NEUROPHYSIOLOGY OF DELIRIUM

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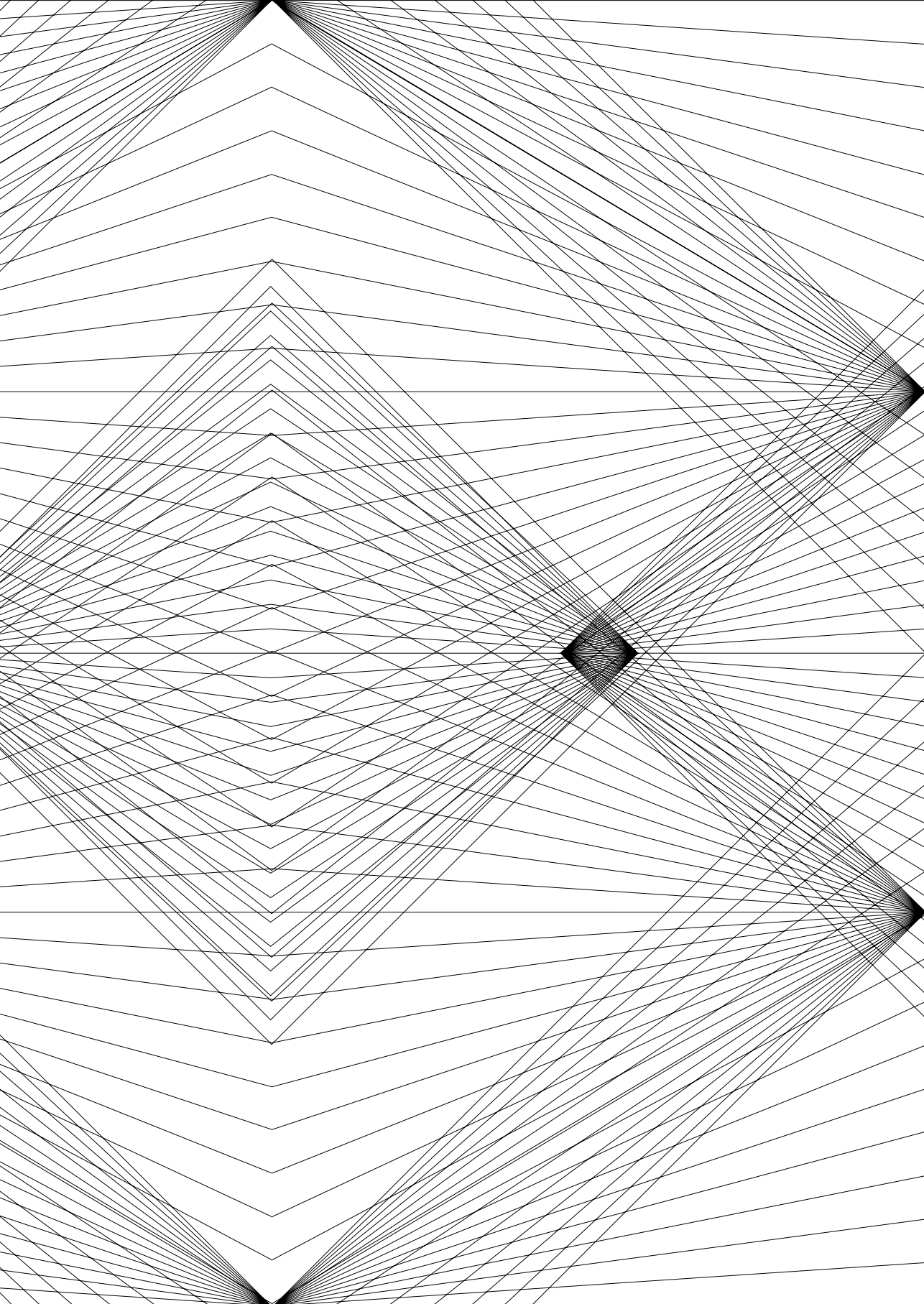

◆ CHAPTER 1 ◆

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Delirium is an acute disturbance of consciousness and cognition that tends to fluctuate over time and is caused by the physiological consequences of a medical condition.[1] It is a common disorder in intensive care unit (ICU)- and post-operative patients, with three different subtypes based on psychomotor behavior: hypoactive, hyperactive and mixed-subtype delirium.[2] Delirium is associated with higher mortality, longer hospital stay, long-term cognitive impairment and increased costs.[3-6] The multifactorial pathophysiology of delirium is not completely understood. Multiple hypotheses have been proposed including neurotransmitter imbalances, neuro-inflammation and aberrant stress responses.[7, 8]

Although changes in the electroencephalogram (EEG) during delirium have been described since the 1940's, little is known about other neurophysiological changes occurring during delirium.[9] Several studies showed that patients with delirium demonstrated slowing of EEG activity, which resolved after the delirium episode ended.[10, 11] Other features, for example changes in heart rate variability or EEG functional connectivity, have never been studied in patients with delirium.

Despite its frequency and impact, recognition of delirium by ICU physicians is poor (sensitivity 29%).[2] Therefore, several delirium assessment tools have become available, such as the Confusion Assessment Method for the ICU (CAM-ICU).[12, 13] These delirium assessment tools are based on cognitive screening and perform well in a research setting. Nevertheless, they fail to provide a reasonable sensitivity in daily, clinical practice (sensitivity CAM-ICU 47%).[14] Furthermore, they may not fit well in the culture of the recovery room and ICU, which is primarily orientated on monitoring of physiological alterations. As a consequence, delirium recognition is impaired and treatment delayed, which could affect patient outcome.[15]

A new approach for delirium detection could be provided by monitoring of physiological alterations, for example EEG. Over the last years, monitoring of EEG by a limited number of electrodes and automatic processing has become technically feasible.[16] This development may provide opportunities for EEG-based detection of delirium, but this is currently unknown. Furthermore, other physiological measures that could be altered during delirium and combined with EEG to increase sensitivity, have barely been studied.

OBJECTIVE OF THIS THESIS

The objective was to characterize the neurophysiology of delirium and assess opportunities for delirium detection based on neurophysiological alterations.

OUTLINE OF THIS THESIS

In the first part of this thesis we study different neurophysiological signals in order to enhance the characterization of delirium. Aiming to improve our understanding of the phenomenology, we explore in chapter two the EEG functional connectivity and network topology in delirium after cardiac surgery. By investigating the variability of the EEG during delirium in chapter three, we try to increase our understanding of the fluctuating nature of delirium symptoms. In chapter four we assess the alteration in sympathovagal balance during delirium, by comparing heart rate variability between ICU patients with and without delirium.

In the second part of this thesis we focus on neurophysiological measures that may provide opportunities for delirium detection. By conducting a systematic review in combination with an observational study in respectively chapter five and six, we aimed to explore the electrode derivation and EEG characteristic that have the best capability of discriminating delirium from non-delirium. In chapter seven, we investigate whether monitoring of blinks and eye movements could provide a new approach for delirium detection. The possibilities for using temperature variability, a measure of temperature regulation, for delirium detection are described in chapter eight.

Finally, the results will be summarized and discussed in chapter nine.

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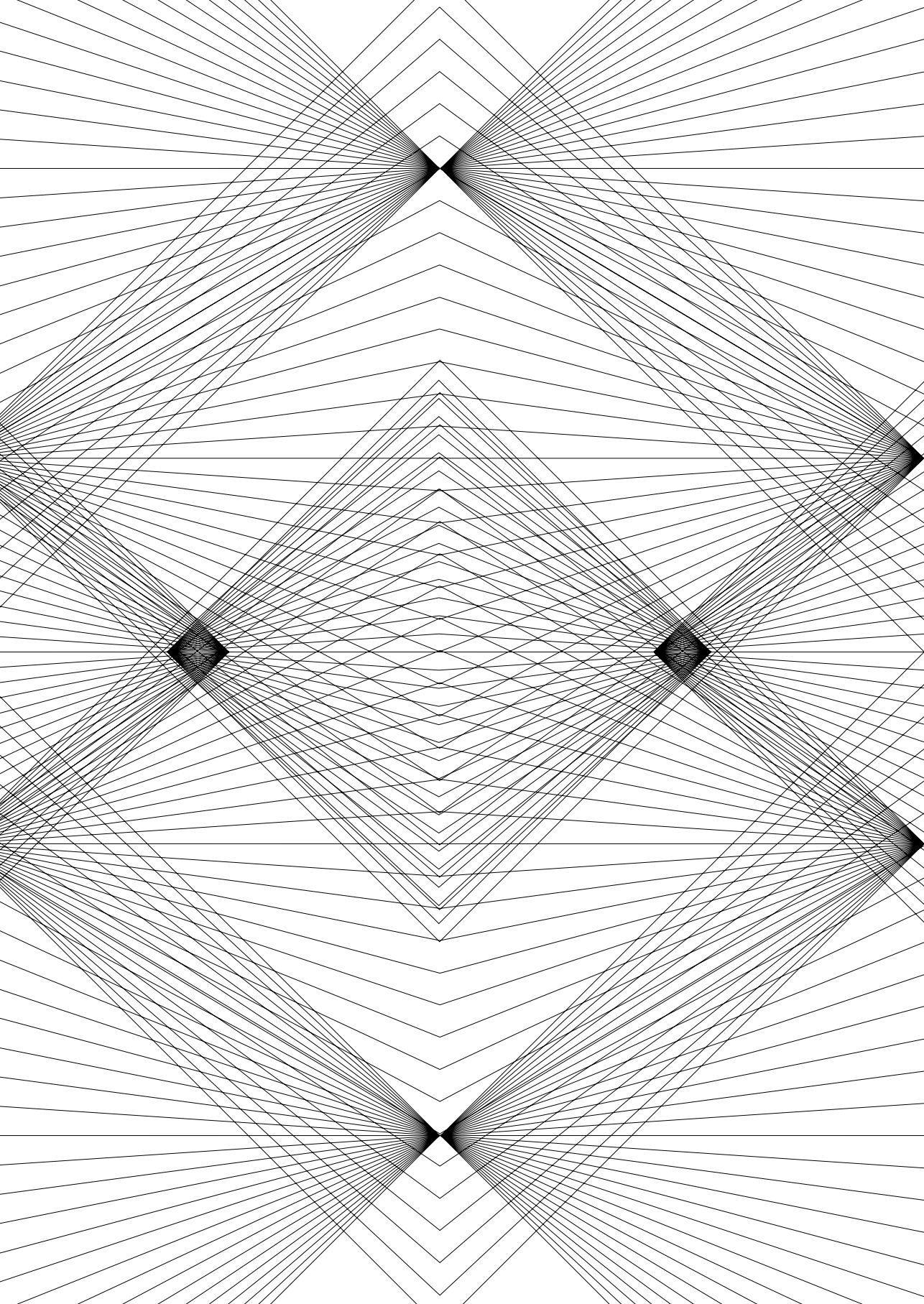
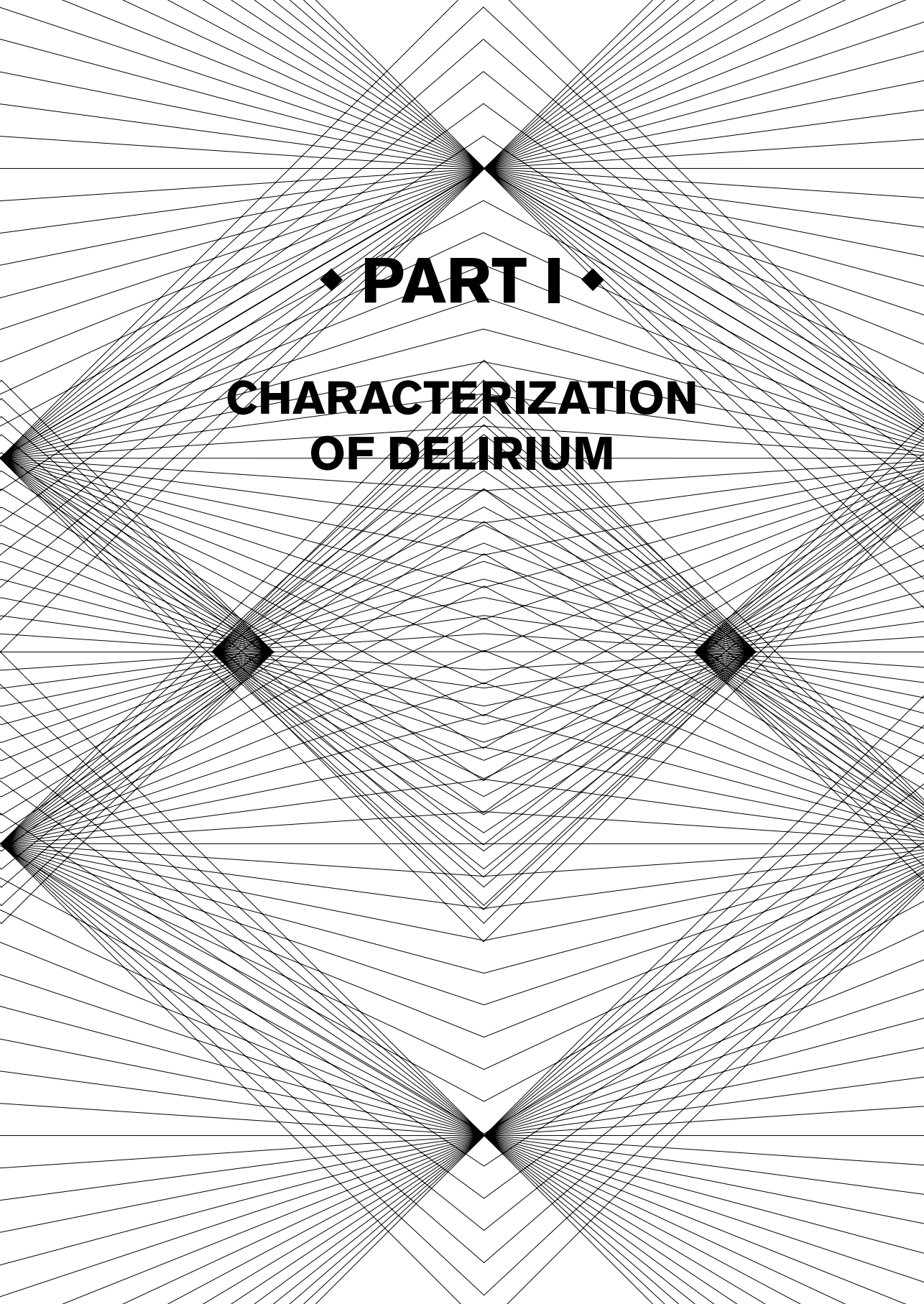
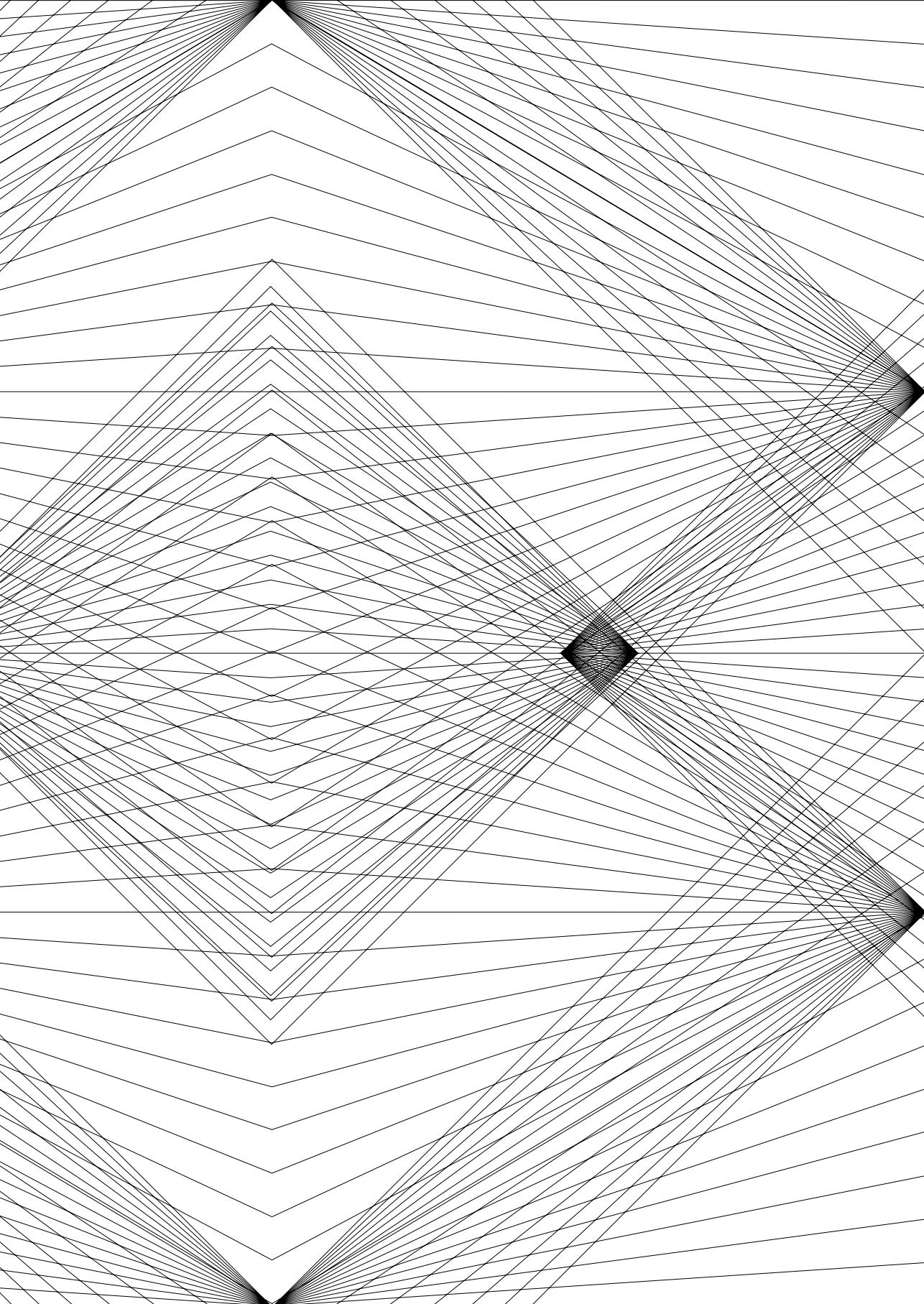




PART I

CHARACTERIZATION OF DELIRIUM



◆ CHAPTER 2 ◆

DECREASED FUNCTIONAL CONNECTIVITY AND LOSS OF SMALL WORLD TOPOLOGY IN THE EEG OF POSTOPERATIVE PATIENTS WITH DELIRIUM

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CORNELIS J. STAM, ARJEN J.C. SLOOTER

** BOTH AUTHORS CONTRIBUTED EQUALLY*

ACCEPTED FOR PUBLICATION IN ANESTHESIOLOGY

ABSTRACT

BACKGROUND In this article we explore EEG functional connectivity and network topology in delirium after cardiac surgery, aiming to improve our understanding of the pathophysiology and phenomenology of delirium. We hypothesize that disturbances in attention and consciousness in delirium may be related to alterations in functional neural interactions.

