Decreased Functional Connectivity and Disturbed Directionality of Information Flow in the Electroencephalography of Intensive Care Unit Patients with Delirium after Cardiac Surgery

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ABSTRACT

Background: In this article, the authors explore functional connectivity and network topology in electroencephalography recordings of patients with delirium after cardiac surgery, aiming to improve the understanding of the pathophysiology and phenomenology of delirium. The authors hypothesize that disturbances in attention and consciousness in delirium may be related to alterations in functional neural interactions.

Methods: Electroencephalography recordings were obtained in postcardiac surgery patients with delirium (N = 25) and without delirium (N = 24). The authors analyzed unbiased functional connectivity of electroencephalography time series using the phase lag index, directed phase lag index, and functional brain network topology using graph analysis.

Results: The mean phase lag index was lower in the α band (8 to 13 Hz) in patients with delirium (median, 0.120; interquartile range, 0.113 to 0.138) than in patients without delirium (median, 0.140; interquartile range, 0.129 to 0.168; $P < 0.01$). Network topology in delirium patients was characterized by lower normalized weighted shortest path lengths in the α band ($t = -2.65$; $P = 0.01$). δ Band–directed phase lag index was lower in anterior regions and higher in central regions in delirium patients than in nondelirium patients ($F = 4.53$; $P = 0.04$, and $F = 7.65$; $P < 0.01$, respectively).

Conclusions: Loss of α band functional connectivity, decreased path length, and increased δ band connectivity directed to frontal regions characterize the electroencephalography during delirium after cardiac surgery. These findings may explain why information processing is disturbed in delirium. **(Anesthesiology 2014; 121:328-35)**

DELIRIUM is an acute disturbance of consciousness and cognition that tends to fluctuate over time.[1] It is a common disorder in critically ill and postoperative patients and is associated with higher mortality, longer duration of hospital stay, long-term cognitive impairment, and increased costs.[2–5] The pathophysiology of delirium is incompletely understood. Several hypotheses have been described, which are not mutually exclusive, including neurotransmitter imbalances, an aberrant stress response, and persistent neuroinflammation.[6]

Proper cognitive functioning requires interactions or functional connectivity between brain regions.[7,8] The brain functions as a complex network, and its topology can be characterized using graph theory.[7] Disturbances in the organization of functional brain networks are seen in

What We Already Know about This Topic

- Delirium, which is characterized by disturbances in awareness and attention and other cognitive functions that fluctuate over time, is a common occurrence in critically ill patients
- Given that proper cognitive function requires functional connectivity between different brain regions, it is possible that functional connectivity is disturbed in patients with delirium

What This Article Tells Us That Is New

- Using sophisticated quantitative electroencephalography analysis, postcardiac surgery patients show loss of α band connectivity, but increased δ band connectivity directed to frontal regions
- Similar to what occurs in other conditions where cognitive function is adversely affected (such as schizophrenia and Alzheimer disease), delirium may be thought of as a syndrome of disconnection of brain regions

This article is featured in "This Month in Anesthesiology," page 3A. Corresponding article on p. 214. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). The first two authors contributed equally to this work.

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anesthetic-induced unconsciousness and various neuropsychiatric disorders.[8,9] These disturbances may reflect a disconnection syndrome, which results in cognitive deficits that characterize these disorders.[8] As delirium is characterized by cognitive deficits, a disturbance in functional brain networks can be expected. The electroencephalography during delirium is characterized by excessive slowing into θ and δ frequencies and decline in α activity.[10] In contrast to a rapidly increasing body of work on other neuropsychiatric diseases, only one functional magnetic resonance imaging study considered delirium in the framework of altered functional brain networks.[11] This previous study showed functional connectivity increases between the dorsolateral prefrontal cortex and the posterior cingulate cortex during delirium.[11] However, functional magnetic resonance imaging recordings provide an indirect measure of neural activity, and a more systematic quantification of functional brain network topology during delirium is currently lacking. Electroencephalography recordings provide a more direct measure of neural activity. Measures of phase synchronization have been used to assess functional connectivity between time series,[12] and graph theory can be used to characterize functional brain network topology.[7,8] A recently introduced measure of directed connectivity, based on phase difference, can be used to characterize the direction of information flow.[13] It was shown that this pattern normally shows an anterior-to-posterior gradient, which is lost with loss of consciousness and regained after recovery of consciousness.[9,13] This may be of interest for delirium because a fluctuating level of consciousness is one of its key symptoms.

