded: a life expectancy shorter than a year; an indication for (early) dementia as indicated with a score of 23 or lower on the Mini Mental State Examination (MMSE) (Folstein et al. 1985); missing EEG data. EEG measurements and clinical assessments were performed on the same day.

2.2. Clinical assessment

The risk factors investigated in this study were based on a high quality review (Inouye et al. 2014). We were not able to evaluate all risk factors described in the review, i.e. participants with dementia, hearing or visual impairment and history of delirium were not available, and comorbidity was not measured within this study.

2.2.1. Age and history of transient ischemic attack or stroke

To determine age and history of transient ischemic attack (TIA) or stroke, the medical records of the participants were used. If this information was not available, participants were asked whether

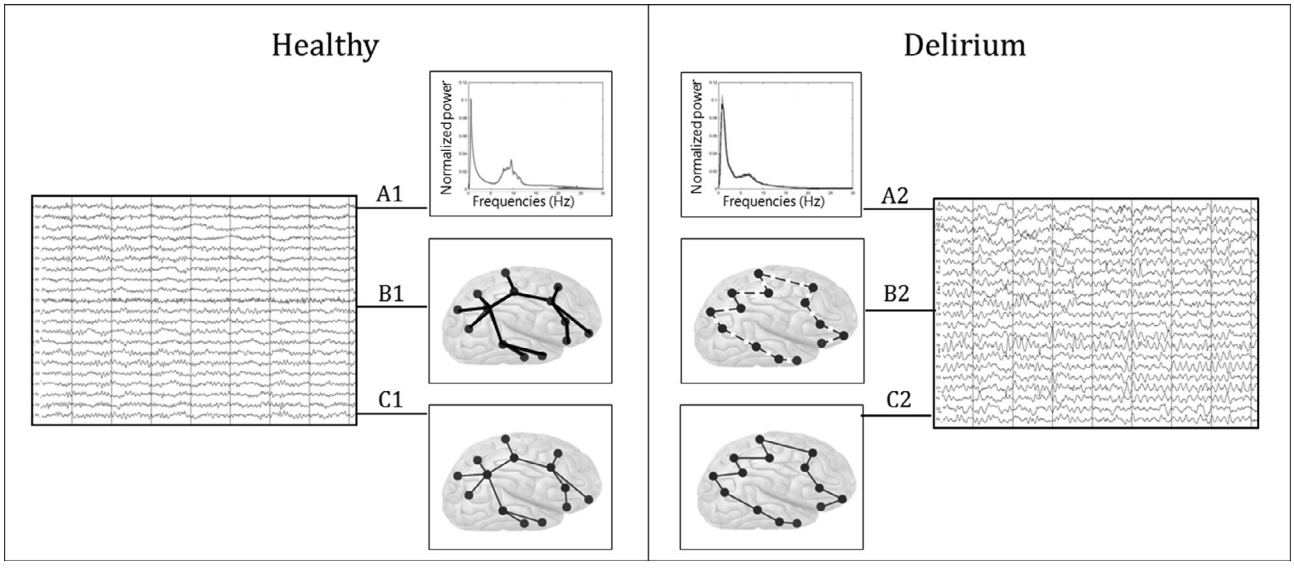

Fig. 1. Hypothetical EEG correlates of thehealthy and the delirious state. During delirium a higher relative delta power (A2) was found compared to healthy controls (A1). From a network perspective the connectivity of the alpha frequency band was decreased (B1) and disintegrated (B2) compared to the normal healthy state (B1 and C1). We hypothesized that these changes may be a biological mechanism underlying vulnerability for delirium, associated with the clinical expression of its risk factors.

they had experienced a TIA or stroke. If either or both were positive, this risk factor was considered present.

2.2.2. Alcohol misuse

The self-reported Alcohol Use Disorders Identification Test (Audit) was used to determine the risk factor of alcohol misuse. The Audit is a validated questionnaire of 10 items that assesses alcohol consumption, drinking behaviors, and alcohol-related problems (Bohn et al. 1995; Reinert and Allen 2007). The questions were scored on a 5-point Likert scale (0–4). A cut-off value of 8 points was used to distinguish between normal and harmful alcohol consumption (Babor et al. 2001).

2.2.3. Cognitive impairment

To determine cognitive impairment, the MMSE was used. The MMSE is a short examination that is often used in clinical practice (Folstein et al. 1985). The continuous outcome measure was the total score.

2.2.4. Depression

To estimate depression, the validated Hospital Anxiety and Depression Scale (HADS) was used (Zigmond and Snaith 1983; Bjelland et al. 2002). For the current study, only the 7 items assessing depression were used. They were scored on a 4-point Likert scale (0–3) with a maximum score of 21. We considered participants with a score of 7 or above as depressed (Vodermaier and Millman 2011).

2.2.5. Functional impairment

Functional impairment was measured with the validated Barthel Index following the Hamburg classification manual (Mahoney and Barthel 1965; Collin et al. 1988; Lübke et al. 2004). The continuous outcome measure was the total score (0–100), where the maximum score of 100 indicates fully independent functional ability.

2.2.6. Physical status

The American Society of Anesthesiologists (ASA) validated classification is widely used for the assessment of preoperative physical status (Aronson et al. 2003; Sankar et al. 2014), ranging from I. healthy; II. mild systematic disease; III severe systematic disease that is not incapacitating; IV. incapacitating systematic disease that is a constant threat to life; to V. moribund status, not expected to survive for 24 hours without surgery (Owens et al. 1978). The used outcome measure was dichotomous, where an ASA-score of I was classified as healthy and an ASA-score of II or higher as unhealthy.