METHODS EEG recordings were obtained in post cardiac surgery patients with delirium (N = 25) and without delirium (N = 24). We analyzed unbiased functional connectivity of EEG time series using the Phase Lag Index (PLI), and functional brain network topology using graph analysis.

RESULTS The mean PLI was lower in the alpha band (8 – 13 Hz) in patients with delirium (median (Inter Quartile Range, IQR) 0.120 (0.113-0.138)) than in patients without delirium (median 0.140 (IQR 0.129-0.168); $p < 0.01$). More random network topology was found in delirium patients, as characterized by lower normalized weighted shortest path lengths in the alpha band (median 0.906 (IQR 0.901-0.917) versus 0.919 (IQR 0.908-0.930), $p < 0.01$).

CONCLUSIONS Loss of alpha band functional connectivity and more random functional networks characterize the EEG during delirium. These findings may explain why information processing is less efficient in delirium.

INTRODUCTION

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 neuro-inflammation.[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 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 EEG during delirium is characterized by excessive slowing into theta and delta frequencies, and decline of alpha activity.[10] In contrast to a rapidly increasing body of work on other neuropsychiatric diseases, only one functional Magnetic Resonance Imaging (fMRI) 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, fMRI recordings provide an indirect measure of neural activity, and a more systematic quantification of functional brain network topology during delirium is currently lacking. Electroencephalography (EEG) recordings provide a more direct measure of neural activity. Measures of phase synchronization have been used to assess functional connectivity between EEG time series,[12] and graph theory can be used to characterize functional brain network topology.[7, 8]

We hypothesized that postoperative delirium is related to disturbances in functional connectivity and network topology. The primary objective of the present study is to compare EEG-based functional brain networks in cardiac surgery patients with and without delirium. The secondary objective is 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 (number 11-073). Cardiac surgery patients aged 50 years or older were included prior to surgery. Exclusion criteria were a history of a neurological or psychiatric disease prior to surgery or any neurological complication other than delirium after surgery, as these may confound the diagnosis of delirium. For non-delirious 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)[13] and medication.

Daily mental status was assessed by research nurses and -physicians with the Richmond Agitation and Sedation Scale (RASS)[14] and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[15] during the first five post-operative days, or when surgery was complicated, the first five 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.[14, 16]

When the CAM-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 (DSM) IV criteria for delirium.[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 EEG recording of the patient was included for the study. When it was equivocal, the EEG recording of the patient was excluded.

When a patient was CAM-ICU negative, his or her age and sex were compared to 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 DSM 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 non-

delirious patient, the EEG recording of the patient was included for the study. When the neuropsychiatric evaluation was equivocal, the EEG recording of the patient was excluded.

The motor subtype of delirium was registered during the EEG recording. The hypoactive subtype was defined as a continuous negative RASS score during the EEG 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 the EEG 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 suffered from hallucinations or not were excluded from hallucinations analysis.

EEG ACQUISITION

Twenty-one channel EEG recordings were conducted using Ag/AgCl electrodes, according to the international 10/20 system. These were recorded with a Micromed EEG apparatus (Micromed, Trevisio, Italy), using a sample frequency of 512 Hz, a high pass input filter of 0.15 Hz (40dB/decade) and a second order infinite impulse response filter of 0.1-70 Hz (40 dB/decade). EEG electrodes were adhered to the scalp using electrode gel and on the forehead using tape, in order to prevent dislodging of electrodes.

Thirty minute EEGs were recorded, in which patients were asked to keep their eyes open for 15 minutes and close them for the last 15 minutes 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 seconds after the tasks. The first 4 artifact free epochs of 8.0 seconds during the eyes-closed condition were used for analyses, which was sufficient for stable results (see appendix).[17, 18]

After digital storage the data were pre-processed and filtered in the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-20 Hz) bands. This bandpass filter uses a Fourier transform of the whole epoch. All bins outside of the passband are made zero, after which an inverse Fourier transform is performed. Since EEG acquisition was performed in a clinical setting and recordings were possibly contaminated by electromyography (EMG) artifacts, we did not analyze data in frequency bands above 20 Hz.[19] 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), and BrainWave software was used for further analysis (v0.9.100; freely available at: http://home.kpn.nl/stam7883/).

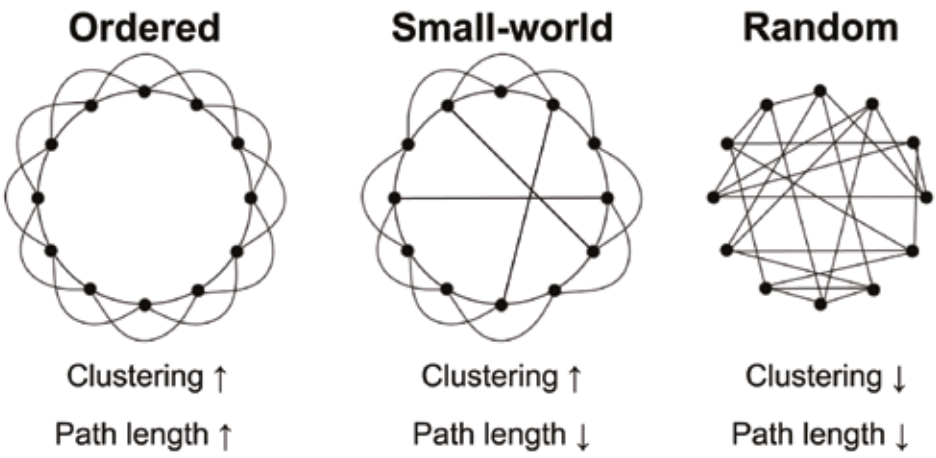
FUNCTIONAL CONNECTIVITY

To assess functional connectivity between EEG time series, the phase lag index (PLI) was used (see appendix 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 EEG 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 EEG electrodes were considered as vertices (nodes) and the strength of the phase coupling between the EEG channels as edges. We further computed the following most fundamental network measures (figure I), as described by Watts and Strogatz,[20] which were modified for weighted networks (see appendix for a detailed description).[21] The weighted normalized clustering coefficient (gamma) defines the level of local clustering or segregation in the network. The normalized average weighted shortest path length (lambda) describes the level of global integration of the network. Network parameters were only calculated for frequency bands with a significant difference in mean PLI between delirium and non-delirium patients.

FIGURE I *Three network types* [20]



In an ordered network (left) nodes are connected to their nearest neighbors, resulting in high local clustering (i.e. high clustering coefficient). However, there are no long-distance connections, and it takes a lot of steps to reach the opposite side of the network (i.e. high shortest path length). When all connections are randomly distributed between the nodes (right), the network has a low shortest path length, but the local clustering is also lost. When a few connections in an ordered network are randomly rewired, a small-world network is constructed (middle), resulting in a high clustering coefficient combined with a low shortest path length.

STATISTICAL ANALYSIS

Continuous variables were screened for normal distribution using Kolmogorov Smirnov tests. Normally distributed variables were compared between delirious and non-delirious patients using the student's 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 5 cases or less). Null hypotheses regarding differences in average PLI between delirious and non-delirious patients were rejected for $p < 0.05$ 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 gamma and lambda 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 non-delirium patients were assumed to be possible confounders. Therefore, a general linear model was used to adjust for possible confounding. Statistical analyses were performed using SPSS (IBM SPSS Statistics 20, Chicago, USA).

RESULTS

PATIENT CHARACTERISTICS

Data were available of 28 delirious- and 26 non-delirious cardiac surgery patients. Three patients with delirium and two patients without delirium were excluded because of EEG artifacts. The characteristics of the remaining 25 delirious and 24 non-delirious patients are shown in Table I. Of the patients with delirium, 14 were hypoactive, 5 hyperactive, and 6 patients had a mixed type of delirium. After EEG 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 I). In the delirium group, 7 patients had hallucinations during the EEG recording, 9 patients had no hallucinations during the EEG recording, and in 9 patients it was unclear whether hallucinations were present or not. All 7 patients with hallucinations suffered from visual hallucinations and 2 from additional auditory hallucinations.

FUNCTIONAL CONNECTIVITY

The average PLI was significantly lower in the alpha band in delirium patients compared to non-delirium patients (median (Inter Quartile Range, IQR) delirium = 0.120 (0.113-0.138); non-delirium = 0.140 (0.129-0.168); $p < 0.01$; Figure II). The average PLI in the delta, theta, and beta bands were not related to delirium. Within the delirium patients, there was no difference with regard to the alpha band average PLI between patients with hallucinations (median = 0.122 (IQR 0.109-0.141) and without hallucinations (median = 0.131 (IQR 0.114-0.145; $p = 0.71$).

Since 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 alpha band PLI adjusted for these possible confounders. For this purpose, alpha band PLI was first log transformed (10log(x)), after which the assumption of a normal distribution was no longer violated. The corrected model still showed a significant difference in alpha band PLI between delirium and non-delirium patients ($F(4,48) = 3.12$; $p = 0.02$).

NETWORK ANALYSIS

Alpha band normalized path length (lambda) was significantly decreased in delirium patients compared to non-delirium patients ($p < 0.01$), indicating a more random network topology (Figure III). The results remained significant after adjusting for APACHE IV score, duration of surgery, and haloperidol use ($F(4,48) = 2.77$; $p = 0.039$). Alpha band lambda was significantly correlated with the average PLI in the alpha band (Kendall's tau = 0.411; $p < 0.01$). There was no significant difference in the normalized clustering coefficient (gamma) between both groups in de alpha band ($p = 0.78$).

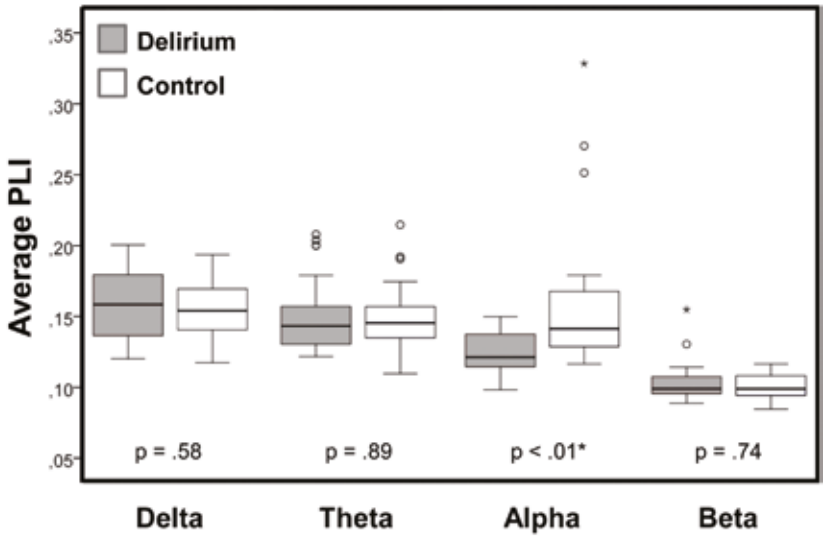
Post-hoc tests were performed to study whether network parameters were related to the presence of hallucinations, in which we excluded patients in whom it was unclear whether hallucinations were present or not. Alpha band gamma was significantly lower in delirium patients with hallucinations (median = 0.999 (IQR 0.991-1.007)) compared to delirious patients without hallucinations (median = 1.008 (IQR 1.003-1.025); $p = 0.02$), while lambda showed no significant differences (Hallucinations+ median = 0.909 (IQR 0.895-0.912); Hallucinations- = 0.904 (0.903-0.918; $p = 0.56$).

TABLE I *Patient characteristics*

	DELIRIUM (N=25)	CONTROLS (N=24)	P-VALUE
Sex (male)	13 (52%)	14 (58%)	0.78
Age (years)	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	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

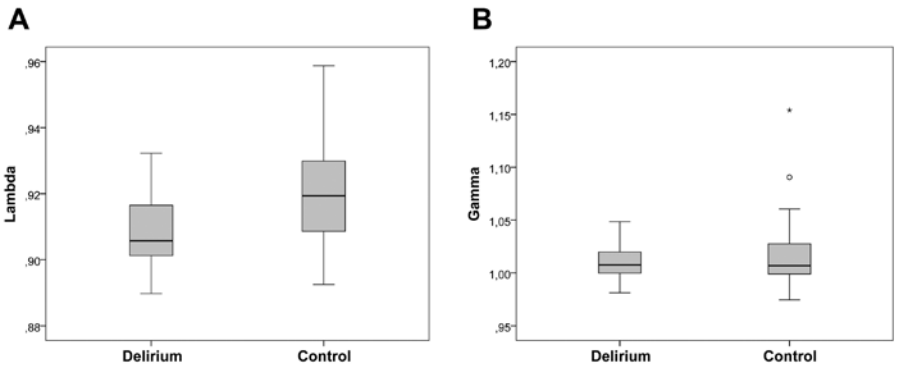
Data represent mean ± standard deviation, median (interquartile range) or numbers (%). Medication in the 24 hours before EEG registration in frequencies (%), benzodiazepines include temazepam, oxazepam, lorazepam, and midazolam, whereas opiates include morphine and oxicodon. Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; min = minute; n = number.

FIGURE II *Average phase leg index (PLI) for delta, theta, alpha, and beta frequency band for patients with and without delirium.*



Significant difference was found in the alpha frequency band (8-13 Hz), $p < 0.01$.

FIGURE III *Lambda and gamma for alpha frequency band.*



A) Normalized path lengths (lambda) in alpha frequency band were significantly lower in delirium patients compared to patients without delirium ($p < 0.01$).

B) Normalized clustering coefficient (gamma) was not significantly different between both groups.

DISCUSSION

In summary, we observed in patients with delirium decreased functional connectivity combined with a decreased normalized path length in the alpha frequency band. These results indicate that the functional brain network is less connected during delirium and shifts towards a more random, and thus less efficient network.

The only previous study on neural networks in delirium applied resting state fMRI of fluctuations in blood-oxygen level dependent (BOLD) signal.[11] Delirium was found to be associated with increased functional connectivity between the dorsolateral prefrontal cortex and posterior cingulate cortex.[11] These regions are hypothesized to be part of a highly interconnected backbone in the structural brain network.[22] Moreover in this fMRI study, functional connectivity between the intralaminar thalamic and various subcortical regions was reduced during delirium.[11] Unfortunately, the EEG recordings analyzed in the present study did not allow for anatomical source reconstruction, and functional connectivity based on EEG and fMRI BOLD recordings cannot easily be compared yet.[8] We therefore think that our study and the work of Choi and colleagues provide complementary information on functional connectivity in delirious patients as our study describes functional network characteristics based on a more direct measurement of neural activity.

More extended EEG network research has been conducted in other neuropsychiatric diseases that cause cognitive decline, especially in Alzheimer's disease.[8, 23] Altered network topology has been reported in AD patients compared to controls, especially in the alpha and beta band. However, there is no consensus yet about the exact alterations in network topology induced by AD, partly because of methodological differences for calculation of connectivity and network topology that may influence the results.[23]

Our study suggests that in delirious patients hallucinations may coincide with decreased local clustering in the alpha band compared to delirious patients without hallucinations. However, these results should be interpreted with caution due to small sample sizes (9 versus 7 patients). No previous work known to the authors describes network alterations in EEG recordings related to hallucinations during delirium. However, decreased alpha band local clustering has been described in schizophrenia patients when compared to healthy controls.[24] Unfortunately, information on the occurrence of hallucinations in the schizophrenia patient group was not described in this study. In resting state fMRI recordings of individuals with auditory verbal hallucinations, but without schizophrenia, increased overall connectivity has been described.[25] In these individuals an increased hub-status (i.e. strength and central role in the network) was found especially

in the default mode network and auditory cortex.[25] Although difficult to obtain, it would be interesting to study neurophysiological recordings during hallucinations in delirium patients that allow reconstruction to anatomical sources, in order to understand more precisely which functional alterations in brain networks take place.