We hypothesized that postoperative delirium is related to disturbances in functional connectivity and network topology. The primary objective of the current study was to compare electroencephalography-based functional brain networks in cardiac surgery patients with and without delirium. The secondary objective was to determine the association between disturbances in functional brain network parameters and clinical characteristics of delirium.

Materials and Methods

Study Design and Patient Population

This cross-sectional, observational, single-center study was approved by the medical ethics committee of the University Medical Center Utrecht, Utrecht, The Netherlands (number 11-073). Cardiac surgery patients aged 50 yr or older were included before surgery. Exclusion criteria were a history of a neurological or psychiatric disease before surgery or any neurological complication other than delirium after surgery, as these may confound the diagnosis of delirium. For nondelirious patients, a diagnosis of delirium in the month before surgery was an exclusion criterion. After complete description of the study to the subjects, written informed consent was obtained. Cases with delirium were group matched to patients without delirium on age and sex.

Data Collection

Several clinical parameters were registered, such as duration of surgery, bypass time, Acute Physiology and Chronic Health Evaluation (APACHE) IV score (score for disease severity at intensive care admission), and medication.[14]

Daily mental status was assessed by research nurses and physicians with the Richmond Agitation and Sedation Scale (RASS)[15] and the confusion assessment method for the intensive care unit (ICU) [16] during the first 5 postoperative days or when surgery was complicated, the first 5 days that the patient was not in a comatose state. A comatose state was defined as a RASS score lower than −3 or Glasgow Coma Score lower than 9.[15,17]

When the confusion assessment method for the ICU score was positive, the patient was evaluated for delirium by a psychiatrist, geriatrician, or neurologist using the Diagnostic and Statistical Manual of Mental Disorders IV criteria.[1] The evaluation included assessment of the level of consciousness, attention, language, thinking, memory, psychomotor behavior, and perception. When this neuropsychiatric evaluation indicated delirium, the electroencephalography recording of the patient was included for the study. When it was equivocal, the recording of the patient was excluded.

When a patient had a negative score for the confusion assessment method for the ICU, his or her age and sex were compared to the already included delirious patients. When age and sex corresponded with the delirious patients group, he or she received a neuropsychiatric evaluation by a psychiatrist, geriatrician, or neurologist using the Diagnostic and Statistical Manual of Mental Disorders IV criteria for delirium. A difference in age was allowed as long as the average age in both groups remained similar. There was no one-to-one but only group level matching. The neuropsychiatric evaluation was used to confirm that the patient was indeed not delirious. When the neuropsychiatric evaluation indicated a nondelirious patient, the electroencephalography recording of the patient was included for the study. When the neuropsychiatric evaluation was equivocal, the recording of the patient was excluded.

The motor subtype of delirium was registered during electroencephalography recording. The hypoactive subtype was defined as a continuous negative RASS score during electroencephalography recording, the hyperactive subtype as a continuous positive RASS score, and the mixed type when RASS scores varied between positive and negative. Delirious patients were further observed during electroencephalography registration for signs of hallucinations and asked if they heard, saw, smelled, or felt something that other people did not. We registered hallucinations as present, not present, or equivocal. Only the groups "hallucinations present" and "hallucinations not present" were compared to each other. Patients in whom it was not clear whether they experienced hallucinations or not were excluded from hallucinations analysis.

Electroencephalography Acquisition

Twenty-one–channel electroencephalography recordings were conducted using Ag/AgCl electrodes, according to

the international 10/20 system. These were recorded with a Micromed electroencephalography apparatus (Micromed, Trevisio, Italy), using a sample frequency of 512 Hz and a hardware high pass input filter of 0.15 Hz (40 dB per decade). Electrodes were adhered to the scalp using electrode gel and on the forehead using tape, to prevent dislodging of electrodes.