2.2.7. Estimated intelligence coefficient (IQ)

The validated Dutch reading test for adults 'Nederlandse leestest voor volwassenen' (NLV) was used to estimate premorbid IQ (Mulder, et al. 2012). The participant was requested to read aloud a list of 50 words. The pronunciation of each word was scored on correctness by a trained assessor. The raw score ranges from 0 to 100 and was converted to an estimated IQ score using the NLV norm table (Mulder, et al. 2012).

2.3. EEG recordings, selection and preprocessing

A 5-minute EEG recording was performed using a 32-electrode cap (Braincap MR, Brain Products GmbH, Germany) at the positions of the 10–20 system. BrainVision Recorder (Brain Products GmbH, Germany) was used at a sample frequency of 5000 Hz. During recording, the participants sat upright and were awake with their eyes closed. Electrode impedance was kept below 5 kΩ.

The quality of the EEG recordings was visually inspected by two researchers independently (ED and LW) in BrainVision Analyzer 2 software (Brain Products GmbH, Germany). The first 10 artifact-free epochs of 8 seconds were selected for further analyses, as this was previously shown to be sufficient for stable results (van Dellen et al. 2014; van Diessen et al. 2015; Fraschini et al. 2016). Signals from electrodes TP9 and TP10 were excluded due to muscle artifacts and signals from the electrocardiography (ECG) electrode were additionally discarded from the analysis, leaving a total of 29 electrodes included in the analysis. Data was re-referenced towards an average reference that included all electrodes (except A1 and A2). The unfiltered EEG recordings were down sampled to 512 Hz using cubic spline interpolation.

BrainWave software was used for further analysis (v0.9.152.12.5; freely available at: http://home.kpn.nl/stam7883/). Data were band-pass filtered into five frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–25 Hz) and gamma (25–48 Hz).

2.4. EEG outcomes

2.4.1. Relative delta power

For each subject, the relative spectral power was computed using a fast Fourier transformation and averaged over all channels and epochs. Relative spectral power was calculated as the ratio of the power of the corresponding band (i.e. delta, theta, alpha, beta or gamma) and the total power. As previous studies have shown, slowing of resting state EEG activity during delirium is most accurately characterized by an increase in relative delta power (van Dellen et al. 2014; Numan et al. 2017b). Therefore, we have only used the relative delta power for further analyses.

2.4.2. Mean phase lag index (PLI)

The mean phase lag index (PLI) was used to measure functional connectivity strength with minimal bias due to volume conduction (Boersma et al. 2013; van Dellen et al. 2015). The PLI was calculated between each channel i and j based on their instantaneous phase difference ($\Delta\varphi_t$) using the following definition:

$$PLI_{ij} = |\langle sign(\Delta\varphi_t)\rangle|$$

The sign($\Delta\varphi_t$) is 1 for all positive phase differences and −1 for all negative phase differences, which was averaged over an epoch. The absolute value of this average is the PLI, giving a score between 0 (i.e. no phase synchronization or equal in leading and lagging over the epoch) and 1 (i.e. complete phase-locking) between each channel i and j in the alpha frequency band, resulting in a connectivity matrix of PLI values. As previous studies have shown an impaired connectivity strength specifically in the alpha frequency band during delirium (van Dellen et al. 2014; Numan et al. 2017b), only PLI values of the alpha frequency band were calculated.

The minimum spanning tree (MST) can be regarded as the backbone of the original network, connecting all nodes without forming loops (Stam et al. 2014; Tewarie et al. 2015) (Fig. 2). The MST of a network with N nodes always contains $N-1$ edges, which allows a reliable comparison with another network with the same number of nodes (Stam et al. 2014; Tewarie et al. 2015; van Diessen et al. 2015). PLI values of the connectivity matrix were ranked and the highest PLI value was included as the first MST connection using Kruskal's algorithm (Kruskal 1956). The second highest PLI value was then added as an MST connection, until all nodes (EEG channels) were connected. If adding a connection would result in a loop or triangle, this connection was discarded and the next PLI value was evaluated. For each participant, functional connectivity strength was calculated by averaging the alpha frequency band PLI values of included connections in the MST of all 10 epochs.

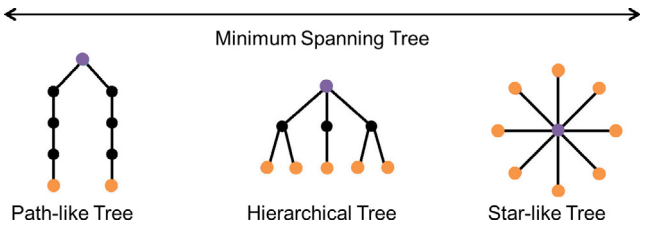

Fig. 2. Schematic representation of the minimum spanning tree. Minimum spanning trees can conceptually range between a path-like tree (a sparsely integrated network) and a star-like tree (a highly integrated network). The shown path-like tree has two leaf nodes (orange), i.e. nodes that are connected to only one other node, describing a network that is sparsely integrated. A path-like tree has a small leaf fraction. At the other end of the spectrum is a star-like tree, which has in this example one central node (purple) and eight leaf nodes (orange). It thus has a high leaf fraction and information can spread easily across the network, but the central node in the star-like tree will easily be overloaded with information. A hierarchical tree is a hypothesized optimal topology, combining a relatively high efficiency, while the relatively low maximum number of connections per node prevents the overload of central hub regions. This figure was based on Fig. 2 in van Dellen et al. (2014). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

For readability purposes, the term 'mean PLI' is used in the following parts of the article to indicate these mean alpha frequency band PLI values of the MST.