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.[26,27] In AD global disconnection is thought to be the result of targeted attacks of key regions in the network, so-called hub regions.[21, 28, 29] We speculate that in delirium the global decrease in alpha band functional connectivity may be related to the cognitive deficits, especially attention deficits, [30, 31] which should be investigated in future studies. Unfortunately, cognitive deficits prior to, during and after delirium were not systematically documented in our study. The alterations in functional connectivity during delirium may also be related to consciousness disturbances, as described with fMRI, as altered consciousness is one of the symptoms of delirium.[11] Decreased PLI in the alpha and theta band have also been described in patients in a vegetative state as compared to patients in a minimally conscious state.[32]

This study is the first to describe the functional network during delirium using graph theory. The control group is similar to the delirium group with regard to age, sex, and a post-cardiac surgery state. Results seem to remain significant when adjustments were made for 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 non-delirium patients.[33, 34]

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 4 epochs of 8 seconds 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 suffered from 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 EEG and not eyes open, as EEG recordings in this setting reflect functionally relevant interactions between brain regions.[35] The fluctuating nature of delirium could affect the EEG 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. 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. Although the normalization procedure which we applied is not optimal, consensus on a better alternative is currently not available.[36] 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 post cardiac 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 post cardiac 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.[29, 37, 38] 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 EEG during delirium shows loss of functional connectivity and a more random functional network. These findings are consistent with altered functional connectivity and network topology in other diseases that affect cognitive functioning, such as schizophrenia and AD. Delirium may therefore be regarded as a disconnection syndrome.

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APPENDIX

PHASE LAG INDEX

The instantaneous phase difference for each time sample is computed using the analytical signal concept and the Hilbert transform. The PLI characterizes the asymmetry in the distribution of instantaneous phase differences between two signals. The reason for using the asymmetry of this distribution as a measure of functional interaction, is that a nonzero phase lag between these signals cannot be explained by volume conduction. The PLI ranges between 0 (no phase locking) and 1 (total synchronization). An index of the asymmetry of the phase distribution can be obtained from a time series of phase differences $\Delta(t_k)$, $k = 1 \ldots N_s$ in the following way:

$$\mathrm{PLI} = \left| \left\langle sign[\sin(\Delta\varphi(t_k))] \right\rangle \right|$$

where the phase difference is defined in the interval $[-\pi,\pi]$, $\langle\rangle$ denotes the mean value, N_s is the number of samples. For each subject, the PLI was calculated for all possible pairs.

GRAPH THEORETICAL ANALYSIS

The unweighted clustering coefficient describes the likelihood that neighbors of a vertex are also connected, and it quantifies the tendency of network elements to form local clusters. We used the weighted equivalent of this measure to characterize local clustering. For each vertex i, it is defined as:

$$C_{w,i} = \frac{\sum_{k\neq i} \sum_{\substack{l\neq i \\ l\neq k}} W_{ik} W_{il} W_{kl}}{\sum_{k\neq i} \sum_{\substack{l\neq i \\ l\neq k}} W_{ik} W_{il}}$$

where w_{ik} and w_{il} are the weights between vertex i and vertices k and l, respectively, and w_{kl} is the weight between vertices k and l. The average weighted clustering coefficient is computed by averaging $C_{w,i}$ over all vertices. The average (weighted) shortest path length indicates the level of global integration of the network. In unweighted networks, it depends

on the average number of edges used to connect any two vertices in the network.[1] The average weighted shortest path length (L_w) is defined as the harmonic mean of shortest paths between all possible vertex pairs in the network, where the shortest path L_{ij} between vertices i and j is defined as the path with the largest total weight:[2]

$$L_w = \frac{1}{(1/N(N-1))\sum_{i\neq 1}^{N}\sum_{j\neq 1}^{N}(1/L_{ij})}$$

with N the number of vertices. Network properties are determined not only by edge weights and network topology, but also by network size. In order to facilitate comparison of results with other studies, we compared the calculated C_w and L_w values to a reference, C_{ws} and L_{ws}, derived from 500 surrogate networks of the same size. The surrogate networks were constructed by randomly shuffling the edge weights over the network. The resulting C_w/C_{ws} (gamma) and L_w/L_{ws} (lambda) are thus the normalized average weighted clustering coefficient and normalized average weighted shortest path length of the network.

PLI STABILITY

Before we started our analysis, we studied the first 7 non-delirious patients and evaluated the length and number of epochs needed to reach stable PLI values (see Figure I and II below). Epochs of 8 seconds resulted in stable PLI values, as can be see Figure I for alpha band PLI. Elongation of the epoch length resulted in a decrease of PLI, as the PLI characterizes asymmetry in distribution of a consistent phase lag. The direction of this phase lag, however, may fluctuate over time. We therefore consider the epoch length of 8 seconds sufficient to obtain stable PLI values. With this epoch length of 8 seconds, 4 epochs were needed to obtain stable PLI values, as shown in Figure II. The use of more epochs may increase the stability of the results, since connectivity values were averaged over multiple epochs. However, a trade-off must be made between epochs that meet the conditions of a consistent resting-state, eyes-closed recording versus using as much epochs possible Using more epochs will inevitably lead to analysis of epochs of less quality in terms of artifacts, eyes-closed and awake state.

FIGURE I *Effect of increasing epoch length on PLI for alpha frequency band.*

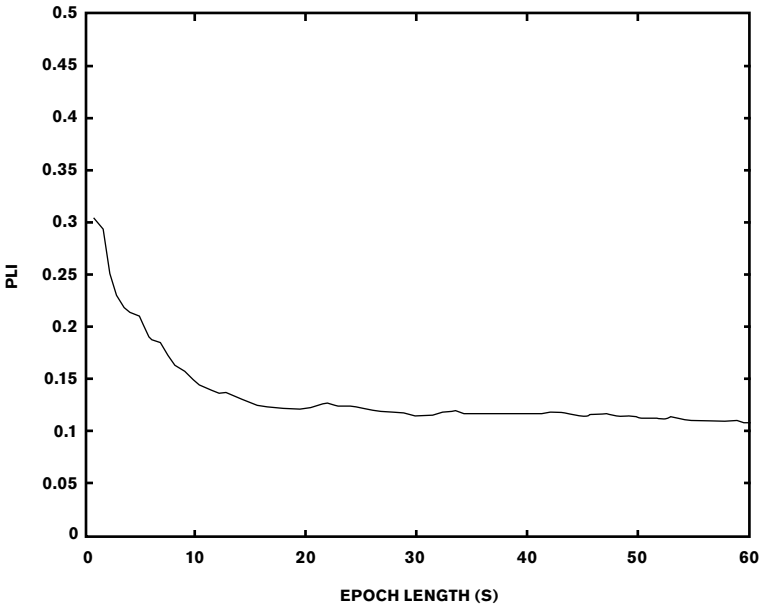
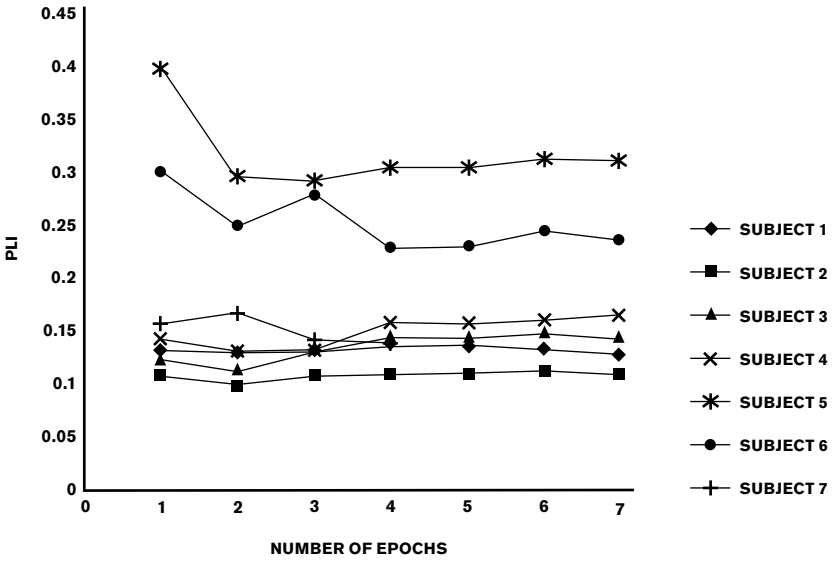


FIGURE II *Effect of averaging increasing number of epochs in 7 non-delirious patients.*



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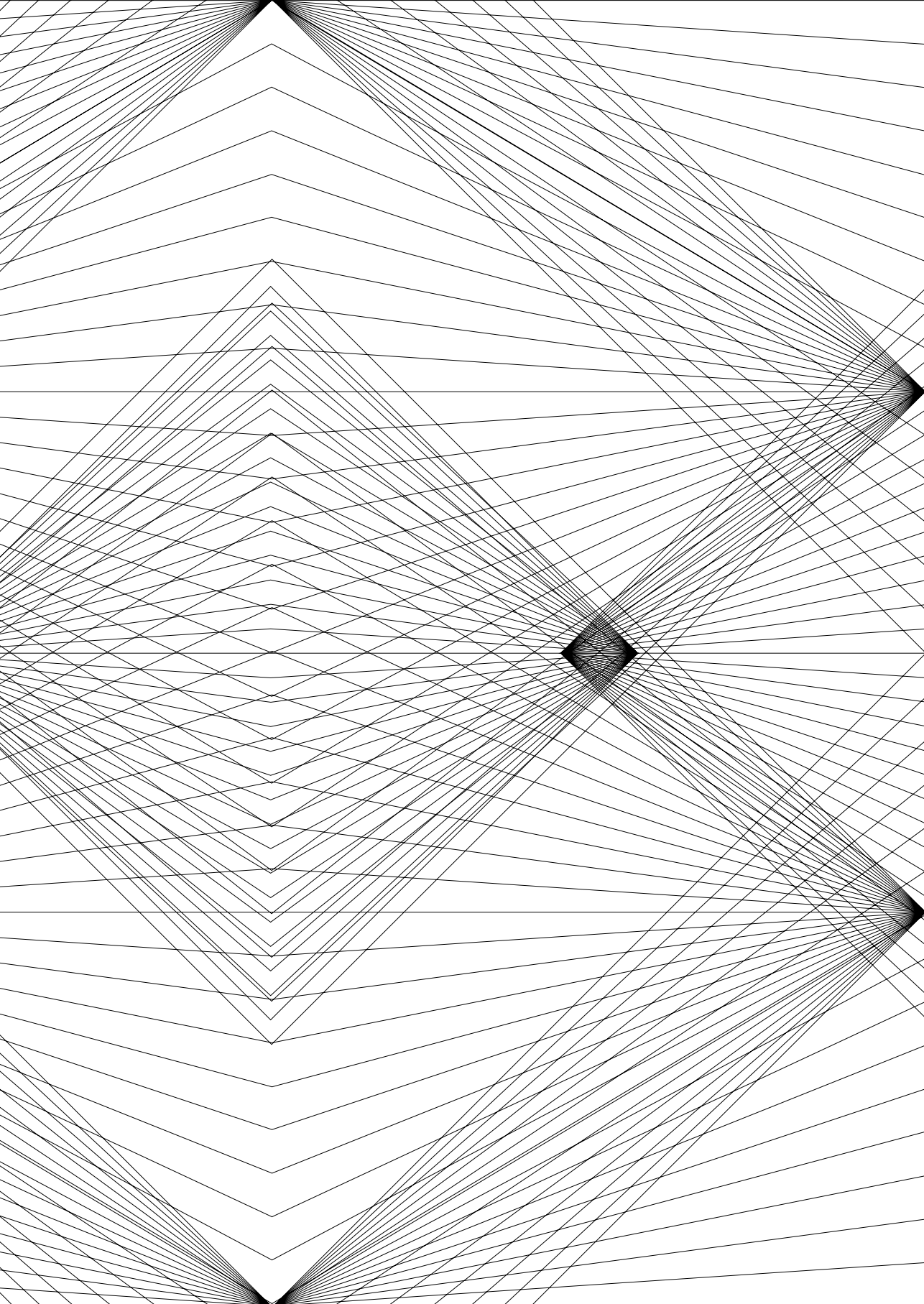

◆ CHAPTER 3 ◆

DELIRIUM: INCREASED SPECTRAL VARIABILITY AND DECREASED COMPLEXITY OF THE EEG

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ACCEPTED FOR PUBLICATION IN CLINICAL NEUROPHYSIOLOGY

TO THE EDITOR,

Delirium is an acute disturbance of attention and cognition that tends to fluctuate over time.[1] The electroencephalogram (EEG) during delirium is characterized by excessive slowing into theta and delta frequencies, and decline of the alpha rhythm.[2] The degree of these EEG changes corresponds with the severity of the cognitive disturbances during delirium.[2] Not only attention and cognition characteristically fluctuate during delirium, there may be fluctuations in the EEG as well, but these have, as far as we know, never been studied in a quantitative way. Recently, we conducted an EEG study in delirious and non-delirious patients to investigate minimal EEG requirements for delirium monitoring (unpublished data considering stationary spectral characteristics, study was approved by institutional review board of the University Medical Centre Utrecht, IRB number 11-073). Using the same recordings, we took the opportunity to study EEG variability in the spectral domain expecting an increase during delirium. We also assessed complexity in the time domain.

After cardiac surgery, 26 delirious and 28 non-delirious patients underwent a 21 electrode scalp EEG (using the 10/20 system). Patients were classified by a psychiatrist, geriatrician or neurologist using the 'Diagnostic and Statistical Manual of Mental Disorders' criteria for delirium.[1] EEG recordings (Micromed, Trevisio, Italy) were acquired to FzCz using a sample frequency of 512 Hz. Data was band-pass filtered (0.5-30 Hz) and the first minute of artefact-free data with eyes closed was selected and divided into 14 epochs of 8 seconds with 50% overlap. Per epoch the relative powers in the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-20 Hz) band were calculated. Spectral variability was determined by the coefficient of variation (CV), calculated as the standard deviation (StD) of the relative power over the 14 epochs divided by the mean relative power. Spectral variability was calculated in each frequency band for the average of all 19 (A1 and A2 excluded) EEG electrode derivations and for 3 scalp regions: frontal (Fp1, Fp2, F7, F3, Fz, F4, F8), central (T7, C3, Cz, C4, T8) and parieto-occipital (P7, P3, Pz, P4, P8, O1, O2). Complexity in the time domain was represented by the approximate entropy (ApEn), for which window length 'm' was 1 and tolerance 'r' was 0.25 times the StD.[3] Statistical analyses of patient characteristics were performed in SPSS (IBM SPSS, version 20, New York, U.S.A.) using Chi-square, Fisher exact, Mann-Whitney U or T-tests where appropriate. All other analyses were conducted in Matlab (Version 7.9.0.529, The MathWorks Inc, Natick, Massachusetts U.S.A). Bonferoni correction was applied by dividing 0.05 by the number of comparisons (20). P-values smaller than 0.0025 were considered statistically significant.

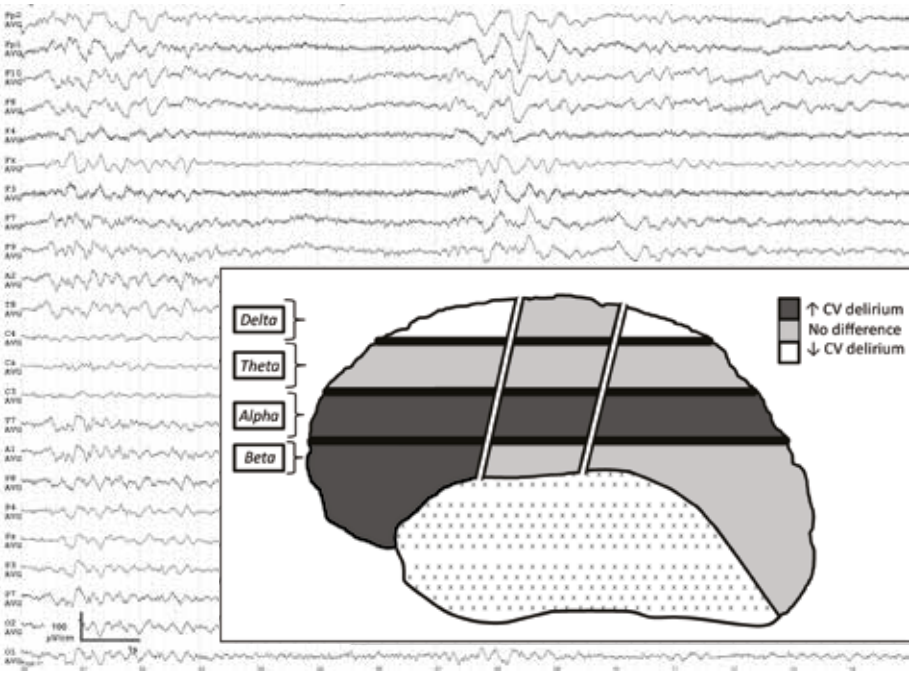
Delirious patients did not differ from non-delirious patients in age (mean±StD 76±5.7 vs. 74±8.6 years; p = 0.21), gender (n = 14 males vs. n = 16 males; p = 0.81), or use of morphinomimetics (n = 8 vs. n = 10; p = 0.70), benzodiazepines (n = 7 vs. n = 6; p = 0.64) and clonidine (n = 3 vs. n = 0; p = 0.06) in the 24 hours preceding the EEG. Use of haloperidol significantly differed between delirious and non-delirious patients (n = 16 vs. n = 2; p<0.001). Two patients categorized as non-delirious had been delirious two days before the EEG recording and still received haloperidol at a tapered dose.