Thirty-minute electroencephalography recordings were made, in which patients were asked to keep their eyes open for 15 min and close them for the last 15 min of the recording. To ensure that patients stayed awake, they were asked to conduct tasks like squeezing their hands at several time points during the recording. Epochs were selected at least 10 s after the tasks. The first four artifact-free epochs of 8.0 s during the eyes-closed condition were used for analyses, which was sufficient for stable results (see Supplemental Digital Content 1, http://links.lww.com/ALN/B54).[18,19]

After digital storage, the data were preprocessed and filtered in the δ (0.5 to 4 Hz), θ (4 to 8 Hz), α (8 to 13 Hz), and β (13 to 20 Hz) bands. This bandpass filter uses a Fourier transform of the whole epoch. All bins outside the passband are made zero, after which an inverse Fourier transform is performed. Because electroencephalography acquisition was performed in a clinical setting and recordings were possibly contaminated by electromyography artifacts, we did not analyze data in frequency bands above 20 Hz.[20] Because of the clinical setting and difficulty in preventing eye movements during eyes-closed registration in delirious patients, we excluded channels Fp1, Fp2, A1, and A2 from analysis. Data were digitally converted into average reference montage (including all channels except Fp1, Fp2, A1, and A2) for phase lag index (PLI) and network analyses, while an A1A2 reference montage was used for directed PLI (dPLI) analyses to obtain an optimal configuration for characterization of the anterior-to-posterior gradient.

Functional Connectivity

To assess functional connectivity between time series, the PLI was used (see Supplemental Digital Content 1, http://links.lww.com/ALN/B54, for a detailed description of the PLI).[12] The PLI is a measure that is relatively insensitive to the effects of volume conduction. The PLI estimates synchronization between time series based on the consistency of the nonzero phase lag with respect to another signal. It ranges between 0 (no phase locking) and 1 (total synchronization). For each subject, the average PLI between all electroencephalography channels was computed in the various frequency bands to characterize the average connectivity strength (similar to the average weighted degree in graph theory).

Graph Theoretical Analysis

We constructed weighted graphs, in which the electroencephalography electrodes were considered as vertices (nodes) and the strength of the phase coupling between the electroencephalography channels as edges. We further computed the following most fundamental network measures, as described by Watts and Strogatz,[21] which were modified for weighted networks (see Supplemental Digital Content 1, http://links.lww.com/ALN/B54, for a detailed description).[22] The weighted normalized clustering coefficient (γ) defines the level of local clustering or segregation in the network. The normalized average weighted shortest path length (λ) describes the level of global integration of the network. The small world index, the ratio of γ to λ, was used to characterize the small worldness of the networks.[23] Network parameters were only calculated for frequency bands with a significant difference in mean PLI between delirium and nondelirium patients.

Directed Connectivity

The PLI describes functional connectivity strength based on a consistent phase difference between time series but discards the direction of phase delay, that is, which signal is leading and which signal is lagging. We used the dPLI to characterize the consistency of a phase lead or lag between electroencephalography signals.[13] The dPLI for time series x and y is defined as $dPLI_{xy} = \frac{1}{N}\sum_{t=1}^{N} H(\phi t)$, where H is the Heaviside step function and ϕ_t with $t = 1 \ldots N$, a time series of phase differences.[13] The dPLI ranges between 0 and 1. When signal x is consistently leading in phase with respect to signal y, the dPLI value is $0.5 < \text{dPLI} \leq 1$, and when x is phase lagging to y, then $0 \leq \text{dPLI} < 0.5$. The dPLI is 0.5 when both signals lead and lag an equal amount of time.

The average dPLI value was computed for each epoch of each subject and for each electrode separately. Because we were interested in the anterior-to-posterior dPLI gradient and to limit the number of statistical comparisons, we grouped the electrodes in three areas: anterior (F7-F8-F3-F4-Fz), central (T7-T8-C3-C4-Cz), and posterior (P7-P8-P3-P4-Pz-O1-O2). We then compared these regional dPLI values between delirium patients and nondelirium patients for each frequency band.