2.4.3. MST leaf fraction

The MST leaf fraction was used to measure network integration. It describes the proportion of nodes with a degree of one, i.e. nodes that are connected to only one other node (Stam et al. 2014; Tewarie et al. 2015). A small leaf fraction means that the network has few nodes that are connected to only one other node, describing a network that is sparsely integrated (Fig. 2). A large leaf fraction means that the network has many nodes that are connected to only one other node, describing a network that is highly integrated (Stam et al. 2014; Tewarie et al. 2015; van Dellen et al. 2016). Since previous studies on delirium have found disruptions in the leaf fraction in the alpha frequency band specifically (van Dellen et al. 2014; Numan et al. 2017b), we focused on the alpha frequency band in our analyses. For each participant, network integration was calculated by averaging the MST leaf fraction values of the alpha frequency band of all 10 epochs. For readability purposes, the term 'MST leaf fraction' is used in the following parts of this article to indicate these alpha frequency band MST leaf fraction values.

2.5. Statistical analysis

The effect of all seven risk factors on the three outcome measures, adjusted for gender and IQ, was tested with multivariate linear regression models. The association of the individual risk factors on the three outcome measures (i.e. relative delta power, mean PLI, MST leaf fraction) was analyzed with univariate linear regression models. We performed additional, exploratory analyses on the extremes of the distribution of a possible indicator (highest versus lowest quintile) to avoid the report of false negative findings.

Multicollinearity between the different risk factors was tested with a Spearman's rank order correlation, revealing no correlations between the seven risk factors ($r < 0.2$). The mean PLI and the MST leaf fraction were not normally distributed and were log transformed for all analyses. A likelihood ratio test revealed linearity of all continuous variables. False Discovery Rate (FDR) correction was performed to control for multiple testing in the univariate and multivariate models using the Benjamini and Hochberg method (Benjamini and Hochberg 1995; Genovese et al. 2002). After FDR correction, a corrected p-value below 0.05 was considered statistically significant (Benjamini and Hochberg 1995). Statistical analyses were performed in IBM SPSS Statistics version 21.

3. Results

3.1. Demographics

In this study, 230 participants were included, of whom 181 subjects were on the waiting list for elective surgery in het UMC Utrecht, and 49 were recruited via a general practitioner. From the included participants, eight were excluded due to insufficient EEG quality and 16 were excluded due to missing clinical data. Our total sample consisted of 206 participants with complete data on all clinical variables. Table 1 shows the demographics and risk factors for delirium in the sample. A mean power spectrum (Fig. S1), a topographical power plot (Fig. S2) and a typical MST network (Fig. S3) can be found in the Supplementary Appendix.

3.2. Multivariate models

The results of the multivariate models, to test the effect of all seven risk factors on the three outcome measures (i.e. relative delta power, mean PLI, MST leaf fraction), are shown in Table 2. Functional impairment was associated with mean PLI, independent of other risk factors, IQ or gender ($F(9,196) = 1.671$, adjusted $R^2 = 0.071$, $\beta = 0.198$, $p = 0.018$, $p < 0.05$ after FDR correction). The multivariate models for relative delta power and MST leaf fraction did not show significant effects of the other delirium risk factors.

3.3. Univariate models

The results of the univariate models on individual risk factors and the three outcome measures, are shown in Table 2. A signifi-

Table 1
Demographics and risk factors for delirium in the total sample.

	Total sample (n = 206)
Male, n (%)	137 (67)
IQ, mean ± SD	104.2 ± 12.4
Age in years, mean ± SD	71.3 ± 4.8
Lowest quintile, cut-off, n (%)	≤67, 37 (18)
Highest quintile, cut-off, n (%)	≥76, 43 (17)
Alcohol misuse	
Yes, n (%)	10 (5)
No, n (%)	196 (95)
MMSE (cognitive impairment), mean ± SD	28.5 ± 1.5
Lowest quintile, cut-off, n (%)	≤26, 15 (12)
Highest quintile, cut-off, n (%)	30, 67 (33)
HADS (depression)	
Yes, n (%)	20 (10)
No, n (%)	186 (90)
BI (functional impairment), mean ± SD	97.7 ± 5.6
Lowest quintile, cut-off, n (%)	≤99, 43 (21)
Highest quintile, cut-off, n (%)	100, 163 (79)
History of TIA/stroke	
Yes, n (%)	26 (13)
No, n (%)	180 (87)
Physical status	
Healthy, n (%)	30 (15)
Unhealthy, n (%)	176 (85)

Abbreviations: IQ = intelligence coefficient, MMSE = Mini Mental State Examination, HADS = Hospital Anxiety and Depression Scale, BI = Barthel Index, TIA = transient ischemic attack.

Table 2
Results of the multivariate and univariate models of risk factors for delirium on EEG relative delta power, mean phase lag index and minimum spanning tree leaf fraction.

	Relative delta power			Mean PLI (functional connectivity)			MST leaf fraction (network integration)		
	adj. R^2	β	Sig. (p)	adj. R^2	β	Sig. (p)	adj. R^2	β	Sig. (p)
Multivariate model[a]	−0.019			0.071			−0.015		
Age		0.036	0.632		−0.117	0.109		−0.113	0.128
Alcohol misuse		−0.060	0.411		−0.012	0.866		−0.051	0.485
MMSE (cognitive impairment)		−0.040	0.602		−0.006	0.940		−0.018	0.814
HADS (depression)		−0.015	0.849		−0.007	0.930		−0.015	0.844
BI (functional impairment)		0.049	0.512		0.201	0.006*		0.089	0.233
History of TIA/stroke		−0.010	0.892		0.144	0.045		0.063	0.392
Physical status		−0.031	0.675		−0.023	0.753		−0.001	0.987
Age	−0.004	0.032	0.652	0.014	−0.136	0.051	0.010	−0.123	0.079
Alcohol misuse	−0.004	−0.035	0.618	−0.005	0.019	0.783	−0.002	−0.056	0.423
MMSE (cognitive impairment)	−0.002	−0.053	0.446	−0.004	0.023	0.901	−0.005	0.009	0.747
HADS (depression)	−0.005	0.009	0.899	0.000	−0.067	0.338	−0.003	−0.047	0.503
BI (functional impairment)	−0.002	0.054	0.442	0.032	0.193	0.006*	0.004	0.094	0.181
History of TIA/stroke	−0.005	−0.015	0.834	0.005	0.098	0.160	−0.003	0.042	0.546
Physical status	−0.004	−0.022	0.754	−0.004	−0.024	0.544	−0.003	−0.042	0.731