Delirious patients showed an increase of CV (median (inter quartile range (IQR)) averaged over all 19 derivations, in the alpha band (delirium 0.25 (IQR 0.23-0.34) vs. non-delirium 0.16 (IQR 0.13-0.25); $p = 6*10^{-4}$) and beta band (0.28 (IQR 0.23-0.36) vs. 0.20 (IQR 0.15-0.24); $p = 3*10^{-4}$). The CV in the alpha band was increased in all three scalp regions, while the CV in the beta band was only increased in the frontal region. The CV in the delta band was decreased in the frontal and parietal-occipital regions during delirium (Figure I). The ApEn averaged over all 19 derivations was lower during delirium (0.17 (IQR 0.15-0.22)) compared to non-delirium (0.28 (IQR 0.26-0.30); $p = 3*10^{-8}$), as in the 3 scalp regions: frontal (0.17 (IQR 0.13-0.24) vs. 0.25 (IQR 0.23-0.28); $p = 8*10^{-6}$), central (0.19 (IQR 0.16-0.22) vs. 0.31 (IQR 0.30-0.36); $p = 5*10^{-7}$) and parietal-occipital (0.16 (IQR 0.15-0.20) vs. 0.27 (IQR 0.25-0.31); $p = 8*10^{-10}$). There were no significant differences in CV or ApEn between delirious patients with haloperidol and delirious patients without haloperidol.

In conclusion, the EEG during delirium shows increased variability in the spectral domain and decreased complexity. This decreased complexity is similar to findings in Alzheimer disease[4] and does not contradict the simultaneous increase in variability, as ApEn is sensitive to non-stationarities (phase shifts) in the signal that do not affect the spectral density.[5] It seems that during delirium brain activity varies between 2 or more states that differ in spectral EEG characteristics, causing increased spectral variability. One or both of these states during delirium may still be more deterministic than in the normal brain and thereby result in an overall decreased complexity. This reduced complexity is characteristic for neural systems with decreased capacity for information processing which translates into decreased cognitive capacity.[5]

Although, delirious patients show increased spectral variability, they have less complex EEG signals, implicating a decreased cognitive capacity. These results fit with the clinical description of delirium as a fluctuating disorder with disturbances in attention and cognition.

FIGURE I *Example of EEG recording during delirium and comparison of the CV between delirium and non-delirium for different frequency bands and different scalp regions.*



The EEG shows periods with fluctuating increased delta activity typical for delirium. Inlay: CV was determined for three scalp regions separately ('Frontal', 'Central', 'Parieto-occipital') and four frequency bands (delta, theta, alpha, beta). The grey scale indicates a significant increase (dark grey), no significant change (light grey) and a significant decrease (white) in delirium versus non-delirium. During delirium, CV in the alpha band was significantly increased in all three scalp regions, while CV in the beta band was only increased in the frontal region. CV in the delta band was significantly decreased in the frontal and parieto-occipital regions.

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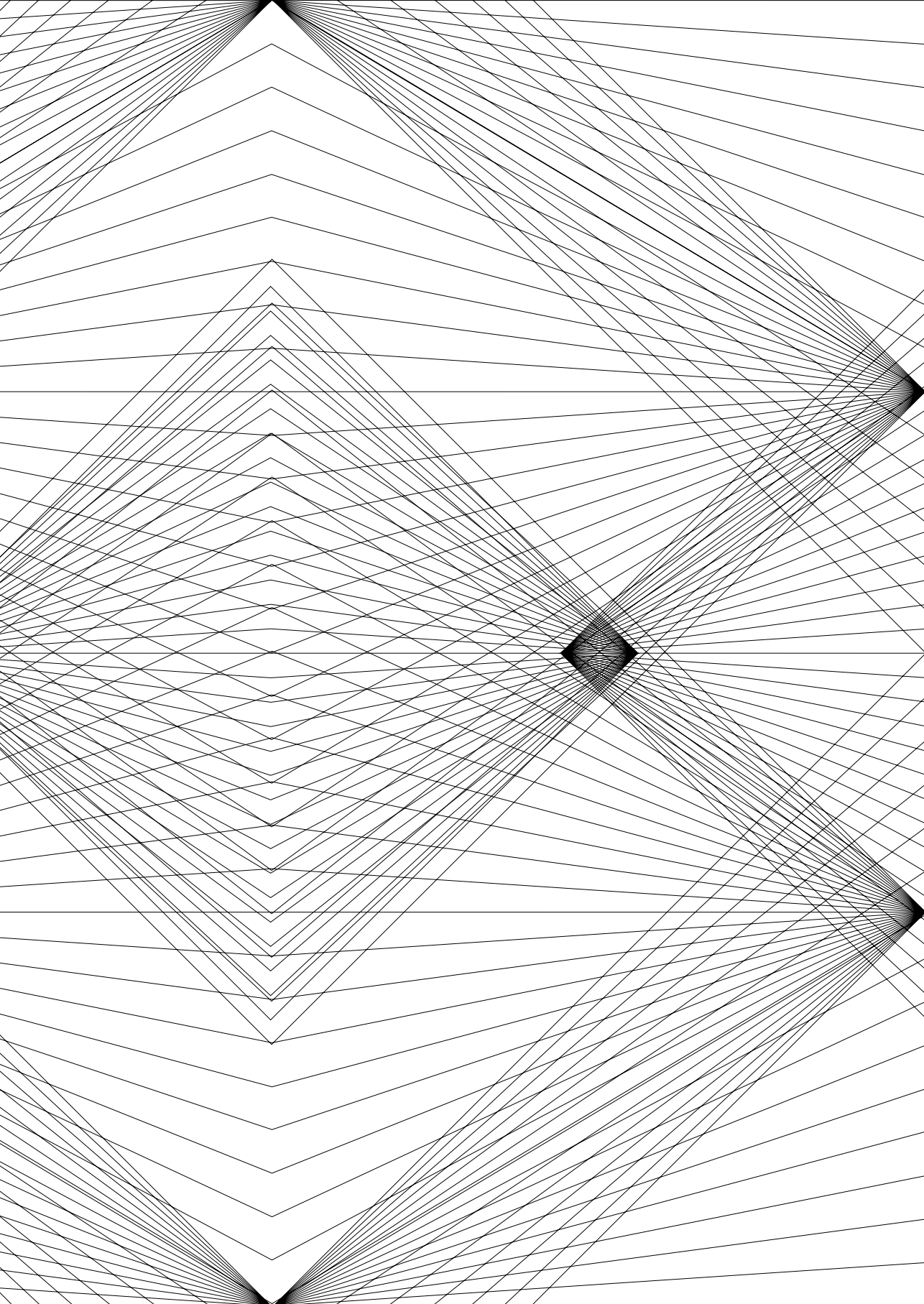

◆ CHAPTER 4 ◆

HEART RATE VARIABILITY IN INTENSIVE CARE UNIT PATIENTS WITH DELIRIUM

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ACCEPTED FOR PUBLICATION IN THE JOURNAL
OF NEUROPSYCHIATRY AND CLINICAL NEUROSCIENCES

ABSTRACT

Sympathovagal balance, assessed with heart rate variability (HRV), may be altered in intensive care unit (ICU) delirium. HRV was measured in the frequency domain (low-frequencies (LF) = 0.04-0.15Hz and high-frequencies (HF) = 0.15-0.40Hz) with HF in normalized units (HFnu) to evaluate parasympathetic tone and LF:HF ratio for sympathovagal balance. We assessed 726 ICU patients and excluded patients with conditions affecting HRV. No difference could be found between patients with (n = 13) and those without (n = 12) delirium by comparing the mean (±standard deviation) of the HFnu (75±7 versus 68±23) and the LF:HF ratio (-0.7±1.0 versus -0.1±1.1). Our study suggests that autonomic function is not altered in ICU delirium.

INTRODUCTION

Delirium is a common disorder in Intensive Care Unit (ICU) patients and described to be an independent risk factor for death.[1,2] The underlying mechanism for this increased mortality remains unclear. The phenomenology of delirium suggests an altered sympathovagal balance. Symptoms of hypertension and tachycardia, suggest increased sympathetic activity, whereas lethargy may be associated with increased parasympathetic activity. However, up until now, autonomic function has never been investigated in patients with delirium.

The activity of the autonomic nervous system can be assessed indirectly by measurement of heart rate variability (HRV).[3] With HRV analysis, changes in the time interval between two consecutive heart beats are computed. Healthy physiologic states contain some degree of random variability in heart rate intervals.[4] As a decrease in HRV was found to be an independent risk factor for death in ICU patients,[4] and delirium is associated with increased mortality,[1, 2] we hypothesized that delirium is related with decreased HRV. The aim of this study was to investigate HRV in ICU patients with and without delirium.

PATIENTS AND METHODS

DESIGN AND PATIENTS

This prospective, observational study was performed in the 32-bed mixed ICU of the University Medical Centre Utrecht (the Netherlands) in a convenient sample. A waiver for informed consent was obtained from the local Medical Ethics Committee (Institutional Review Board number 10-181). All patients were informed of the purpose and measurements of the study, the confidentiality of the data being collected and about their right to refuse to participate.

Patients aged 30 to 80, admitted for more than 24 hours, were eligible for inclusion. Exclusion criteria were those conditions with expected or profound autonomic dysfunction: a history of any neurological disease, diabetes mellitus, end stage renal failure, chronic obstructive pulmonary disease Gold stage IV, depression or anxiety disorder, coronary artery disease, heart transplantation and severe sepsis. Additionally, patients with pre-existing or new-onset cardiac arrhythmias or those receiving any adrenergic blocking agents or – agonists were excluded.

DATA COLLECTION

Demographic data was collected at inclusion. Co-morbidity at hospital admission was registered with the Charlson Co-morbidity Index.[5] Severity of illness at ICU admission was assessed using the Acute Physiology and Chronic Health Evaluation version (APACHE) IV score.[6] The Sequential Organ Failure (SOFA) score was used to estimate the severity of illness.[7]

Eligible patients were screened for delirium using the Dutch version of the confusion assessment method for the ICU (CAM-ICU) by a trained physician.[8] In case of doubt, a neurologist (AJCS) was consulted who applied the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, criteria for delirium, based on clinical assessment for cognitive dysfunction and a review of the medical charts.[9] Additionally, the Richmond Agitation and Sedation Score (RASS)[10] was used to classify different delirium subtypes.[11] Hypoactive delirium was defined in persistent neutral or negative RASS scores (ranging from 0 to -3).[11] Hyperactive delirium was present in patients with all positive RASS scores (ranging from +1 to +4).[11] When both positive and negative RASS values were scored, patients were classified as having mixed-type delirium.[11]

Bipolar chest lead electrocardiogram (ECG) was recorded in each patient for 15 minutes. In 10 patients, data was acquired for 2 days at 4 time points (08:00AM, 11:00AM, 14:00AM, 17:00AM) during the day to assess circadian influence. As no circadian rhythm could be shown, data from all time points for a particular patient could

be pooled. Therefore, subsequently included patients could be measured less frequently with a minimum of 1 measurement to increase feasibility. During HRV measurements, every effort was made to keep the environmental conditions stable throughout data acquisition. All patients were in a temperature controlled room in supine position. During HRV assessment, there were no interventions or changes in ventilator settings. Only patients who were delirious at the moment of the HRV measurements were included in the analysis.

All data were sampled at 500 Hz and monitored on-line (software Poly 5, Physiological Analysis Package, Inspector Research Systems, Amsterdam, the Netherlands). During off-line analyses, we verified all heartbeats detected by the software, and manually corrected the software algorithm when necessary. From each 900 seconds recording, a maximum of three 300 seconds time series were obtained that were devoid of artefacts and of ectopic heartbeats. When no 300 seconds period was available, we used at least 180 seconds periods, which has been described as sufficient.[3, 12] The power spectrum of the tachogram was computed using fast-fourier transformation. For analysis of the power spectrum, fixed frequency bands were used, according to the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[3] Very low frequencies (VLF) were defined as frequencies < 0.04 Hz , low frequencies (LF) as frequencies between 0.04-0.15 Hz and high frequencies (HF) as frequencies between 0.15-0.40 Hz.[3] The area under the power spectral curve is considered the total power (TP).[3] Because of differences in spectral power between patients, HF power was converted to normalized units, (nu) calculated as HFnu = HF/ (TP – VLF) x 100. LFnu was not calculated as it is reciprocal to HFnu and would not provide additional information.[3] It has been shown that the LF is a measure for activity of both the parasympathetic and the sympathetic system, whereas the HF and thus HFnu are solely measures of parasympathetic activity.[3] The LF:HF ratio reflects sympathovagal balance and is therefore a measure for increased or decreased HRV.[3]

STATISTICAL ANALYSIS

Because the HRV frequency domain parameters are known to be skewed, we used log-transformed data of the LF power, HF power and LF:HF ratio for statistical analysis. Differences between groups were assessed using Fisher's Exact test, Student's T-test, Kruskal-Wallis test or Mann-Whitney U test where appropriate. Multivariable linear regression was used to evaluate the effect of delirium on HRV independent from age, gender and severity of disease. Statistical tests were performed against 2-sided alternatives and p-values < 0.05 were defined as being significant. Statistical analysis were performed using R version 3.0.1 and SPSS (SPSS 20, IBM, New York, USA).

RESULTS

A total of 726 patients were screened of whom 694 were excluded for analysis. In total, 32 patients were enrolled for HRV recording. In two patients no 180 seconds intervals could be obtained due to frequent ectopic heartbeats. After careful examination of the medical charts we had to exclude 5 patients from our study population due to a history of myocardial infarction (n = 1) or coronary artery disease (n = 3), and because one patient was about to develop a new septic episode (n = 1). Therefore, our final study population included 13 patients with delirium and 12 patients without delirium. Patients with delirium were slightly older, had little higher SOFA scores and included more females, than patients without delirium, although this did not reach statistical significance. Other clinical characteristics of the study population did not differ between the two groups, as shown in Table I. Within the 13 delirious patients, hypoactive delirium was the most common motoric subtype, present in 7 (54%). Hyperactive delirium was present in 2 patients (15%) and in 4 (31%) patients mixed-typed delirium was observed.

Patients with delirium and those without delirium had a similar respiratory rate during the HRV measurements ($t_{(23)} = -0.23$, $p = 0.82$). There was no difference in mean (± Standard deviation) HFnu between patients with delirium (67±20) and without (57±21), $t_{(23)} = -1.18$, $p = 0.25$ (Figure IA). Further, no significant differences in log transformed HRV parameters were found between patients with and without delirium: mean (±Standard deviation) LF (2.8±1.9 respectively 3.1±1.9, $t_{(23)} = 0.31$, $p = 0.76$), HF (3.7±1.7 respectively 3.4±2.1, $t_{(23)} = -0.34$, $p = 0.73$) and LF:HF ratio (after log transform: -0.7±1.0 respectively -0.1±1.1, $t_{(23)} = 1.46$, $p = 0.16$, before log transform see Figure IB). Multivariable regression analysis showed no influence of delirium on HFnu or LF:HF ratio with coefficients (95% confidence interval) of 11.9 (-7.2 to 30.9) and -0.7 (-1.6 to 0.3) respectively. No differences in HFnu and LF:HF ratio were observed between delirium subtypes ($h_{(2)} = 2.44$, $p = 0.30$ and $h_{(2)} = 1.97$, $p = 0.37$, Figure II).