Statistical Analysis

Continuous variables were screened for normal distribution using Kolmogorov–Smirnov tests. Normally distributed variables were compared between delirious and nondelirious patients using the Student t test. When the assumption of Gaussian distribution was violated, variables were compared using Mann–Whitney U tests. Categorical variables were compared using the chi-square test or Fisher exact test (when categories contained five cases or less). Null hypotheses regarding differences in average PLI between delirious and nondelirious patients were rejected for P value less than 0.05 after Bonferroni correction to eliminate effects of multiple testing (*i.e.*, $P < 0.0125$, as 0.05/4 = 0.0125 as we studied four frequency bands). When significant differences in PLI were found between patients with and without delirium for a specific frequency band, we tested for differences in γ and λ, in that specific frequency band and

for within-delirium group effects of hallucinations. These tests were considered *post hoc* analyses, and therefore, no correction for multiple testing was performed. Patient characteristics that showed significant differences between delirium and nondelirium patients were assumed to be possible confounders. Therefore, a general linear model was used to adjust for possible confounding. We compared dPLI values for each frequency band separately using a multivariate general linear model with dPLI value (anterior, central, posterior) as dependent variable, group as fixed factor, and patient characteristics that showed significant differences between delirium and nondelirium as covariates. Statistical analyses were performed using SPSS (IBM SPSS Statistics 20, Chicago, IL).

Results

Patient Characteristics

Data of 28 delirious and 26 nondelirious cardiac surgery patients were available. Three patients with delirium and two patients without delirium were excluded because of electroencephalography artifacts. The characteristics of the remaining 25 delirious and 24 nondelirious patients are shown in table 1. Of the patients with delirium, 14 were hypoactive, 5 hyperactive, and 6 patients had a mixed type of delirium. After electroencephalography recording, two delirious patients did not recover from cardiac surgery and died in the hospital. Patients with delirium differed from patients without delirium, in that they had higher APACHE IV scores, longer duration of surgery, and were more often treated with haloperidol (table 1). In the delirium group, seven patients had hallucinations during the electroencephalography recording, nine patients had no hallucinations during the electroencephalography recording, and in nine patients it was unclear whether hallucinations were present or not. All seven patients with hallucinations experienced visual hallucinations and two from additional auditory hallucinations. For both delirious and nondelirious patients, an average power spectrum is shown in Supplemental Digital Content 1, http://links.lww.com/ALN/B54.

Table 1. Patient Characteristics

	Delirium (n = 25)	Controls (n = 24)	*P* Value
Sex (male)	13 (52%)	14 (58%)	0.78
Age (yr)	76.8 ± 5.5	73.4 ± 9.1	0.12
Duration of surgery (min)	247 ± 101	196 ± 70	0.04
Duration of bypass (min)	147 ± 74	120 ± 52	0.14
Number of days between surgery and EEG registration	3 (2–4.5)	3 (2–4)	0.81
APACHE IV score	57 ± 13	44 ± 11	<0.01
Medication 24 h before EEG registration (n)			
Benzodiazepines	8 (32%)	5 (21%)	0.52
Haloperidol	15 (60%)	0 (0%)	<0.01
Opiates	8 (32%)	7 (29%)	1
Zopiclon	1 (4%)	1 (4%)	1
Clonidine	4 (16%)	0 (0%)	0.11

Data represent mean ± SD, median (interquartile range), or numbers (%). Medication in the 24 h before electroencephalography registration in frequencies (%), benzodiazepines include temazepam, oxazepam, lorazepam, and midazolam, whereas opiates include morphine and oxicodon.

APACHE = Acute Physiology and Chronic Health Evaluation; EEG = electroencephalography; n = number.

Functional Connectivity

The average PLI was significantly lower in the α band in delirium patients compared to nondelirium patients (delirium: median, 0.119; interquartile range [IQR], 0.111 to 0.138; nondelirium: 0.139 [0.127 to 0.162]; $P < 0.01$; fig. 1). The average PLI in the δ, θ, and β bands were not related to delirium. Within the delirium patients, there was no difference with regard to the α band average PLI between patients with hallucinations (median, 0.121; IQR, 0.111 to 0.146) and without hallucinations (median, 0.132; IQR, 0.114 to 0.146; $P = 0.71$).

Because delirium patients had higher APACHE IV scores, longer duration of surgery, and were more often using haloperidol, we used a generalized linear model to analyze the α band PLI adjusted for these possible confounders. For this purpose, α band PLI was first log transformed ($\log_{10}(x)$), after which the assumption of a normal distribution was no longer violated. The corrected model still showed a significant difference in α band PLI between delirium and nondelirium patients ($F(4,48) = 5.35$; $P = 0.03$).