[a] Model corrected for gender and IQ, *Corrected p-value (after False Discovery Rate correction) < 0.05. Shown p-values are uncorrected for multiple testing. Abbreviations: PLI = phase lag index, MST = minimum spanning tree, adj. = adjusted, Sig. = significance, MMSE = Mini Mental State Examination, HADS = Hospital Anxiety and Depression Scale, BI = Barthel Index, TIA = transient ischemic attack.

cant effect of functional impairment on mean PLI was found ($F(1, 204) = 7.85$, adjusted $R^2 = 0.032$, $\beta = 0.193$, $p = 0.006$, $p < 0.05$ after FDR correction) (Fig. 3). None of the other delirium risk factors were associated with any of the outcome measures. Notably, after FDR correction, age was not significantly associated with mean PLI ($F(1,204) = 3.859$, adjusted $R^2 = 0.014$, $\beta = -0.136$, $p = 0.051$) and MST leaf fraction ($F(1,204) = 3.125$, adjusted $R^2 = 0.010$, $\beta = -0.123$, $p = 0.079$).

3.4. Post-hoc extreme quintiles comparisons

Comparing the extreme quintiles within the continuous variables (i.e. age, cognitive impairment and functional impairment), showed a significant difference of the highest quintile of functional impairment compared to the lowest quintile on mean PLI ($t(106) = -3.502$, $p = 0.001$)) and on MST leaf fraction ($t(99) = -2.690$, $p = 0.008$)) (Table S1 in the Supplementary Appendix). Other comparisons within the extreme quintiles of the continuous variables did not show significant differences.

4. Discussion

In summary, functional impairment in non-delirious individuals was related to a decrease in EEG connectivity strength, but was not related to relative delta power or measures of network integration. A model that combined the seven studied risk factors showed that

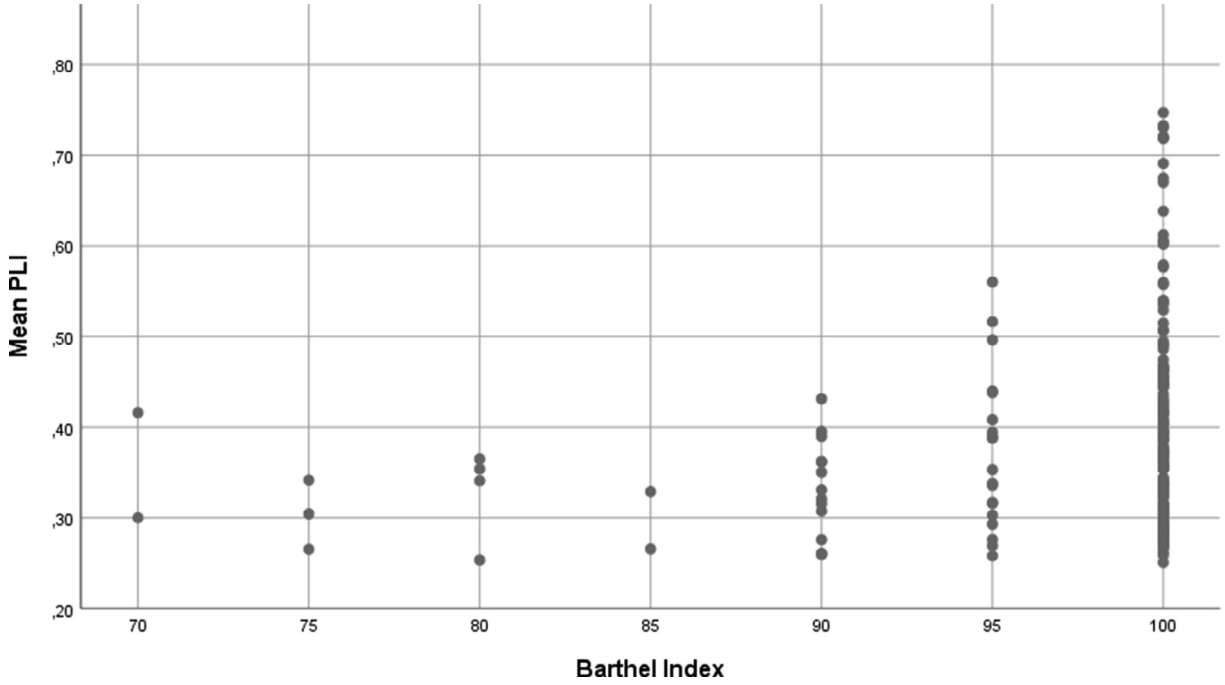

Fig. 3. The relationship between functional impairment and EEG connectivity strength. A significant association was found between functional impairment, as measured with the Barthel Index, and EEG connectivity strength, as measured with the mean phase lag index of the minimum spanning tree in the alpha frequency band. The association was independent of other risk factors for delirium, IQ or gender. Abbreviations: PLI = phase lag index.

this association was independent from the other predisposing risk factors, gender or IQ. No individual or cumulative relation was found between the other risk factors (i.e. age, alcohol misuse, cognitive impairment, depression, history of TIA or stroke, physical status) and relative delta power, connectivity strength or measures of network integration. These findings suggest that predisposing risk factors for delirium do not affect EEG characteristics that are disturbed during delirium, with exception of the risk factor functional impairment. Therefore, predisposition for delirium is not consistently related to alterations in EEG characteristics.