TABLE I *Study population*

CLINICAL CHARACTERISTICS	NO DELIRIUM (N=12)		DELIRIUM (N=13)		STATISTICAL TEST (DF)	P-VALUE
Age, mean (SD)	57	(16)	67	(12)	$t_{(23)}$= -1.76	0.09
Male gender, n (%)	11	(92%)	7	(54%)	*	0.07
BMI; kg/m2, median (IQR)	25	(24-26)	25	(23-26)	$MWU_{(25)}$=78.5	0.98
APACHE IV, median (IQR)	74	(37-82)	74	(62-85)	$MWU_{(25)}$=96.0	0.35
CCI, median (IQR)	1	(0-3)	1	(0-3)	$MWU_{(25)}$=76.0	0.94
Admitting discipline, n (%)						
- General medicine	7	(58%)	5	(38%)	*	0.43
- Surgery	5	(42%)	8	(62%)		
ICU LOS at study inclusion, median (IQR)	4	(3-8)	9	(4-22)	$MWU_{(25)}$=103.5	0.17
Mean SOFA during measurements, mean (SD)	3	(2)	5	(2)	$t_{(23)}$= -1.68	0.11
Mechanical ventilation during measurements, n (%)	6	(50%)	9	(69%)	*	0.43
Agitation during measurements, n (%)	3	(25%)	6	(46%)	*	0.41
Sedation during measurements, n (%)	2	(16.6%)	3	(23%)	*	1.00
Median RASS during measurements, median (IQR)	0	(0-0)	-0.5	(-1.5 - 1.0)	$MWU_{(25)}$=77.0	0.98

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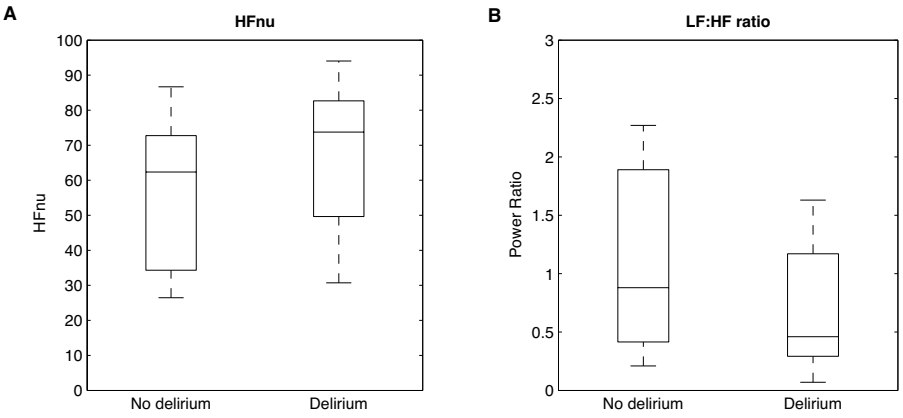
Delirium subtype, n(%)				
- Hypoactive Delirium	-		7	(54%)
- Hyperactive Delirium	-		4	(31%)
- Mixed-type Delirium	-		2	(15%)
Admitting diagnosis, n (%)				
- Primary respiratory failure	2	(16.7%)	2	(15%)
- Pneumonia	2	(16.7%)	3	(23%)
- Haemorrhage	3	(25%)	3	(23%)
- Trauma	2	(16.7%)	1	(8%)
- Postoperative GI surgery	1	(8.2%)	1	(8%)
- Infection, other	2	(16.7%)	3	(23%)

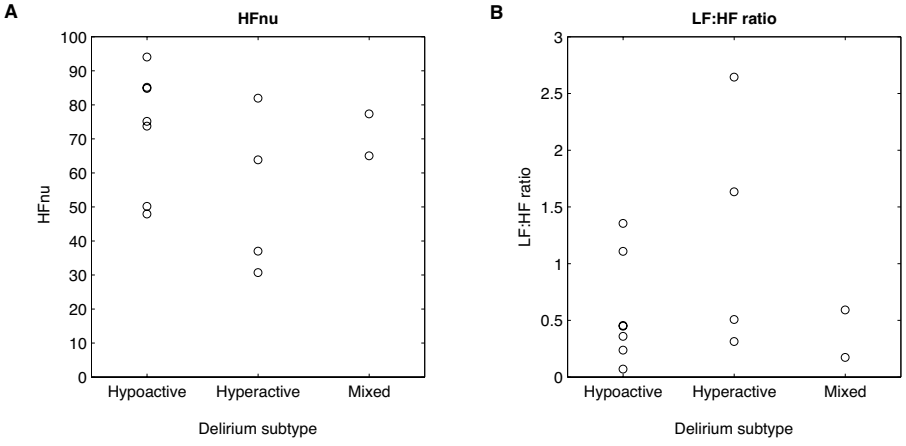
APACHE = Acute Physiology and Chronic Health Evaluation; BMI = Body Mass Index; CCI = Charlson Co-morbidity Index; DF = degree(s) of freedom; GI = Gastro-intestinal; ICU = Intensive Care Unit; IQR = Inter Quartile Range; MWU = Mann-Whitney U test statistic; LOS = Length of Stay; SD = Standard Deviation; SOFA = Sequential Organ Failure Assessment. * Proportions were compared with Fisher's exact test.

FIGURE I *Heart Rate Variability in ICU patients with and without delirium*



HF, high frequency; ICU, Intensive Care Unit; LF, low frequency; nu, normalized unit

FIGURE II *Heart Rate Variability in ICU patients with different subtypes of delirium*



HF, high frequency; ICU, Intensive Care Unit; LF, low frequency; nu, normalized unit

DISCUSSION

This study suggests that HRV is not different between ICU patients with and without delirium. These findings contrast with our hypothesis of a decrease in HRV. Our hypothesis was based on the phenomenology of delirium, which suggests altered sympathovagal balance. Moreover a decreased HRV is associated with increased vagus nerve activity, which limits the innate immune respons.[13, 14] Excessive or persistent activation of this cholinergic anti-inflammatory pathway might lead to an immune-suppressed state that renders the body vulnerable to infection and therefore increased mortality.[13, 14]

To our knowledge, this is the first study assessing HRV in delirium. The extensive list of exclusion criteria ensured a homogeneous population of patients. Because of this homogeneity, we could be sure that any difference in HRV could only be explained by the presence of delirium. Unfortunately, our study is limited by the small number of included patients. Due to the list of exclusion criteria we expected a priori less variance between individuals within the two groups. More specifically, with HFnu effect size of 10±13.5, instead of the observed 10±20 and alpha of 0.05, 15 patients in both arms would have been sufficient to reach a power of 0.80. Indeed, the number of included patients is comparable with other explorative studies on HRV.[15, 16] In our study, patients with delirium were on average slightly older, included more often females and had higher SOFA scores. Increased age has been linked to higher LF:HF ratios,[17] while female gender and higher severity of disease has been associated with lower LF:HF ratios.[4, 17] Importantly, when we adjusted for age, gender and severity of disease, our findings did not change.

In conclusion, this study suggests that the increased mortality that is associated with delirium, is unlikely to be due to an altered sympathovagal balance.

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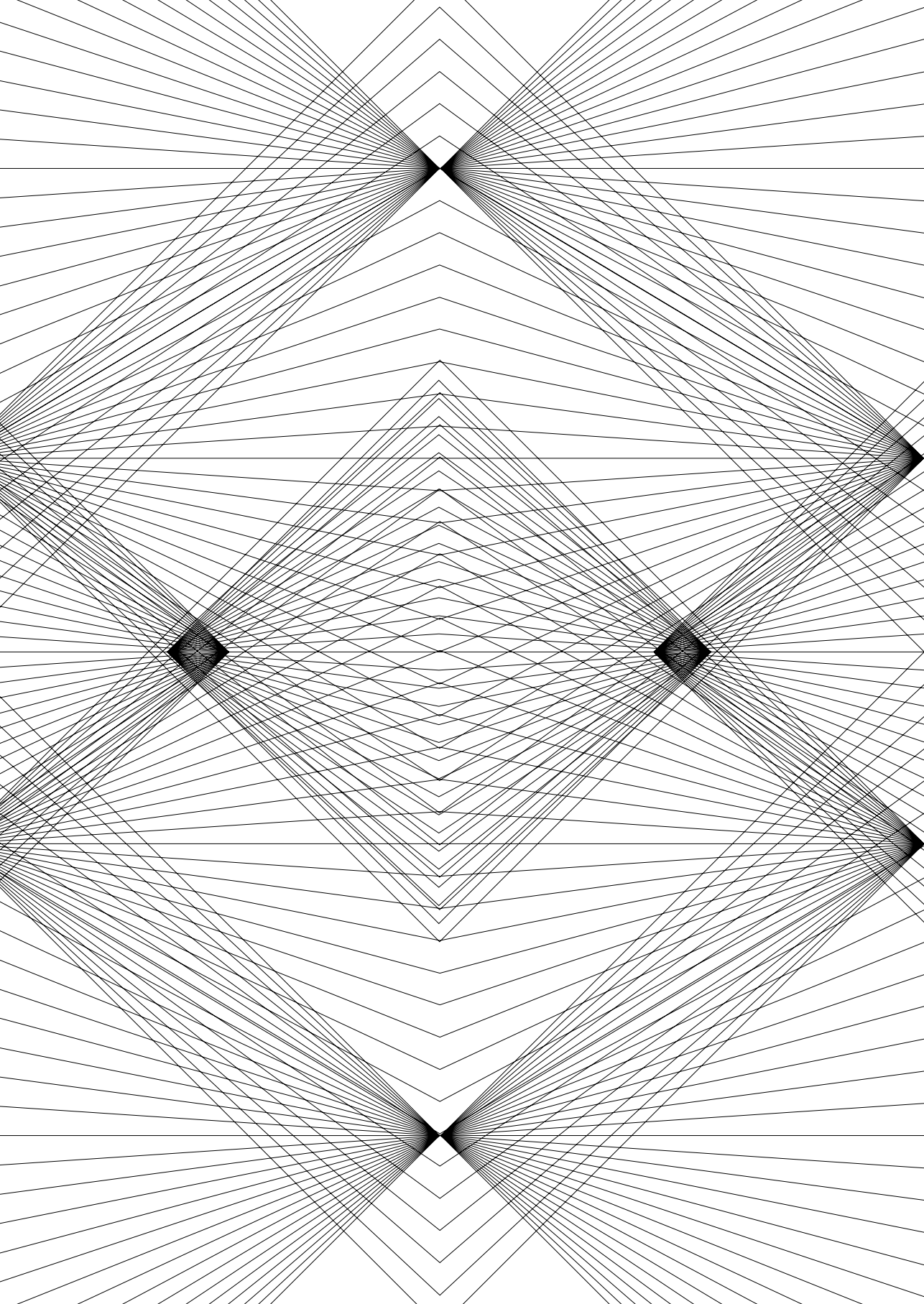
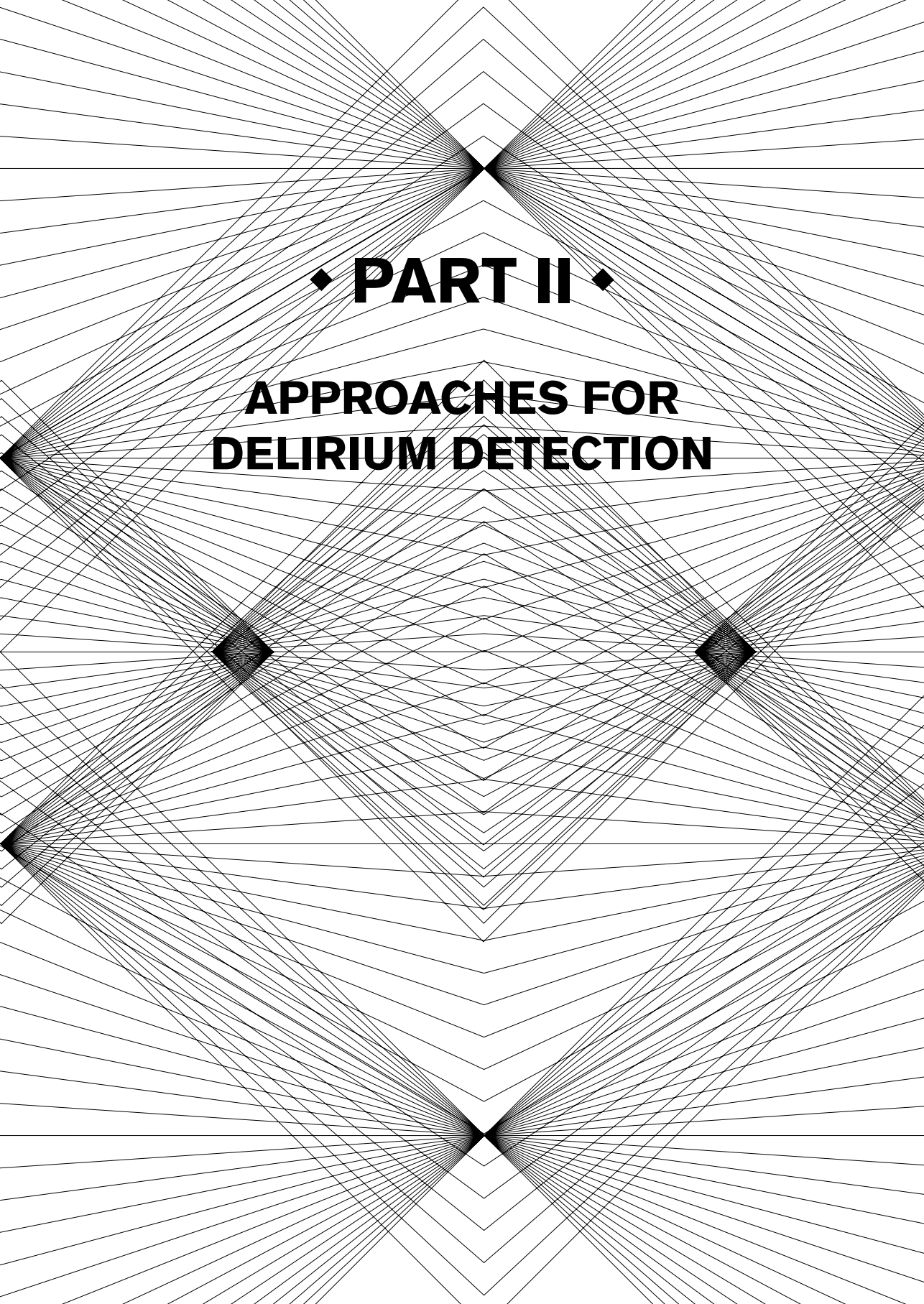
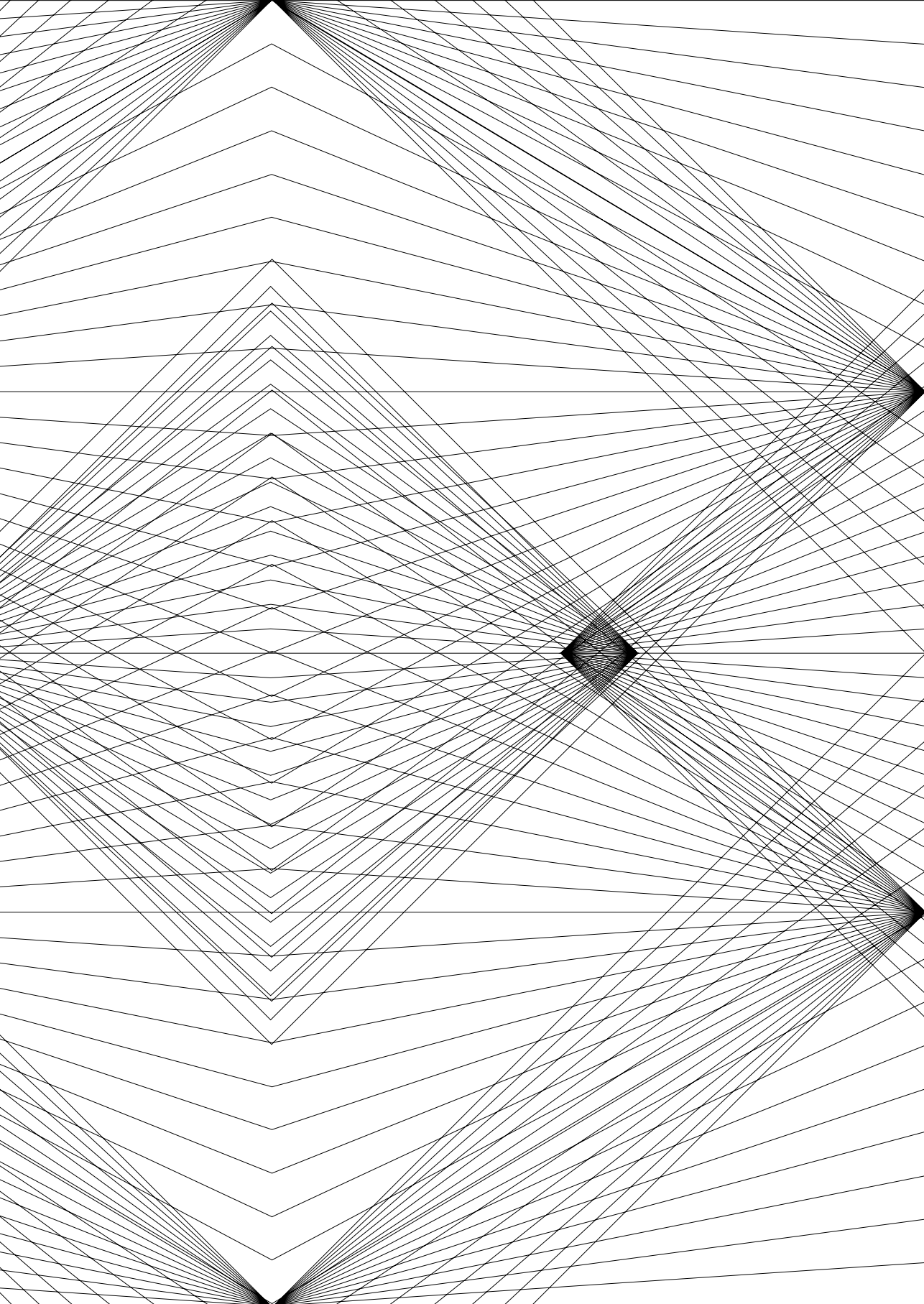




PART II

APPROACHES FOR DELIRIUM DETECTION



◆ CHAPTER 5 ◆

WHAT ARE THE OPPORTUNITIES FOR EEG-BASED MONITORING OF DELIRIUM IN THE ICU?

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ABSTRACT

Recognition of delirium in intensive care unit (ICU) patients is poor, despite the use of screening tools. Electroencephalography (EEG) with a limited number of electrodes and automatic processing may be a more sensitive approach for delirium monitoring. A systematic literature search was conducted on EEG characteristics that define delirium. We detected 14 studies, which were predominantly conducted in elderly patients. The relative power of the theta and alpha frequency band most often (7/14 studies) distinguished delirious from non-delirious subjects. Given the feasibility for continuous EEG monitoring in ICU, EEG delirium monitoring in ICU patients is promising.