Network Analysis

α Band–normalized path length (λ) was significantly decreased in delirium patients compared to nondelirium patients ($t = -2.65$; $P = 0.01$; fig. 2). The results remained significant after adjusting for APACHE IV score, duration of surgery, and haloperidol use ($F(4,48) = 2.77$; $P = 0.01$). α Band λ was significantly correlated with the average PLI in the α band (Kendall $\tau = 0.281$; $P < 0.01$). There was no

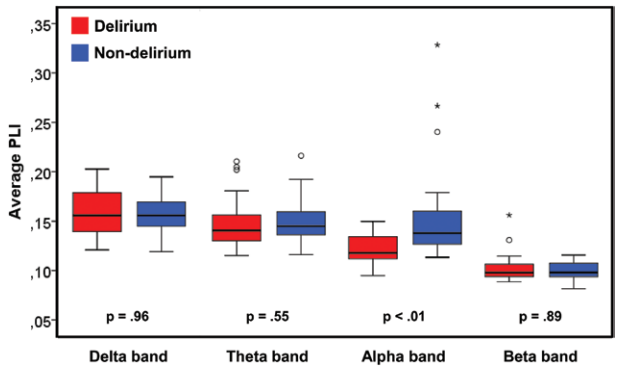

Fig. 1. Boxplots of average phase leg index (PLI) for δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), and β (13–20 Hz) frequency bands for patients with and without delirium. Significant difference was found in the α frequency band (8–13 Hz) ($P < 0.01$), indicating lower functional connectivity in delirium patients than in nondelirium patients. *Asterisks* and *small circles* represent outliers.

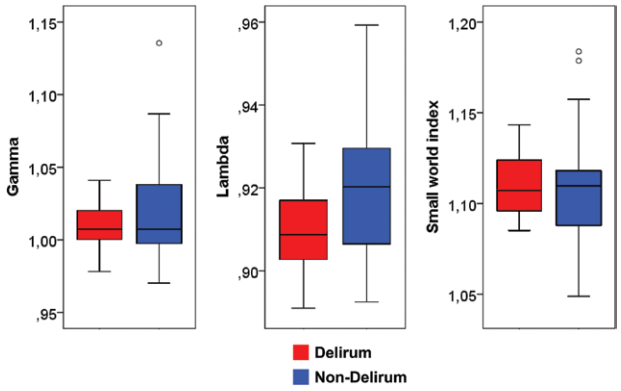

Fig. 2. Boxplots of normalized path lengths (λ), normalized clustering coefficient (γ), and small world index for α frequency band; λ in α frequency band was significantly lower in patients with delirium compared to patients without delirium, indicating functional networks have a shorter average path length in these patients ($P < 0.01$); γ and the small world index were not significantly different between both groups. *Small circles* represent outliers.

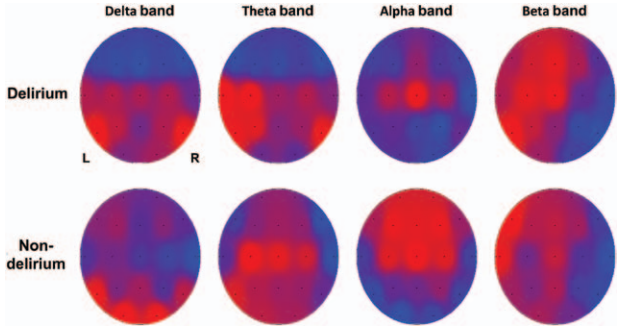

Fig. 3. Topological representation of the directed phase lag index (dPLI) for each frequency band for delirium and nondelirium patients. Values represent the average per sensor for each group. Orientation: nose is *up*, *left* (L) is left hemisphere, *right* (R) is right hemisphere. *Red* indicates relatively high dPLI value, *blue* indicates relatively low dPLI. The colors show relative dPLI within the group and frequency. *Blue* in one picture does not necessarily indicate the same dPLI value in another picture.

significant difference in the normalized clustering coefficient (γ) ($t = -1.40$; $P = 0.17$) or small world index ($t = 0.17$; $P = 0.87$) between both groups in the α band.