Associations between predisposing risk factors for delirium and EEG characteristics were investigated in different ways, i.e. in separate regression models, in combined regression models, and in extreme quintiles comparisons, revealing a robust finding of the relationship between functional impairment and connectivity strength. Although a relationship has been found between physical health and neurophysiological outcomes (Douw et al. 2014), our study is the first to investigate the relationship between functional impairment and neurophysiological alterations in a cohort of non-delirious elderly at risk for delirium. The measurement of functional impairment may provide a reflection of physical frailty in our sample. Physical frailty is defined as an age-related syndrome of decreased reserve causing vulnerability to physiological stressors and could manifest as functional dependency (Fried et al. 2001; Clegg et al. 2013). Previous studies have shown that frailty is strongly associated with the risk of delirium (Pitkala et al. 2005; Eeles et al. 2012; Brown et al. 2016). However, as the risk factors included in this study were based on a landmark paper that did not identify frailty as a risk factor for delirium (Inouye et al. 2014), we did not consider frailty as a separate risk factor. The clinical overlap between frailty and functional impairment may explain why only functionally impaired individuals showed a similarly impaired functional connectivity as previously found during delirium (van Dellen et al. 2014; Numan et al. 2017b), while individuals with other risk factors for delirium did not. However, we found relatively low adjusted R^2 and beta values for the association of functional impairment and decreased connectivity strength (adjusted $R^2 = 0.071$, $\beta = 0.201$). Although this relationship was statistically significant, the explanatory power was weak as only 7.1% of the variation in connectivity strength could be explained by functional impairment. Future research is needed to clarify the exact relationship between frailty, functional impairment and delirium, and the similarity in their underlying biological mechanisms.

The other risk factors for delirium were not related to the studied EEG alterations, which is not compatible with previous studies indicating that age and cognitive impairment were associated with decreased functional connectivity (Frantzidis et al. 2014; Minati et al. 2014; Vysata et al., 2014; Geerligs et al. 2015; Zeng et al. 2015; Chang et al. 2016; Ferreira et al. 2016; Smit et al. 2016). Interestingly, although non-significant, age did show a similar pattern in the univariate model on functional connectivity and cognitive impairment did show a similar pattern comparing the extreme quintiles on functional connectivity, as compared to previous studies (Frantzidis et al. 2014; Minati et al. 2014; Vysata et al., 2014; Geerligs et al. 2015; Zeng et al. 2015; Chang et al. 2016; Ferreira et al. 2016; Smit et al. 2016). Whereas previous studies were mostly performed using a case-control design comparing clinically diagnosed patients to healthy controls (Frantzidis et al. 2014; Minati et al. 2014; Vysata et al., 2014; Geerligs et al. 2015; Zeng et al. 2015; Chang et al. 2016; Ferreira et al. 2016; Smit et al. 2016), we evaluated multiple risk factors for delirium in a group of elderly individuals. These methodological differences may impede a direct comparison of our study to the previous literature.

Our findings suggest that predisposing delirium risk factors do not consistently impact EEG characteristics that are disturbed during delirium. Delirium is a state with an acute onset (American Psychiatric Association 2013). The related neurophysiological changes may only occur during delirium, or as a result of precipitating factors in the days before clinical manifestation of the syndrome (Evans et al. 2017; Numan et al. 2017a). It could be that predisposing risk factors still impair the structural network (i.e. lead to decreased anatomical as opposed to functional connections) (Kyeong et al. 2018), while precipitating risk factors may influence the functional network (Maestú et al. 2010; Lee et al. 2013; Blain-Moraes et al. 2017; Numan et al. 2017b; Mashour and Hudetz, 2018). In severe cases, the structural network may subsequently alter the functional network, as structural and functional networks are robustly linked (Honey et al. 2009; Cabral et al. 2012a, 2012b; Mišić et al. 2015). This alternative hypothesis is supported by the finding that predisposing risk factors were found to be associated with decreased structural connectivity as well as efficiency (Kyeong et al. 2018; van Montfort et al. 2019). Future research evaluating the effects of predisposing risk factors on structural brain network characteristics will provide more insight in the validity of the network theoretical framework for understanding the vulnerability to delirium.

This study is the first to empirically investigate the association between predisposing risk factors for delirium and EEG characteristics in the same study population. It represents a novel approach to unravel the pathophysiological mechanisms of a very common medical condition. Bias-limiting EEG measures on a substantial amount of data, i.e. 80 seconds of EEG recording per participant, were used (van Diessen et al. 2015). Nevertheless, a limitation of the current study is the selection of the participant sample. Since the participants derived from a relatively healthy population, this resulted in low variability and low frequency of some of the (dichotomous) risk factors. Furthermore, the measures for functional impairment and physical status, may not have been sufficiently sensitive. The Barthel Index shows a ceiling effect, and the ASA-score is only a very rough indicator for physical status (Sarker et al. 2012; Sankar et al. 2014). Although the landmark review on delirium risk factors that we used did include the most prominent and robust factors, it did not include all known risk factors. Another possible limitation of the study might be that we could not detect associations between different delirium risk factors. In our study risk factors for delirium were not significantly related to each other. However, due to the limited clinical measurements used in the study, we cannot draw strong conclusions on (lack of) associations among different risk factors for delirium. A significant limitation of the study is that we had no information on medication use of the participants during the EEG measurement. Although the participants were derived from a relatively healthy population and were not hospitalized, we cannot preclude effects of possible medication on the EEG signal. Furthermore, as our aim was to test the hypothesis that predisposing delirium risk factors induce similar neurophysiological alterations as during delirium, we did not evaluated neurophysiological outcomes that are not known as being altered during delirium. Impairments may have shifted to other frequency bands or outcomes in patients at risk for delirium. A more data-driven approach may be used in future studies to learn more about other possible (neurophysiological) alterations in persons at risk of delirium. In addition, as the spatial resolution of EEG is low, we were not able to include anatomical information, which may be of relevance for developing delirium. It would therefore be interesting to replicate our study design with functional magnetic resonance imaging (fMRI).