INTRODUCTION

Delirium is an acute or subacute disturbance of consciousness, cognition and attention that usually fluctuates over time.[1] It is a common disorder in the intensive care unit (ICU) with a reported incidence up to 80% during ICU stay.[2, 3] Delirium is associated with higher mortality, longer hospital stay, more long-term cognitive impairment and increased costs.[4-8] Despite its frequency and impact, recognition of delirium by ICU physicians is poor (sensitivity 29%).[9] Therefore, the Society of Critical Care Medicine (SCCM) and the American Psychiatric Association (APA) recommend daily monitoring of delirium in ICU patients to improve early diagnosis and treatment.[10, 11] Various delirium assessment tools have been developed for use by non-psychiatric personnel. Of these tools, the Confusion Assessment Method for the ICU (CAM-ICU) showed highest sensitivity in a research setting, ranging from 64 to 97 %.[9, 12] However, in routine, daily practice the sensitivity of the CAM-ICU appeared to be much lower (47%).[13] Sensitivity of hypoactive delirium was particularly poor (31%), which is the subtype most difficult to recognize by ICU physicians.[9, 13] In this multicentre study, 282 patients were assessed by teams of three delirium experts including psychiatrists, geriatricians and neurologists, who based their assessment on cognitive examination, inspection of medical files and established criteria1 for delirium.[13] The low sensitivity of the CAM-ICU in daily practice hampers early detection of delirium. Other drawbacks of the CAM-ICU are that it cannot quantify delirium severity and that it assesses delirium at a certain moment in time,[12] while delirium may fluctuate considerably over the day.[1] These factors impede recognition and thereby delay treatment. Delayed treatment of delirium was found to be related with mortality.[14] Therefore, an objective detection tool for continuous monitoring of delirium is needed.

Another approach to detect delirium is by monitoring physiological alterations. Delirium is a manifestation of encephalopathy, although these terms are sometimes used interchangably. Since decades it is known that during delirium, electroencephalography (EEG) shows generalized slowing of background activity.[15] Recently, continuous EEG monitoring with automatic processing has become technically feasible.[16] An example is the assessment of the depth of anesthesia, which can be monitored with a limited number of EEG electrodes.[17] In ICU patients, continuous EEG monitoring is increasingly used to detect non-convulsive, epileptic seizures.[18] EEG based encephalopathy monitoring with a limited number of electrodes and automatic processing, is therefore feasible. It is however currently unclear which EEG characteristic is particularly altered in delirium, and which EEG lead is most informative. In this systematic review, we aimed to explore which parameter and which EEG lead show the largest difference between delirious and non-delirious patients.

METHODS

SEARCH STRATEGY

We systematically searched literature on delirium and EEG on November 25th 2011 using the databases of Embase (January 1980 to November 2011) and Pubmed (January 1966 to November 2011). Synonyms for delirium and corresponding Mesh terms were combined with search terms for EEG synonyms and Mesh terms as can be seen in Table I and II in appendix 1. Resulting English, French, German and Dutch scientific articles on humans were imported into reference manager (Reference manager professional edition version 11, Thomson ISI ResearchSoft). The reference lists of all full text articles were also screened and relevant publications were imported into the database.

SELECTION OF STUDIES

The results of the literature search were evaluated independently by two authors (AWvdK, RJvdW). Based on title and abstract, we excluded case reports, animal studies, reviews, letters and studies in children. Furthermore, articles that described the EEG of delirious subjects only in a descriptive way were excluded. Moreover, when the statistical significance of the difference in quantitative EEG characteristics between delirious and non-delirious subjects was not tested, articles were also excluded, unless the statistical significance could be determined based on the published data. All eligible studies were retrieved in full text. The reference lists of all full text articles were also screened, following the same criteria used for screening titles and abstracts. In case of disagreement between the two authors, references were evaluated by three authors (AWvdK, RJvdW, AJCS) to reach consensus on inclusion for this systematic review.

DATA EXTRACTION

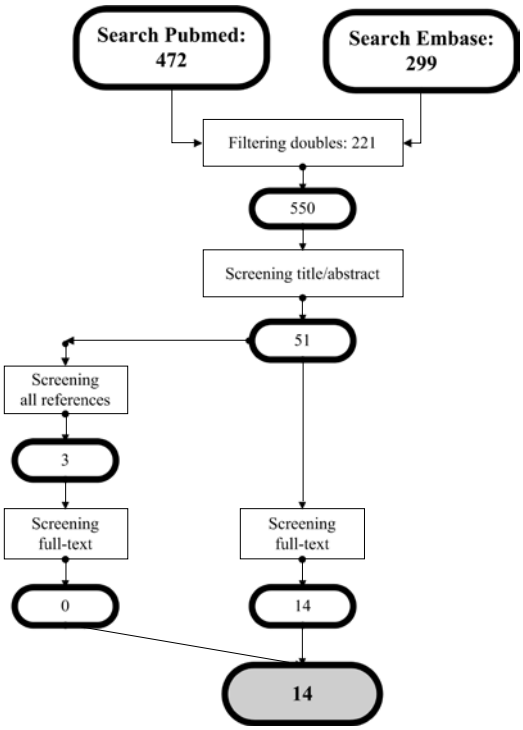
The selected full-text articles were closely reviewed, and the first author, title and year of publication were noted. Furthermore, the following features were tabulated: size and characteristics of the study population, methods to diagnose delirium, time between delirium diagnosis and EEG recording, EEG derivations for quantitative EEG analysis, use of artifact free or raw data for quantitative EEG analysis, length of EEG period used for quantitative analysis, studied EEG parameters and differences between patients with and without delirium with regard to these EEG parameters that reached statistical significance ($p<0.05$). Background information concerning quantitative EEG parameters can be found in appendix 2. For those articles in which the statistical significance had to be determined based on the published data, a student's t-test was used to compare delirious subjects to non-delirious subjects. When data were not normally distributed, a Mann-Whitney U test was used.

RESULTS

LITERATURE SEARCH

The literature search resulted in 550 eligible publications (Figure I). The search term "encephalopathy" combined with "EEG" was also considered, and resulted in a large number of articles (2420 in Pubmed and 1627 in Embase). When we screened in Pubmed as in Embase 100 articles on EEG and encephalopathy, we did not find any additional publications. Therefore, encephalopathy was not further used as a search term. After excluding 499 articles based on title and abstract, 51 papers were selected and retrieved in full text. By screening the references of these articles, 3 extra full text articles were selected and retrieved. As we excluded another 40 publications, 14 articles fulfilled inclusion- but not exclusion criteria. Two of these did not describe the statistical significance of the differences between delirious and non-delirious subjects. This was computed using the published data.[15, 19]

FIGURE I *Summary of literature search concerning delirium and quantitative EEG*



STUDY CHARACTERISTICS

The study populations of the included publications are described in Table III in appendix 3. The number of included delirium patients per publication varied between 10 and 51 subjects, whereas one article did not mention which fraction of the population was delirious.[20] Six of the 14 studies were conducted in elderly patients (mean age above 75 years) and 3 in ICU patients (Table III appendix 3). Four studies compared delirious, demented patients to demented patients without delirium or to patients without dementia and delirium.[15, 21-23] Delirium was diagnosed in the majority of studies (9 out of 14) by a psychiatrist using criteria of various editions of the Diagnostic and Statistical Manual of Mental Disorders.[21-29] In 3 publications the CAM-ICU was used to diagnose delirium.[20, 30, 31] One study used patient records to diagnose delirium[15] and another one the diagnosis of the ward physician.[19]

The time frame between the delirium diagnosis and EEG recording varied considerably among the different investigations. In 3 of these the delirium diagnosis and EEG recording were performed at almost the same time.[20, 27, 30] Three other investigations mentioned a time frame of 4-5 hours,[22, 23, 31] and another 3 of maximal 24 hours.[21, 26, 29] In the other 5 investigations the time frame was not reported.[15, 19, 24, 25, 28] The duration of EEG recording for quantitative analyses varied between 30 and 600 seconds, and was not specified in one publication.[28] The EEG derivations used for recording were in two publications not specified.[28, 31] In 5 studies only posterior (parietal-occipital) derivations were used.[22-26]

EEG CHARACTERISTICS

As shown in Table III in appendix 3, the most frequently studied variable was the relative power of the alpha frequency band (8 out of 14 studies), next to the relative power of the theta frequency band (7/14), the relative power of the delta frequency band (5/14) and the peak frequency (5/14).

The relative power of the theta frequency band was significantly different between delirious and non-delirious patients in all seven studies that investigated this variable. However, in two of these seven publications, only the lower part of the theta frequency band was significantly increased in delirium and not the higher part of the frequency band.[22, 23] The relative power of the alpha frequency band was related to delirium in 7 out of 8 studies. One of these studies showed an increase in the relative power of the theta and a decrease in the relative power of the alpha frequency band in several groups of delirious patients, but not in delirious Parkinson's disease patients.[21] Two studies showed that the relative power of the theta, the alpha and also the delta frequency band, were not only different between delirious and not delirious patients, but also within patients before and during an episode of delirium.[24, 25]

Other variables that often differed between delirious and non-delirious patients included the relative power of the delta frequency band (increased in delirium in 5/5 investigations that studied this) and the peak frequency (decreased in delirium in 4/5 investigations that studied this, Table III appendix 3). Two studies focused on bispectral index (BIS) EEG monitoring during delirium. In both studies, the BIS was significantly decreased in delirium patients as compared to non-delirious controls.[20, 30] However, one study noted that after controlling for level of arousal, BIS could not distinguish between the presence or absence of delirium.[20]

DISCUSSION

To develop EEG-based delirium monitoring with a limited number of electrodes and automatic processing, it is essential to know which parameter and which EEG lead show the largest difference between delirious and non-delirious patients. We evaluated various EEG parameters. Of these, the relative power of the theta frequency band was most frequently studied and without exception different between delirious and non-delirious subjects. Investigations on quantitative EEG and delirium were mostly conducted in elderly subjects and often used posterior EEG derivations only.

In order to perform continuous monitoring of delirium, a minimal number of electrodes are needed to increase feasibility and minimize the burden for the patient. Several publications mention that EEG changes in delirium are most prominent in the posterior regions, although this was not supported by original studies.[22-24] Furthermore, none of the 14 included studies determined at which EEG derivation the EEG changes in delirium were strongest.

All 14 included studies used rather short periods of artifact-free EEG data to determine EEG characteristics. Fluctuation of EEG characteristics during these periods was not considered, although fluctuation of EEG characteristics over several days was studied by a number of authors.[19, 24-27] Therefore, the exact relation between the clinical fluctuation of delirium and the EEG characteristics of delirium is still uncertain.

Because of these fluctuations,[1] it is important to diagnose delirium soon before or after the EEG recording. Therefore, a large time frame between delirium diagnosis and recording of EEG, is a serious shortcoming. In only three studies, the delirium diagnosis and EEG recording were performed at almost the same time.[20, 27, 30]

To allow continuous EEG monitoring of delirium, it is necessary to distinguish delirium from other conditions. Slowing of background activity occurs not only in delirium, but also in dementia and sleep.[23, 32] The reported prevalence of dementia is 17%

in intensive care unit (ICU) patients older than 65 years.[33] However, studies about the prevalence of dementia in the ICU are limited. In a recent multicentre study including 2116 ICU patients, a prediction model was developed for delirium in the ICU.[34] In this study 1.7% of the patients were suffering from dementia, and therefore dementia was excluded as a risk factor for the prediction model.[34] Moreover, patients with dementia are treated substantially less aggressively than patients without dementia and are less likely to be admitted to the ICU.[35] We suspect that in a general ICU population the prevalence is much lower than 17%, and is therefore less likely to affect EEG-based delirium monitoring in a general ICU. Furthermore, delirium and dementia can be distinguished, for example by recording an active (eyes constantly open) EEG. The upper half of the alpha and delta frequency band determined from an active EEG revealed to be of great importance for reliable discrimination between delirium and dementia.[23] However, deep sleep is also characterized by slow wave activity.[32] The 14 studies included in this review all measured EEG during wake or light sedation and did not compare EEG characteristics of delirium with EEG characteristics of physiological sleep. EEG in sleep, however, has certain characteristics like, k-complexes and sleep-spindles[32] which could be used to distinguish sleep from delirium, but this has not been investigated yet.

Despite an extensive literature search, only 14 articles could be detected on quantitative EEG in delirium patients. Delirium is a frequent and serious problem in the ICU, but almost half of the of quantitative EEG studies in delirium focuses on elderly non-ICU subjects. Furthermore, we could not consider medication use in the different studies, although medication as haloperidol, which is often used during delirium,[10] may influence the EEG. Several studies reported EEG changes in healthy volunteers during haloperidol use when compared to placebo. These changes were however not uniform. One study reported only a decrease in absolute power in the alpha frequency band after 3 mg of haloperidol, while another investigation reported an increase in alpha and beta root mean square after 1 mg of haloperidol.[36, 37] A third study described an increase in the relative power of delta and theta and decrease in the relative power of alpha frequency band after 3 mg of haloperidol.[38] Therefore the exact effect of haloperidol at a certain dose on the EEG is unknown.

Future studies should determine whether the relative power of the theta frequency band is indeed the most affected EEG characteristic. Furthermore, it is important to determine which EEG deviation is most sensitive for EEG changes related to delirium. If the most informative electrode deviations are known, one can limit the amount of electrodes needed for continuous monitoring. Next we should focus on continuous monitoring with a limited number of electrodes and determine the sensitivity of EEG-based delirium monitoring in a random sample of Intensive Care Unit patients over time.

In this study the fluctuating nature of delirium in relation to EEG characteristics can also be studied, as well as differentiation of delirium from sleep. Given the feasibility of continuous EEG monitoring for epilepsy in Intensive Care Unit patients, this seems to be a promising approach to overcome the underdiagnosis of current delirium screening tools.

Although, some aspects of EEG in relation to delirium still have to be addressed, continuous EEG monitoring offers opportunities. Delirium can be adequately diagnosed in different populations using EEG. The relative power of the theta frequency band is the most promising parameter to study in a future prospective investigation in ICU patients.

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APPENDIX 1: SEARCH STRINGS

TABLE I *Pubmed search for EEG and delirium*

	PUBMED	
NR	**SEARCH TERM**	**HITS**
1	"delirium" [Title/Abstract] OR "delirious" [Title/Abstract] OR "icu syndrome" [Title/Abstract] OR "intensive care syndrome" [Title/Abstract] OR "intensive care unit syndrome" [Title/Abstract] OR "delusion" [Title/Abstract] OR "delusions" [Title/Abstract] OR "delusional" [Title/Abstract] OR "factual" [Title/Abstract] OR "ICU psychosis" [Title/Abstract] OR "acute confusional state" [Title/Abstract] OR "brain failure" [Title/Abstract]	**16,446**
2	"Delirium"[Mesh]	**4,612**
3	#1 OR #2	**17,638**
4	"eeg" [Title/Abstract] OR "electroencephalogram" [Title/Abstract] OR "electroencephalography" [Title/Abstract] OR "brain waves" [Title/Abstract] OR "alpha rhythm" [Title/Abstract] OR "beta rhythm" [Title/Abstract] OR "delta rhythm" [Title/Abstract] OR "theta rhythm" [Title/Abstract]	**57,165**
5	"Electroencephalography"[Mesh]	**111,827**
6	#4 OR #5	**123,948**
7	#3 AND #6 AND [humans]/lim AND ([english]/lim] OR [french]/lim] OR [dutch/lim] OR [german]/lim])	**472**
	TOTAL	**472**

TABLE II *Embase search for EEG and delirium*

EMBASE		
NR	**SEARCH TERM**	**HITS**
1	'delirium':ab,ti OR 'delirious':ab,ti OR 'icu syndrome':ab,ti OR 'intensive care syndrome':ab,ti OR 'intensive care unit syndrome':ab,ti OR 'delusion':ab,ti OR 'delusions':ab,ti OR 'delusional':ab,ti OR 'factual':ab,ti OR 'icu psychosis':ab,ti OR 'acute confusional state':ab,ti OR 'brain failure':ab,ti	**21,894**
2	'eeg':ab,ti OR 'electroencephalogram':ab,ti OR 'electroencephalography':ab,ti OR 'brain waves':ab,ti OR 'alpha rhythm':ab,ti OR 'beta rhythm':ab,ti OR 'delta rhythm':ab,ti OR 'theta rhythm':ab,ti	**75,391**
3	#1 AND #2 AND [humans]/lim AND ([english]/lim] OR [french]/lim] OR [dutch/lim] OR [german]/lim])	**299**
	TOTAL	**472**

APPENDIX 2: QUANTITATIVE EEG

BACKGROUND QUANTITATIVE EEG

In quantitative electroencephalography (QEEG), multichannel recordings of EEG are visually or automatically edited to create a sample of artifact-free data. These artifact free-data samples are analyzed using the Fast Fourier Transform. With this technique the power can be quantified at each EEG frequency. The power represents the amount of EEG activity in a particular frequency band measured in μV^2.[1] Visually this can be represented in a *power spectrum*. The power spectrum of clinical interest is usually considered to extend from about 1.5 Hz to 20 Hz.[2] This frequency range has traditionally been separated into 4 frequency bands: delta (1.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-20 Hz).[1]

QUANTITATIVE EEG PARAMETERS

Absolute power

Amount of EEG activity in a particular frequency band measured in μV^2.[1]

BIS index

The Bispectral (BIS) index is determined from frontal EEG data using a complex mathematical algorithm.

Dominant/Peak frequency

Frequency with the maximal power.

Mean/Centroid frequency

The mean or centroid frequency is the frequency that divides the area of the spectrum into two equal parts.[3]

Peak power

Value of maximal power in certain frequency interval.

Relative power

Quotient between power in one frequency band and total power across all bands, expressed as a percentage.[1]

Spectral edge frequency

The frequency below which 95 percent the total power of a given signal is located.