Post hoc tests were performed to study whether network parameters were related to the presence of hallucinations, in which we excluded patients in whom it was unclear whether hallucinations were present or not. α Band γ was significantly lower in delirium patients with hallucinations (median, 0.994; IQR, 0.991 to 1.002) compared to delirious patients without hallucinations (median, 1.015; IQR, 1.007 to 1.025; $P < 0.01$), while λ showed no significant differences (hallucinations + median = 0.908; IQR, 0.903 to 0.917; hallucinations = 0.910; 0.903 to 0.917; $P = 0.68$). α Band small world index was significantly lower in delirium patients with hallucinations (median, 1.095; IQR, 1.091 to 1.099) compared to delirious patients without hallucinations (median, 1.110; IQR, 1.106 to 1.125; $P < 0.01$).

Directed Connectivity

Directed PLI differed between delirium patients and controls in the δ band in anterior and central regions ($F = 4.53$; $P = 0.04$ and $F = 7.65$; $P < 0.01$, respectively; figs. 3 and 4). In delirium patients, anterior dPLI (mean, 0.48; SD, 0.03) was lower and central dPLI (mean, 0.51; SD, 0.01) was higher than in nondelirium patients (mean, 0.50; SD, 0.02 and mean, 0.49; SD, 0.01, respectively), indicating higher information flow toward anterior regions in the δ band. No other differences in dPLI were found between groups. *Post hoc* analyses showed no significant differences between delirium patients with and without hallucinations ($P > 0.05$; figs. 5 and 6).

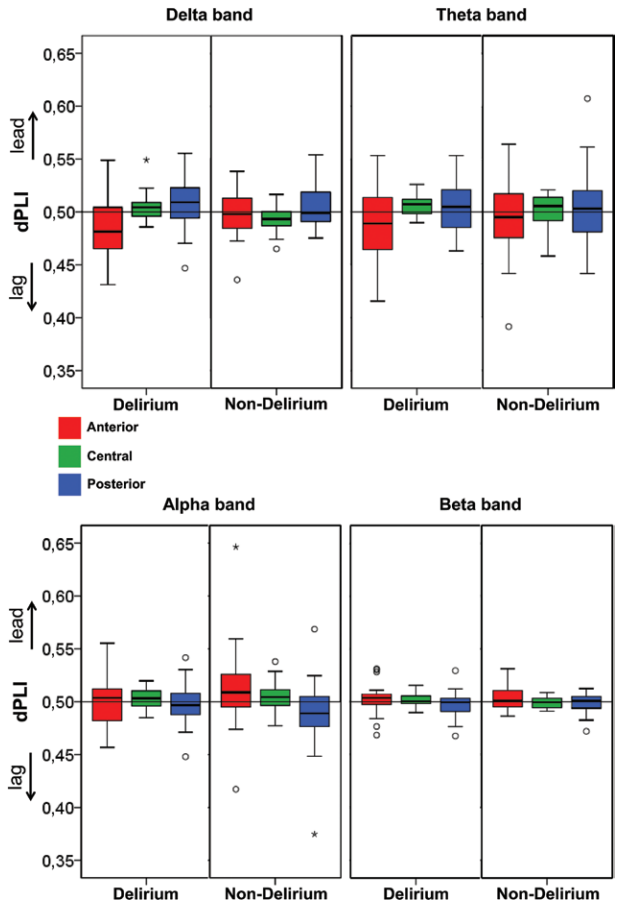

Fig. 4. Directed phase lag index (dPLI) comparison (*box plots*) for delirium and nondelirium patients for δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), and β (13–20 Hz) frequency bands. A significant difference between both groups was found in the δ band for anterior and central regions. *Asterisks* and *small circles* represent outliers.

Discussion

In summary, we observed decreased functional connectivity combined with a decreased normalized path length in the α frequency band in patients with delirium. Furthermore, delirious patients showed disturbances in the anterior-to-posterior directed connectivity in the δ band. These results indicate that

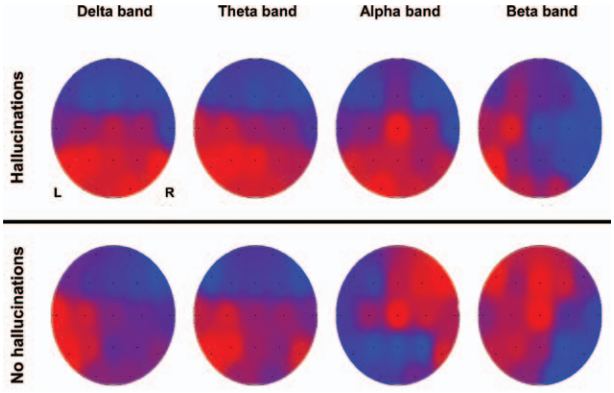

Fig. 5. Topological representation of the directed phase lag index for δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), and β (13–20 Hz) frequency bands for delirium patients with and without hallucinations. Values represent the average per sensor for each group. Orientation: nose is *up*, *left* (L) is left hemisphere, *right* (R) is right hemisphere. *Red* indicates relatively high directed phase lag index value, *blue* indicates relatively low directed phase lag index.