5. Conclusions

Although functional impairment was related to a decrease in connectivity strength, other predisposing delirium risk factors

were not found to be associated with EEG characteristics of delirium. Therefore, vulnerability for delirium is not consistently associated with alterations in EEG characteristics, and the onset of delirium may reflect new neurophysiological alterations.

Funding

This work was supported by funding from the European Union Seventh Framework Program under Grant Agreement No. 602461 [FP7/2007–2013] and funding from the Dutch Organization for Health Research and Development (ZonMW) under Grant Agreement No. 60-63600-98-711. EEG hardware and analysis software was provided by the BioCog Consortium partner Pharmaimage Biomarker Solutions GmbH, Berlin Germany (www.pi-pharmaimage.com).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.01.023.

References

Aertsen AM, Gerstein GL, Habib MK, Palm G. Dynamics of neuronal firing correlation: modulation of "effective connectivity". J Neurophysiol. 1989;61:900–17. http://www.ncbi.nlm.nih.gov/pubmed/2723733.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Washington, DC; 2013.

Aronson WL, McAuliffe MS, Miller K. Variability in the American society of anesthesiologists physical status classification scale. AANA J 2003;71:265–74. http://www.ncbi.nlm.nih.gov/pubmed/13677221.

Babor T, Higgins-Biddle J, Saunders J. AUDIT: the alcohol use disorders identification test: guidelines for use in primary health care. 2001; Available from: http://apps.who.int/iris/bitstream/handle/10665/67205/WHO_MSD_?sequence=1.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B. 1995;57:289–300. http://doi.wiley.com/10.1111/j.2517-6161.1995.tb02031.x.

Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002;52:69–77. https://www.sciencedirect.com/science/article/pii/S0022399901002963.

Blain-Moraes S, Tarnal V, Vanini G, Bel-Behar T, Janke E, Picton P, et al. Network efficiency and posterior alpha patterns are markers of recovery from general anesthesia: a high-density electroencephalography study in healthy volunteers. Front Hum Neurosci 2017;11:328. http://journal.frontiersin.org/article/10.3389/fnhum.2017.00328/full.

Boersma M, Smit DJA, Boomsma DI, De Geus EJC, Delemarre-van de Waal HA, Stam CJ. Growing trees in child brains: graph theoretical analysis of electroencephalography-derived minimum spanning tree in 5- and 7-year-old children reflects brain maturation. Brain Connect 2013;3:50–60.

Bohn MJ, Babor TF, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. J Stud Alcohol 1995;56:423–32. http://www.jsad.com/doi/10.15288/jsa.1995.56.423.

Brandt SA, Kraft A, Traenkner S, Schreiber SJ, Fleischmann R, Schmidt S. Delirium is associated with frequency band specific dysconnectivity in intrinsic connectivity networks: preliminary evidence from a large retrospective pilot case-control study. Pilot Feasibility Stud 2019;5:1–13. https://doi.org/10.1186/s40814-018-0388-z.

Brown CH, Max L, LaFlam A, Kirk L, Gross A, Arora R, et al. The association between preoperative frailty and postoperative delirium after cardiac surgery. Anesth Analg 2016;123:430–5. http://www.ncbi.nlm.nih.gov/pubmed/27096563.

Bullmore E, Sporns O. Complex brain networks: Graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 2009;10:186–98. http://www.nature.com/doifinder/10.1038/nrn2575.

Cabral J, Hugues E, Kringelbach ML, Deco G. Modeling the outcome of structural disconnection on resting-state functional connectivity. Neuroimage 2012a;62:1342–53. http://www.ncbi.nlm.nih.gov/pubmed/22705375.

Cabral J, Kringelbach M, Deco G. Functional graph alterations in schizophrenia: a result from a global anatomic decoupling?. Pharmacopsychiatry 2012b;45:S57–64. http://www.thieme-connect.de/DOI/DOI?10.1055/s-0032-1309001.

Chang T-Y, Huang K-L, Ho M-Y, Ho P-S, Chang C-H, Liu C-H, et al. Graph theoretical analysis of functional networks and its relationship to cognitive decline in patients with carotid stenosis. J Cereb Blood Flow Metab 2016;36:808–18. http://journals.sagepub.com/doi/10.1177/0271678X15608390.

Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752–62. https://www.sciencedirect.com/science/article/pii/S0140673612621679.

Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Stud 1988;10:61–3. http://www.ncbi.nlm.nih.gov/pubmed/3403500.

Douw L, Nieboer D, van Dijk BW, Stam CJ, Twisk JWR. A healthy brain in a healthy body: brain network correlates of physical and mental fitness. Lambiotte R, editor. PLoS One. 2014;9 e88202.

Eeles EMP, White SV, O'Mahony SM, Bayer AJ, Hubbard RE. The impact of frailty and delirium on mortality in older inpatients. Age Ageing. 2012;41:412–6. https://academic.oup.com/ageing/article-lookup/doi/10.1093/ageing/afs021.