α/θ or θ/α

Quotient of relative power of alpha and theta frequency bands.[1]

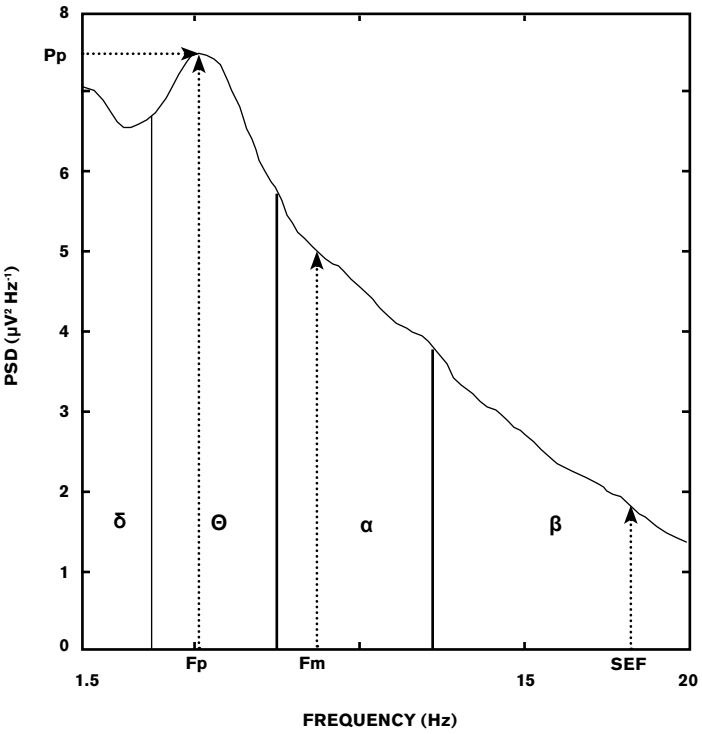
β+α/θ+δ

Quotient of the relative power of alpha plus beta frequency bands and the relative power of theta + delta frequency bands.[1]

% theta time/% alpha time

The ratio of wave output over time (wave % time) of theta waves (indicative of slowing of EEG activity) to alpha waves.[4]

FIGURE I *Power spectrum*



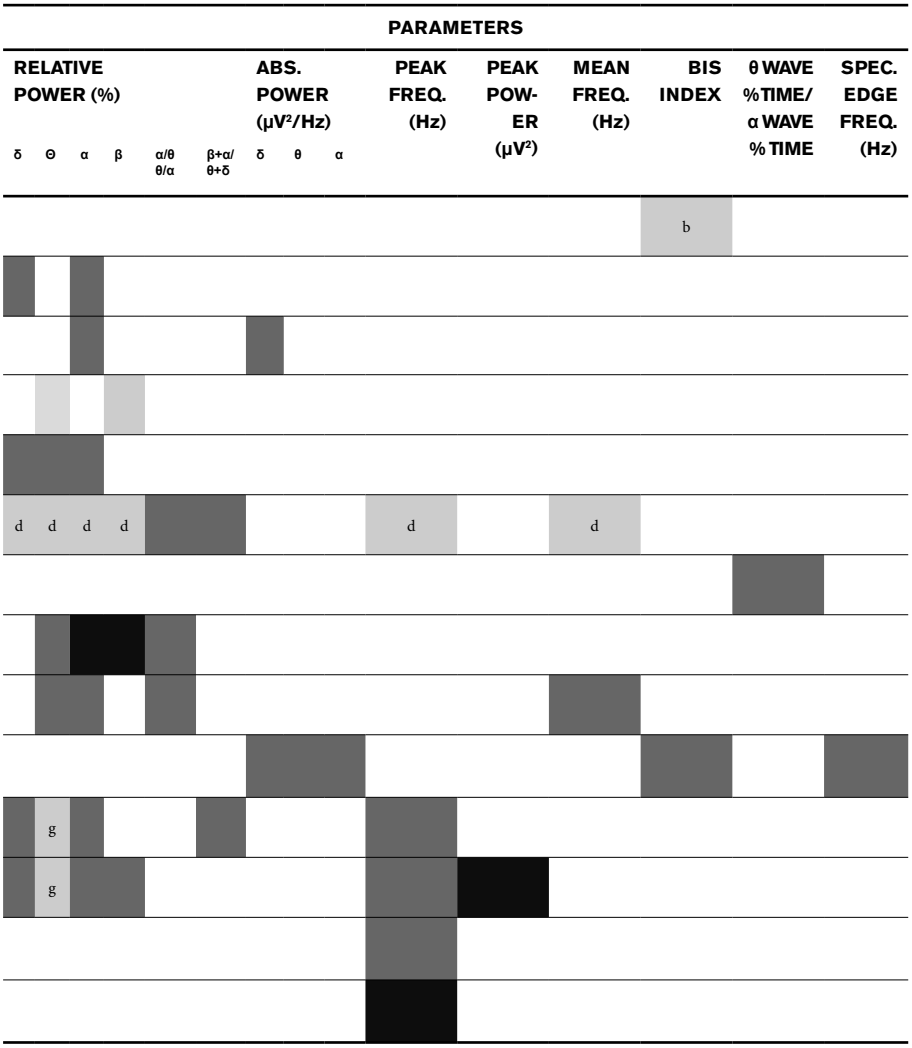
Definitions of abbreviations: PSD = Power Spectral Density; Pp = Peak Power; Fp = Peak Frequency; Fm = Mean Frequency; SEF = Spectral Edge Frequency.

APPENDIX 3: STUDY CHARACTERISTICS

TABLE III *Summary of reviewed articles*

ARTICLES		POPULATION			ANALYSIS
FIRST AUTHOR - *YEAR*	**TYPE**	**DELIRIUM (N)**	**NON-DELIRIUM (N)**	**DEMENTIA (N)**	**ANALYSIS PERIOD (S)**
ELY - *2004*[5]	ICU patients		124[a]		120
JACOBSEN - *1993*[6]	Elderly	8+10[c]	7	9	30-120
JACOBSEN - *1993*[7]	Elderly	15	8	10	30-120
KATZ - *1991*[8]	Elderly	10	18		40
KATZ - *2001*[9]	Elderly	12	35		40
KOPONEN - *1989*[10]	Delirium patients	51[d]	19		97.5
MATSUSHIMA - *1997*[4]	CCU patients	10	10		60
PLASCHKE - *2007*[3]	ICU patients	20	17		600
PLASCHKE - *2010*[11]	ICU patients	32	82		300
REISCHIES - *2005*[12]	Depressed patients	12[e]			42
THOMAS - *2008*[13]	Elderly	15[f]	15	31	200
THOMAS - *2008*[14]	Elderly	12[f]	13	23	100
TRZEPACZ - *1988*[15]	Liver transpl. patients	18	90		NM
TRZEPACZ -*1989*[16]	Liver transpl. patients	23	23		240

Colors indicate whether the parameter was significantly different between delirium and non-delirium, non-dementia patients: White = Not described; Black = Not statistically significant; Light grey = Parameter studied in several situations, for which at least one statistically significant; Dark grey = Statistically significant. Definitions of abbreviations: Abs = Absolute; CCU = Cardiac Care Unit; ICU = Intensive Care Unit; Spec = Spectral; NM = Not mentioned; Transpl = Transplantation patients. [a]Not specified which fraction of 124 patients was delirious. [b]Before controlling for arousal: significant, after: non-significant.



[c]8 delirium patients without dementia and 10 delirium patients with dementia. [d]12 delirium patients without central nervous system disorders, 30 with multi infarct dementia, 7 with Alzheimer's disease and 2 with Parkinson's disease. The Parkinson's disease patients showed non-significant differences when compared to non-delirium group. [e]Depressed patients before and after electro convulsive therapy. [f]Delirium patients with dementia. [g]Theta separated in 2 smaller frequency bands: θ1 (significant) and θ2 (not-significant).

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4. Matsushima E, Nakajima K, Moriya H, et al. A psychophysiological study of the development of delirium in coronary care units. Biol Psychiatry 1997;41:1211-7.
5. Ely EW, Truman B, Manzi DJ, et al. Consciousness monitoring in ventilated patients: bispectral EEG monitors arousal not delirium. Intensive Care Med 2004;30:1537-43.
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9. Katz IR, Curyto KJ, TenHave T, et al. Validating the diagnosis of delirium and evaluating its association with deterioration over a one-year period. Am J Geriatr Psychiatry 2001;9:148-59.
10. Koponen H, Partanen J, Pääkkönen A, et al. EEG spectral analysis in delirium. J Neurol Neurosurg Psychiatry 1989;52:980-5.
11. Plaschke K, Fichtenkamm P, Schramm C, et al. Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. Intensive Care Med 2010;36:2081-9.
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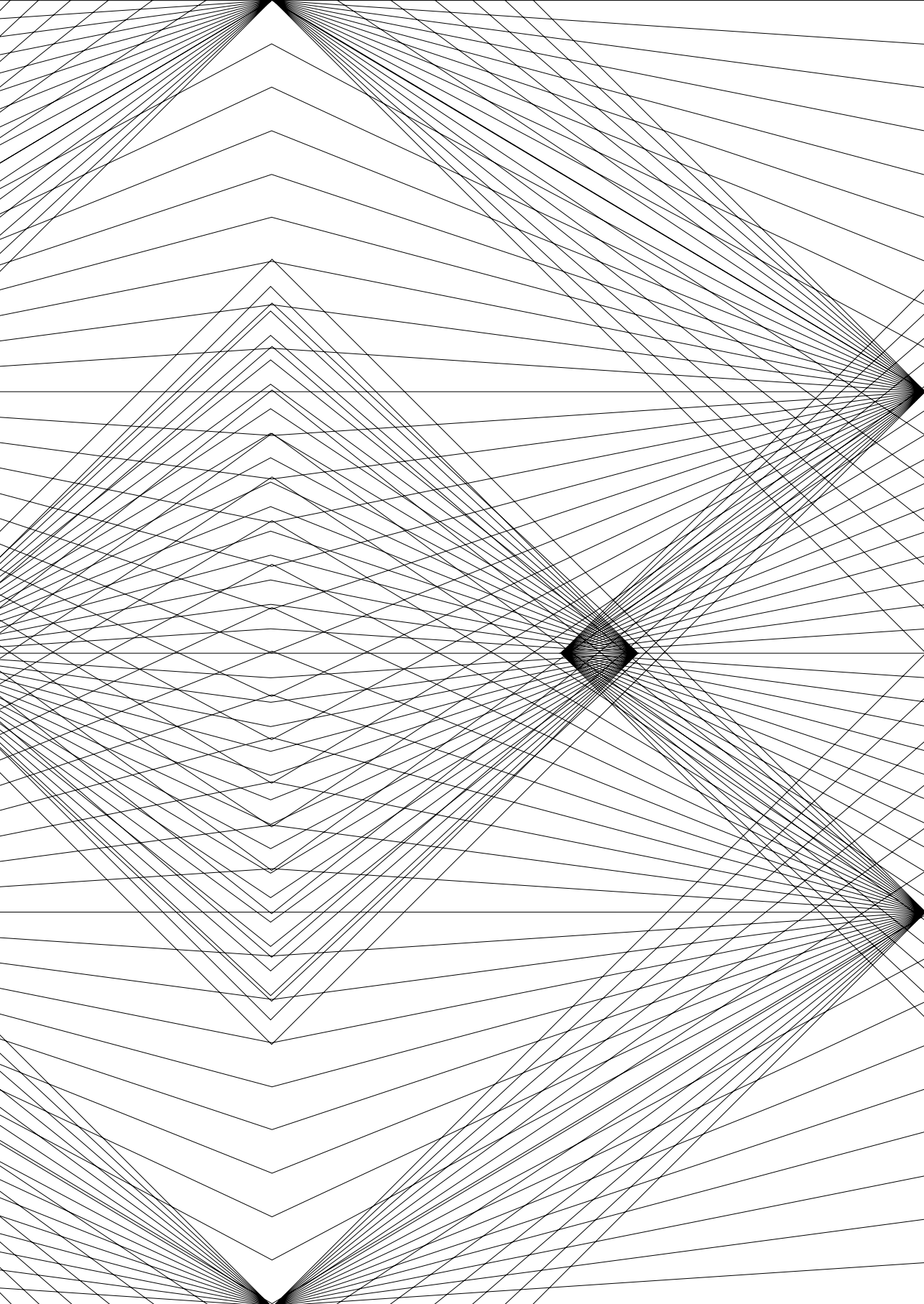
13. Thomas C, Hestermann U, Kopitz J, et al. Serum anticholinergic activity and cerebral cholinergic dysfunction: An EEG study in frail elderly with and without delirium. BMC Neurosci 2008;9:86-95.
14. Thomas C, Hestermann U, Walther S, et al. Prolonged activation EEG differentiates dementia with and without delirium in frail elderly patients. J Neurol Neurosurg Psychiatry 2008;79:119-25.
15. Trzepacz PT, Brenner RP, Coffman G, et al. Delirium in liver transplantation candidates: discriminant analysis of multiple test variables. Biol Psychiatry 1988;24:3-14.
16. Trzepacz PT, Sclabassi RJ,Van Thiel DH. Delirium: a subcortical phenomenon? J Neuropsychiatry Clin Neurosci 1989;1:283-90.



◆ CHAPTER 6 ◆

DELIRIUM DETECTION USING EEG: WHAT AND HOW TO MEASURE?

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SUBMITTED

ABSTRACT

RATIONALE Despite its frequency and impact, delirium is poorly recognized in postoperative- and critically ill patients. EEG is a sensitive tool to diagnose delirium, but inconvenient in routine patient care.

OBJECTIVES To develop an EEG-based tool for delirium detection with a limited number of electrodes, we determined the optimal electrode derivation and EEG characteristic in order to discriminate delirium from non-delirium.

METHODS Standard EEGs were recorded in 28 delirious and 28 age- and sex-matched non-delirious post-cardiothoracic surgery patients, as classified by experts using Diagnostic and Statistical Manual of mental disorders-IV criteria. The first minute of artifact-free EEG data with eyes-closed as well as with eyes-open was selected. For each derivation, six EEG parameters were evaluated. Using Mann-Whitney U-tests, all combinations of derivations and parameters were compared between delirious and non-delirious patients. Corresponding p-values, corrected for multiple testing, were ranked.

MEASUREMENTS AND MAIN RESULTS The largest difference between patients with and without delirium was found during eyes-closed, using electrode derivation F8-Pz (frontal-parietal) and relative delta power (Median (Inter Quartile Range) delirium = 0.59 (0.47-0.71); non-delirium = 0.20 (0.17-0.26); $p = 1.8*10^{-12}$).

CONCLUSIONS Relative delta power in an eyes-closed EEG recording with only two electrodes in a frontal-parietal derivation can distinguish post-cardiothoracic surgery patients with delirium from those without.

INTRODUCTION

Delirium is an acute disturbance of attention and cognition.[1] It is a common disorder in postoperative- and critically ill patients and associated with higher mortality and long-term cognitive impairment.[2, 3] Despite its frequency and impact, recognition of delirium by Intensive Care Unit (ICU) physicians appeared to be poor (sensitivity 29%).[4] Therefore, several delirium assessment tools have been developed. The delirium assessment tool with the highest sensitivity in postoperative patients was the Nursing Delirium Symptom Checklist (Nu-DeSC, sensitivity 29-95%),[5, 6] whereas the Confusion Assessment Method for the ICU (CAM-ICU) had the highest sensitivity in ICU patients (64-100%).[4, 7-9]

It should however be noted that in these studies, delirium assessments were performed by a limited number of dedicated research-nurses, and it is questionable whether these findings can be generalized to routine, daily practice, where numerous bedside-nurses use these tools. The sensitivity of the Nu-DeSC in a real-life, postoperative setting has never been investigated,[5] whereas the sensitivity of the CAM-ICU in routine ICU care appeared to be much lower than in a research setting.[10] In this investigation in 10 different ICUs, teams of three delirium experts (geriatricians, psychiatrists and neurologists) served as gold standard. The sensitivity of the CAM-ICU for delirium in routine, daily practice was not more than 47%, whereas the specificity was high (98%).[10] As the CAM-ICU is primary used for screening, the sensitivity is of more importance than the specificity. Furthermore, the CAM-ICU cannot be used to quantify the severity of delirium. As a consequence, delirium recognition is impaired and treatment is delayed, which may impair outcome.[11]

A new approach to detect delirium, which may fit better in the culture of the post anaesthesia care unit (PACU) and ICU, is to use monitoring of physiological alterations. Delirium is a manifestation of encephalopathy with altered function of neural networks.[12] Since decades it is known that during delirium, electroencephalography (EEG) shows slowing of background activity.[13] To use EEG for daily delirium screening is, however, time consuming and unpractical as it can only be performed and interpreted by trained personnel. Recently, EEG monitoring with automatic processing has become technically feasible.[14] EEG-based detection with a limited number of electrodes and automatic processing is more practical and could possibly increase recognition of delirium. However, it is unclear which combination of EEG characteristic and electrode derivation would be the best in differentiating delirium from non-delirium.[15] The objective of this study was to determine the electrode derivation and EEG characteristic that have the best capability to distinguish patients with delirium from patients without delirium. As a first step, we focused on a homogeneous population of cardiothoracic surgery patients admitted postoperatively to the ICU.