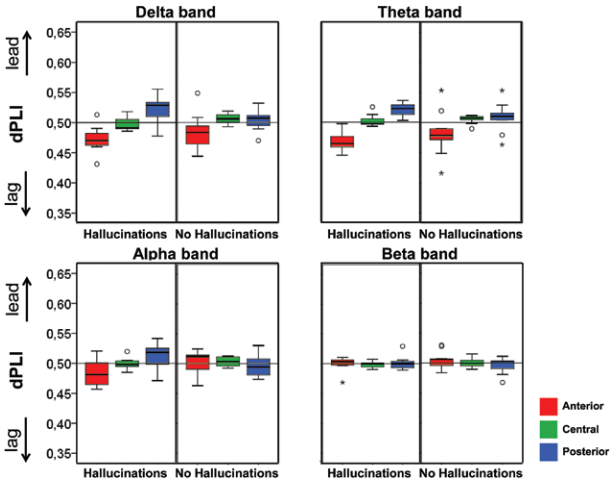

Fig. 6. Directed phase lag index (dPLI) comparison (*box plots*) for δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), and β (13–20 Hz) frequency bands for delirium patients with (n = 7) and without (n = 9) hallucinations. No significant difference between both groups was found, possibly due to small sample sizes. *Asterisks* and *small circles* represent outliers.

the functional brain network is less connected during delirium and that the dominant direction of information flow is altered.

In the electroencephalography of healthy subjects, the dPLI showed an anterior-to-posterior gradient.[9,13] It was recently shown that this gradient is lost in the α band during loss of consciousness, while it is regained after recovery of consciousness.[9] During delirium, a loss of phase leading to connectivity was found in the δ frequency band compared to nondelirious patients. We suggest that the altered dPLI gradient in delirious patients may be related to the disturbances in consciousness in these patients. It is important to stress that our control subjects were nondelirious patients and not healthy subjects, which is reflected in the power spectrum of their electroencephalography recordings and also in the less outspoken anterior-to-posterior dPLI gradient (figs. 3 and 4). We speculate that differences in the dPLI gradient may also be found in other frequency bands when healthy subjects would have been used as a control group.

Our study suggests that in delirious patients hallucinations may coincide with decreased local clustering and less small world topology in the α band compared to delirious patients without hallucinations. However, these results should be interpreted with caution due to small sample sizes (nine *vs.* seven patients). No previous work known to the authors describes network alterations in electroencephalography recordings related to hallucinations during delirium. However, decreased α band local clustering has been described in schizophrenia patients compared to healthy controls.[24] Unfortunately, information on the occurrence of hallucinations in the schizophrenia patient group was not described in this study.

Functional disconnection of various brain regions in different diseases may result in specific cognitive deficits. This hypothesis is most thoroughly studied in schizophrenia, where both structural and functional connectivity appears to be decreased.[25,26] In Alzheimer disease, global disconnection is thought to be the result of targeted attacks of key regions in the network, so-called hub regions.[22,27,28] We speculate that in delirium the global decrease in α band functional connectivity may be related to the cognitive deficits, especially attention deficits,[29,30] which should be investigated in future studies. The alterations in functional connectivity during delirium may also be related to consciousness disturbances, as described with functional magnetic resonance imaging, as altered consciousness is one of the symptoms of delirium.[11] Decreased PLI in the α and θ band have also been described in patients in a vegetative state compared to patients in a minimally conscious state.[31] Decreased PLI in the α band has also been described in healthy subjects who were anesthetized with propofol.[9] The PLI was decreased after loss of consciousness due to propofol but did not increase again when consciousness was regained.