Evans JL, Nadler JW, Preud'homme XA, Fang E, Daughtry RL, Chapman JB, et al. Pilot prospective study of post-surgery sleep and EEG predictors of post-operative delirium. Clin Neurophysiol 2017;128:1421–5.

Ferreira LK, Regina ACB, Kovacevic N, Martin MDGM, Santos PP, Carneiro CDG, et al. Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. Cereb Cortex. 2016;26:3851–65. https://academic.oup.com/cercor/article-abstract/26/9/3851/2389172.

Folstein M, Anthony JC, Parhad I, Duffy B, Gruenberg EM. The meaning of cognitive impairment in the elderly. J Am Geriatr Soc. 1985;33:228–35. http://www.ncbi.nlm.nih.gov/pubmed/3989183.

Frantzidis CA, Vivas AB, Tsolaki A, Klados MA, Tsolaki M, Bamidis PD. Functional disorganization of small-world brain networks in mild Alzheimer's disease and amnestic Mild cognitive impairment: An EEG study using Relative Wavelet Entropy (RWE). Front Aging Neurosci. 2014;6:224. http://journal.frontiersin.org/article/10.3389/fnagi.2014.00224/abstract.

Fraschini M, Demuru M, Crobe A, Marrosu F, Stam CJ, Hillebrand A. The effect of epoch length on estimated EEG functional connectivity and brain network organisation. J Neural Eng. 2016;13:36015. http://stacks.iop.org/1741-2552/13/i=3/a=036015?key=crossref.9f1dc2af7d6dd9138c149a9daa70e8f4.

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56. https://academic.oup.com/biomedgerontology/article-lookup/doi/10.1093/gerona/56.3.M146.

Geerligs L, Rubinov M, Cam-Can Henson RN. State and trait components of functional connectivity: individual differences vary with mental state. J Neurosci 2015;35:13949–61.

Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 2002;15:870–8. https://www.sciencedirect.com/science/article/pii/S1053811901910377.

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci USA 2009;106:2035–40. http://www.ncbi.nlm.nih.gov/pubmed/19188601.

Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911–22. https://www.sciencedirect.com/science/article/pii/S0140673613606881.

Kruskal JB. On the shortest spanning subtree of a graph and the traveling salesman problem. Proc Am Math Soc 1956;7(1):48–50. https://www.jstor.org/stable/pdf/2033241.pdf.

Kyeong S, Shin JE, Yang KH, Lee WS, Chung T-S, Kim J-J. Neural predisposing factors of postoperative delirium in elderly patients with femoral neck fracture. Sci Rep 2018;8:7602. http://www.nature.com/articles/s41598-018-26030-2.

Lee H, Mashour GA, Noh G-J, Kim S, Lee U. Reconfiguration of network hub structure after propofol-induced unconsciousness. Anesthesiology 2013;119:1347–59. http://anesthesiology.pubs.asahq.org/Article.aspx?doi=10.1097/ALN.0b013e3182a8ec8c.

Lübke N, Meinck M, Von Renteln-Kruse W. The Barthel Index in geriatrics. A context analysis for the Hamburg Classification Manual. Z Gerontol Geriatr 2004;37:316–26.

Maestú F, Boccaletti S, Castellanos NP, Pascua CL, Ordóñez VE, Del-Pozo F, et al. Principles of recovery from traumatic brain injury: Reorganization of functional networks. Neuroimage 2010;55:1189–99. https://www.sciencedirect.com/science/article/pii/S1053811910016320.

Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J 1965;14:61–5. http://www.ncbi.nlm.nih.gov/pubmed/14258950.

Marcantonio ER. Delirium in hospitalized older adults. Solomon CG, editor. N Engl J Med 2017;377:1456–66.

Mashour GA, Hudetz A. Neural correlates of unconsciousness in large-scale brain networks. Trends Neurosci 2018;41:150–60. https://www.sciencedirect.com/science/article/pii/S016622361830016X.

Minati L, Chan D, Mastropasqua C, Serra L, Spano B, Marra C, et al. Widespread alterations in functional brain network architecture in amnestic mild cognitive impairment. J Alzheimers Dis 2014;40:213–20. https://content.iospress.com/articles/journal-of-alzheimers-disease/jad131766.

Mišić B, Betzel RF, Nematzadeh A, Goñi J, Griffa A, Hagmann P, et al. Cooperative and competitive spreading dynamics on the human connectome. Neuron 2015;86:1518–29. http://linkinghub.elsevier.com/retrieve/pii/S0896627315004742.

Mulder J, Bouma JM, Schmand B. Handboek neuropsychologische diagnostiek. Amsterdam: Pearson Assessment and Information B.V; 2012.

Numan T, van den Boogaard M, Kamper AM, Rood PJT, Peelen LM, Slooter AJC. Recognition of delirium in postoperative elderly patients: a multicenter study. J Am Geriatr Soc 2017a;65:1932–8. http://doi.wiley.com/10.1111/jgs.14933.

Numan T, Slooter AJC, van der Kooi AW, Hoekman AML, Suyker WJL, Stam CJ, et al. Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. Clin Neurophysiol 2017b;128:914–24. http://linkinghub.elsevier.com/retrieve/pii/S1388245717300846.

Owens WD, Felts JA, Spitznagel EL. ASA physical status classifications: a study of consistency of ratings. Anesthesiology 1978;49:239–43. http://www.ncbi.nlm.nih.gov/pubmed/697077.

Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. Dement Geriatr Cogn Disord 2005;19:158–63. http://www.ncbi.nlm.nih.gov/pubmed/15627764.

Reinert DF, Allen JP. The alcohol use disorders identification test: An update of research findings. Alcohol Clin Exp Res 2007;31:185–99. http://www.ncbi.nlm.nih.gov/pubmed/17250609.

Sanders RD. Hypothesis for the pathophysiology of delirium: Role of baseline brain network connectivity and changes in inhibitory tone. Med Hypotheses 2011;77:140–3. https://www.sciencedirect.com/science/article/pii/S0306987711001605.

Sankar A, Johnson SR, Beattie WS, Tait G, Wijeysundera DN. Reliability of the American Society of Anesthesiologists physical status scale in clinical practice. Br J Anaesth 2014;113:424–32. https://linkinghub.elsevier.com/retrieve/pii/S000709121731766X.

Sarker S-J, Rudd AG, Douiri A, Wolfe CDA. Comparison of 2 extended activities of daily living scales with the Barthel Index and predictors of their outcomes: cohort study within the South London Stroke Register (SLSR). Stroke 2012;43:1362–9. https://www.ahajournals.org/doi/10.1161/STROKEAHA.111.645234.

Smit DJA, de Geus EJC, Boersma M, Boomsma DI, Stam CJ. Life-span development of brain network integration assessed with phase lag index connectivity and minimum spanning tree graphs. Brain Connect 2016;6:312–25. http://online.liebertpub.com/doi/10.1089/brain.2015.0359.

Stam CJ, van Straaten ECW. The organization of physiological brain networks. Clin Neurophysiol 2012;123:1067–87. https://www.sciencedirect.com/science/article/pii/S1388245712000570.

Stam CJ, Tewarie P, Van Dellen E, van Straaten ECW, Hillebrand A, Van Mieghem P. The trees and the forest: Characterization of complex brain networks with minimum spanning trees. Int J Psychophysiol 2014;92:129–38. http://linkinghub.elsevier.com/retrieve/pii/S0167876014000907.

Tewarie P, van Dellen E, Hillebrand A, Stam CJ. The minimum spanning tree: An unbiased method for brain network analysis. Neuroimage 2015;104:177–88. http://linkinghub.elsevier.com/retrieve/pii/S1053811914008398.

van Dellen E, Bohlken MM, Draaisma L, Tewarie PK, van Lutterveld R, Mandl R, et al. Structural brain network disturbances in the psychosis spectrum. Schizophr Bull 2016;42:782–9. http://www.ncbi.nlm.nih.gov/pubmed/26644605.

van Dellen E, van der Kooi AW, Numan T, Koek HL, Klijn FAM, Buijsrogge MP, et al. Decreased functional connectivity and disturbed directionality of information flow in the electroencephalography of intensive care unit patients with delirium after cardiac surgery. Anesthesiology 2014;121:328–35. http://insights.ovid.com/crossref?an=00000542-201408000-00023.

van Dellen E, de Waal H, van der Flier WM, Lemstra AW, Slooter AJC, Smits LL, et al. Loss of EEG network efficiency is related to cognitive impairment in dementia with Lewy bodies. Mov Disord 2015;30:1785–93. http://doi.wiley.com/10.1002/mds.26309.

van Diessen E, Numan T, van Dellen E, van der Kooi AW, Boersma M, Hofman D, et al. Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. Clin Neurophysiol 2015;126:1468–81. http://linkinghub.elsevier.com/retrieve/pii/S1388245714008104.

van Montfort SJT, van Dellen E, van den Bosch AMR, Otte WM, Schutte MJL, Choi S-H, et al. Resting-state fMRI reveals network disintegration during delirium. NeuroImage Clin 2018;20:35–41. https://www.sciencedirect.com/science/article/pii/S2213158218302079.

van Montfort SJT, van Dellen E, Stam CJ, Ahmad AH, Mentink LJ, Kraan CW, et al. Brain network disintegration as a final common pathway for delirium: a systematic review and qualitative meta-analysis. NeuroImage Clin 2019;23. https://www.sciencedirect.com/science/article/pii/S2213158219301597 101809.

van Straaten ECW, Stam CJ. Structure out of chaos: Functional brain network analysis with EEG, MEG, and functional MRI. Eur Neuropsychopharmacol 2013;23:7–18.

Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. Support Care Cancer 2011;19:1899–908. http://link.springer.com/10.1007/s00520-011-1251-4.

Vysata O, Kukal J, Prochazka A, Pazdera L, Simko J, Valis M. Age-related changes in EEG coherence. Neurol Neurochir Pol 2014; 48. Available from: https://www.sciencedirect.com/science/article/pii/S0028384314000061

Winterer G, Androsova G, Bender O, Boraschi D, Borchers F, Dschietzig TB, et al. Personalized risk prediction of postoperative cognitive impairment - rationale for the EU-funded BioCog project. Eur Psychiatry 2018;50:35–9. https://www.sciencedirect.com/science/article/pii/S0924933817329863.

Young JWS. The network model of delirium. Med Hypotheses 2017;104:80–5. http://www.medical-hypotheses.com/article/S0306-9877(16)30821-0/abstract.

Zaal IJ, Devlin JW, Peelen LM, Slooter AJC. A systematic review of risk factors for delirium in the ICU*. Crit Care Med 2015;43:40–7. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003246-201501000-00006.

Zeng K, Wang Y, Ouyang G, Bian Z, Wang L, Li X. Complex network analysis of resting state EEG in amnestic mild cognitive impairment patients with type 2 diabetes. Front Comput Neurosci 2015;9:133. http://journal.frontiersin.org/Article/10.3389/fncom.2015.00133/abstract.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70. http://doi.wiley.com/10.1111/j.1600-0447.1983.tb09716.x.