This study is the first to describe the functional network during delirium using graph theory. In the study by Lee *et al.*,[9] the normalized path length and clustering coefficient increased after propofol-induced loss of consciousness. In contrast, we found a decrease of the normalized path length in delirium. Although the functional network alterations are not exactly similar, it should be considered that functional network alterations due to postsurgery delirium could, in part, also be the effects of anesthetics.

In our study, delirium was associated with slowing of background activity, including an increase in delta power and decrease in alpha power. This agrees with results from previous studies.[32,33] A recent study described a first attempt to use neural mass models to elucidate electroencephalography phenomena as seen in delirium, which indicated that

these may be caused by imbalances between inhibitory and excitatory activity.

The control group in our study was similar to the delirium group with regard to age, sex, and a postcardiac surgery state. Results seem to remain significant when adjustments were made for the duration of surgery, APACHE IV scores, and haloperidol use, in multivariate analyses, which suggests that the underlying pathology in network structure can be assigned to delirium. As the APACHE score and duration of surgery are risk factors for delirium, it is not surprising that these factors were different between delirium and nondelirium patients.[34,35]

Limitations of this study may include a possible measurement bias due to the problem that not all delirious patients could adhere to the measurement protocol because delirious patients were hard to instruct. However, all patients showed four epochs of 8 s with eyes closed, so it is unlikely that this will have affected our findings. The resting-state condition in delirious patients may be somewhat dissimilar to control patients because patients in the delirium group were more difficult to instruct and experienced fluctuating levels of consciousness. By using epochs recorded shortly after the patient had conducted a task, we tried to avoid the selection of epochs during sleep. We only considered eyes-closed resting-state electroencephalography and not eyes open, as electroencephalography recordings in this setting reflect functionally relevant interactions between brain regions.[36] The fluctuating nature of delirium could affect the electroencephalography data and thereby the stability of the PLI value per epoch. However, the between-subject variance in PLI, path length, and clustering for the delirium group was equal to or lower than the variance in the control group, which indicates that there can only be a minimal effect of the fluctuating nature of delirium on the PLI stability. Our study compared patients shortly after cardiac surgery that did and did not develop delirium. This design allowed for comparison of functional network characteristics in delirium patients compared to controls that were otherwise in similar conditions regarding the treatment they had undergone, including effects of anesthetics. A within-subject analysis of functional network alterations, where the patient could serve as his own control after the most outspoken aspects of the clinical syndrome have resolved, would be of additional interest. However, delirium is known to have long-term impact on cognitive performance, indicating that neural functioning before and after delirium is not the same. A baseline measurement before the occurrence of delirium would provide an unbiased control condition for this type of study. This study design could also elucidate whether altered connectivity appears only during delirium or also in patients at risk of delirium before surgery. Furthermore, during the network analysis, we needed a normalization procedure to eliminate the influence of synchronization strength, but the normalized weighted path length was still significantly related to average PLI, and an interdependence may therefore be present. The normalization procedure that we applied is not optimal, but consensus on a better alternative is currently not available. Minimum spanning tree analysis may be a promising approach that should be the subject of further studies.[37] However, the fact that the path length but not the small world index differed between delirium patients and nondelirium patients further suggests that other models than the small world model may be needed to better interpret these findings.[8] Finally, it is unclear whether our results can be inferred to all delirious ICU patients, as it is unclear whether patients with other underlying pathology show the same functional connectivity features as delirious postcardiac surgery ICU patients.

Future studies should elucidate whether delirium always results from similar patterns of disconnection and network reorganization, irrespective of the underlying cause, as our study focused specifically on delirium in postcardiac surgery ICU patients. The use of computational models to simulate neurophysiological disturbances of cortical activity and connectivity may be used to increase our insight in these mechanisms.[28,38,39] In addition, it remains to be studied whether the network changes that we observed induce permanent reorganization of functional networks and whether these changes are predictive of long-term cognitive deficits after delirium. Future studies should also indicate whether individuals at risk of delirium can be identified based on functional network alterations.

The electroencephalography during delirium shows loss of α band functional connectivity, decreased path length, and increased δ band connectivity directed to frontal regions. These findings are consistent with altered functional connectivity and network topology in other diseases that affect cognitive functioning, such as schizophrenia and Alzheimer disease, and show similarities with findings in subjects with loss of consciousness. Delirium may therefore be regarded as a disconnection syndrome.

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Competing Interests

The authors declare no competing interests.

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