METHODS

STUDY DESIGN AND PATIENTS

In this single-center observational study, EEGs were recorded in post cardiothoracic surgery patients with and without delirium, who were matched, on group level, on age and sex. The included patients were admitted postoperatively to the ICU of the University Medical Center Utrecht. The institutional review board approved the study protocol (IRB number 11-073), and written informed consent was obtained at the pre-operative outpatient clinic or at hospital admission prior to surgery. Patients aged 50 years or older were eligible for this study if they were to undergo cardiothoracic surgery. We excluded patients with a history of any neurological or psychiatric disease that may confound the diagnosis of delirium or the EEG. Patients with a previous cerebrovascular event were not excluded, unless the event resulted in focal EEG alterations. In that case the patient was replaced by another patient after evaluation of the EEG recording.

DIAGNOSIS OF DELIRIUM AND DATA COLLECTION

Daily mental status assessment, including delirium screening, was conducted by research nurses and -physicians with the Richmond Agitation and Sedation Scale (RASS) and CAM-ICU during the first five post-operative days.[7, 16] When surgery was complicated, daily mental status assessment was performed on the first five days that the patient was not in a comatose state, defined by a RASS score lower than -3 or a Glasgow Coma Score lower than 9.[16, 17] CAM-ICU positive patients received a neuropsychiatric evaluation conducted by a geriatrician, neurologist or psychiatrist, based on revised Diagnostic and Statistical Manual of mental disorders IV-R criteria for delirium.[1] This neuropsychiatric evaluation included assessment of the level of consciousness, attention, orientation, memory, language and disorganized thinking. When the delirium expert classified the patient as 'definite delirium', the patient received an EEG recording. Equivocal cases were excluded. After matching on group level on age and sex, CAM-ICU negative patients also received a similar neuropsychiatric evaluation. When a CAM-ICU negative patient was classified as 'definite no delirium' by the delirium expert, an EEG recording was conducted.

Several patient characteristics were registered: age, sex, Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score,[18] Charlson comorbidity index,[19] Euroscore,[20] surgery type, bypass time and medication use during, and in the 24 hours prior to the EEG recording.

Thirty minutes EEGs were recorded, in which patients were asked to keep their eyes open for 15 minutes and close them for the last 15 minutes of the recording. To avoid sleep during the EEG recording, patients were asked to conduct tasks like squeezing their

hands at several time points during the recording. In addition to these tasks, delirious patients received multiple reminders for eyes-closed and eyes- open instructions in order to optimize the adherence to the protocol. EEG recordings were conducted according to the international 10/20 system with an extra electro-oculogram electrode below the right eye. Recordings were performed with Micromed (Micromed, Trevisio, Italy), using a sample frequency of 512 Hz and FzCz as ground electrode. Analog filter settings were set between 0.1 and 70 Hz. The data was pre-processed using a band pass FIR filter with cut-off frequencies of 0.5 and 30 Hz. The signal processing toolbox EEGlab (version 9.0.4.5s)[21] was used for pre-processing of the EEG data in combination with MATLAB (Matlab, version 7.9.0.529, The MathWorks Inc, Natick, Massachusetts U.S.A).

For quantitative analysis, we selected the first 60 seconds of artifact-free data with eyes-open as well as the first 60 seconds of artifact-free data with eyes-closed. When specific electrode channels still contained artifacts, these channels were removed from the data. Eyes-open and eyes-closed data were analyzed separately. For eyes-open, only occipital and parietal (P8, P3, P4, P7, O1, O2) electrodes were analyzed to avoid artifacts due to eye movements or blinking. For eyes-closed data, all 21 electrode channels were used (F10, F9, Fp2, Fp1, F8, F4, Fz, F3, F7, T8, C4, Cz, C3, T7, P8, P4, Pz, P3, P7, O2 and O1). For eyes-open and eyes-closed data separately, all EEG electrodes were combined with each other to create all possible bipolar EEG derivations. This resulted in 15 EEG derivations for eyes-open and 210 EEG derivations for eyes-closed recordings. Based on previous literature, the most promising EEG characteristics were determined a priori, and these included the relative power in the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-20 Hz) frequency band, the peak frequency and the slow-fast ratio ((relative delta + relative theta)/(relative alpha + relative beta)).[15] These six EEG characteristics were calculated per patient for every EEG derivation for both eyes-open and eyes-closed recordings.

STATISTICAL ANALYSIS

Patient characteristics were tested for normality using the Kolmogorov-Smirnov test. Continuous, normally distributed variables were presented using the mean and standard deviation and compared using a T-test. Continuous, not normally distributed variables were described with median and interquartile range (IQR) and compared using a Mann-Whitney U test. Categorical variables were compared using a Chi-square test or Fisher exact test. Statistical analysis of patient characteristics was conducted with SPSS (IBM SPSS Statistics, version 20, Armonk, New York, U.S.A.).

In explorative analyses, all possible combinations of EEG derivations and characteristics were compared between delirious and non-delirious patients. It was assumed that not all EEG characteristics were normally distributed and therefore all

comparisons were conducted using the Mann-Whitney U test. A Bonferoni correction was applied to correct for multiple testing, this resulted for eyes-closed in an $alpha_{adjusted}$ of $4.0*10^{-5}$ and for eyes-open in an $alpha_{adjusted}$ of $5.6*10^{-4}$. For registrations with eyes-closed and eyes-open separately, all p-values were ranked and the smallest p-value was assumed to be the optimal EEG derivation and optimal EEG characteristic to distinguish delirious from non-delirious patients. For the 10 most optimal combinations of a certain EEG characteristic and derivation, a receiver operating curve was created and the area under the curve was determined. In addition to the analyses described above, we compared delirium patients with and without haloperidol for the most optimal EEG derivation and EEG characteristic. The statistical analyses of the EEG data were performed with Matlab.

RESULTS

Fifty-eight patients were initially selected, but two equivocal cases were excluded after neuropsychiatric evaluation. Because of strict follow-up, there was no missing data. In total, 56 patients remained, of whom 28 were delirious and 28 were not delirious. Of the patients with delirium, 14 had a hypoactive subtype (negative RASS scores), 7 a hyperactive (positive RASS scores), and 7 a mixed subtype (both positive RASS and negative RASS scores) during the EEG registration. Five delirious patients did not show an artifact free epoch of 1 minute with eyes-open and were excluded for eyes-open analysis only. One delirious patient did not have a 1-minute epoch of artifact free data with eyes-closed and was excluded for eyes-closed analysis.

Patient characteristics are shown in Table I. Delirious patients differed from non-delirious patients in APACHE IV scores, Charlson comorbidity index scores and haloperidol use. Two non-delirious patients used haloperidol in the 24 hours previous to the EEG, because of delirium two days before the EEG recording and tapering of the haloperidol medication.

TABLE I *Characteristics of the study population*

	DELIRIOUS PATIENTS (N=28)	NON-DELIRIOUS PATIENTS (N=28)	P-VALUE
Age, mean (StD)	77 (5.6)	74 (8.6)	0.16
Gender: male, n (%)	16 (57%)	16 (57%)	1.00
Apache IV score, median (IQR)[18]	58 (45-65)	43 (35-51)	<0.01
Charlson comorbidity index, median (IQR)[19]	2 (1-3)	1 (0-1)	0.02
EuroSCORE, median (IQR)[20]	7 (6-9)	7 (5-8)	0.17
Surgery type			0.49
- CABG, n (%)	3 (11%)	5 (18%)	
- valve, n (%)	8 (28%)	11 (39%)	
- other, n (%)	17 (61%)	12 (43%)	
Bypass time, median (IQR)	129 (95-158)	108 (77-168)	0.07
Bypass time, median (IQR)	10 (36%)	10 (36%)	1.00
Benzodiazepines past 24 hours, n (%)	7 (25%)	6 (21%)	0.75
Alpha-2-agonist past 24 hours, n (%)	4 (14%)	0 (0%)	0.11
Haloperidol past 24 hours, n (%)	17 (61%)	2 (7%)	<0.01
Postsurgical day of EEG, median (IQR)	3 (2-5)	3 (2-4)	0.78

Abbreviations: Apache IV = Acute Physiology and Chronic Health Evaluation IV; CABG = Coronary Artery Bypass Graft; EEG = Electroencephalography; IQR = Inter Quartile Range; n = number; StD=Standard Deviation. Other surgery type refers to cardiothoracic surgery that includes two or more of the following procedures: Coronary Artery Bypass Graft, Valve surgery or Maze procedure.

Table II lists the 10 combinations of EEG derivations and EEG characteristics with the lowest p-values, for the eyes-closed condition. All combinations were statistically significantly different between delirium and non-delirium. The derivation F8-Pz for relative delta power showed the lowest p-value ($1.8*10^{-12}$), and the largest area under the receiver operating curve (0.99). Also neighboring electrodes of both F8 (for example Fp2) and Pz (for example P3 or O1) in combination with relative delta power were in the top five of smallest p-values (Figure I).

Table III shows the 10 combinations with the lowest p-values for the eyes-open condition. Again, all combinations were statistically significantly different between delirium and non-delirium. The electrode derivation with the lowest p-value was P7-P4 in combination with relative alpha power ($p = 2.0*10^{-7}$), which was associated with an area under the receiver operating curve of 0.90.

When we restricted our analyses to patients with delirium, and compared patients with to patients without haloperidol, there was no difference in the best combination for eyes-closed (relative delta power at F8-Pz): haloperidol+ median = 0.58 (inter quartile range, IQR 0.40-0.70) versus haloperidol- median = 0.64 (IQR 0.53-0.71); p = 0.39. Furthermore, for the best combination with eyes-open (P7-P4, relative alpha), there was no difference between delirium patients with or without haloperidol either (haloperidol+ median=0.11 (IQR 0.08-0.14) versus haloperidol- median = 0.15 (IQR 0.10-0.15); p = 0.37).

TABLE II *The 10 combinations of EEG derivation and characteristic that showed the lowest p-value in discriminating delirium from non-delirium with eyes-closed.*

EYES CLOSED								
RANK	**P-VALUE***	**DERIVATION**	**CHARACTERISTIC**	**DELIRIUM, MEDIAN (IQR)**	**NON-DELIRIUM, MEDIAN (IQR)**	**AUC**	**SENS (%)**	**SPEC (%)**
1	$1.8*10^{-12}$	F8-Pz	Relative delta	0.59 (0.47-0.71)	0.20 (0.17-0.26)	0.99	100	96
2	$3.7*10^{-12}$	F8-P3	Relative delta	0.59 (0.46-0.69)	0.19 (0.15-0.26)	0.99	96	96
3	1.1*10-[11]	F8-O2	Relative delta	0.60 (0.49-0.73)	0.23 (0.18-0.30)	0.99	96	96
4	$1.5*10^{-11}$	Fp2-O1	Relative delta	0.66 (0.60-0.75)	0.27 (0.23-0.36)	0.99	96	95
5	$1.7*10^{-11}$	F8-F4	Relative delta	0.60 (0.43-0.70)	0.20 (0.17-0.26)	0.98	96	92
6	$2.2*10^{-11}$	F8-O1	Relative delta	0.62 (0.48-0.72)	0.22 (0.17-0.26)	0.99	96	95
7	$2.4*10^{-11}$	F8-Cz	Relative delta	0.57 (0.46-0.67)	0.26 (0.20-0.33)	0.98	91	96
8	$2.4*10^{-11}$	F8-C3	Relative delta	0.57 (0.49-0.67)	0.21 (0.17-0.30)	0.98	91	92
9	$2.9*10^{-11}$	Fp2-Pz	Relative delta	0.64 (0.53-0.72)	0.28 (0.22-0.36)	0.99	100	95
10	3.0*10-[11]	Cz-O1	Relative delta	0.50 (0.37-0.57)	0.17 (0.10-0.25)	0.96	92	88

* All p-values were smaller than $4.0*10^{-5}$. Therefore, all combinations in this table showed a statistically significantly difference between delirium and non-delirium. Abbreviations: AUC = Area Under the Curve of the receiver operating curve; IQR = Inter Quartile Range; Relative delta = Relative power in the delta frequency band; Sens = Sensitivity; Spec = Specificity.

FIGURE I *Most optimal electrode locations for delirium detection, based on first four rankings of eyes-closed condition.*

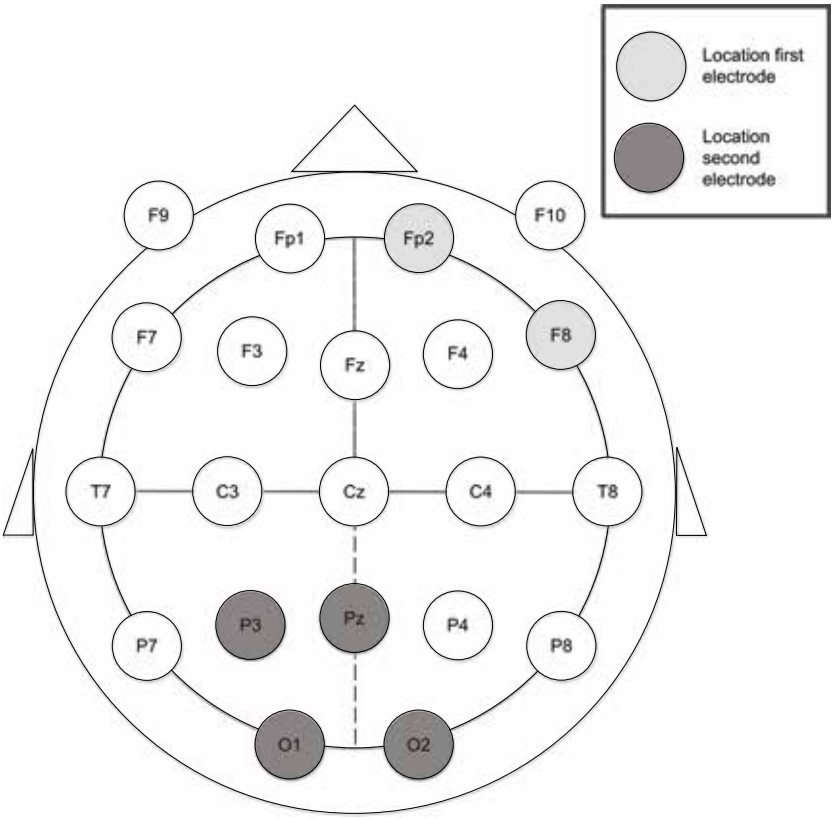

TABLE III *The 10 combinations of EEG derivation and characteristic that showed the lowest p-value in discriminating delirium from non-delirium with eyes- open.*

EYES OPEN								
RANK	**P-VALUE***	**DERIVATION**	**CHARACTERISTIC**	**DELIRIUM, MEDIAN (IQR)**	**NON-DELIRIUM, MEDIAN (IQR)**	**AUC**	**SENS (%)**	**SPEC (%)**
1	$2.0*10^{-7}$	P7-P4	Relative alpha	0.12 (0.09-0.15)	0.33 (0.19-0.39)	0.90	85	91
2	$4.2*10^{-7}$	P3-P4	Relative alpha	0.14 (0.11-0.17)	0.34 (0.23-0.43)	0.89	81	91
3	$1.6*10^{-6}$	P7-O1	Relative delta	0.44 (0.36-0.54)	0.24 (0.17-0.33)	0.88	86	85
4	$3.2*10^{-6}$	P7-O1	Relative alpha	0.10 (0.08-0.14)	0.26 (0.19-0.33)	0.87	81	90
5	$3.5*10^{-6}$	P3-P4	Slow Fast ratio	4.0 (2.5-5.2)	1.0 (0.6-1.7)	0.87	77	89
6	$4.0*10^{-6}$	P4-O1	Relative alpha	0.13 (0.09-0.17)	0.29 (0.19-0.39)	0.87	78	90
7	$6.1*10^{-6}$	P7-P8	Relative alpha	0.11 (0.09-0.16)	0.31 (0.19-0.39)	0.86	81	95
8	$7.9*10^{-6}$	P7-P4	Slow Fast ratio	4.0 (2.9-5.6)	1.1 (0.7-2.2)	0.86	77	88
9	$9.4*10^{-6}$	P3-P8	Relative alpha	0.13 (0.09-0.16)	0.32 (0.19-0.43)	0.86	78	90
10	$1.1*10^{-5}$	P7-O2	Relative alpha	0.11 (0.09-0.15)	0.29 (0.19-0.37)	0.86	76	95

* All p-values were smaller than $5.6*10^{-4}$. Therefore, all combinations in this table showed a statistically significantly difference between delirium and non-delirium. Abbreviations: AUC = Area Under the Curve; IQR = Inter Quartile Range; Relative alpha = Relative power in the alpha frequency band; Relative delta = Relative power in the delta frequency band; Sens = Sensitivity; Slow Fast ratio = Ratio between the sum of the relative power in the delta and theta frequency band and the sum of the relative power in the alpha and beta frequency band ; Spec = Specificity.

DISCUSSION

In summary, we found that in post-cardiothoracic surgery patients, cases with delirium can be distinguished from those without, based on EEG with only two electrodes. The largest difference between delirium and non-delirium (i.e. the lowest p-value) was observed in EEG epochs with eyes-closed. In this condition, the optimal EEG characteristic and electrode derivation was the relative delta power in F8 (frontal, lateral) to Pz (midline, parietal).

This study represents an innovative, new approach to detect delirium. Using EEG with a limited number of electrodes and automatic processing may offer an objective tool to detect the encephalopathy that underlies delirium. Patients in the post anesthesia care unit and ICU are monitored for various physiological alterations. Consequently, EEG-based detection of delirium may fit better in the local culture than cognitive testing. Our study is the first to systematically investigate what the best electrode derivation and EEG characteristic is to detect delirium. We showed that with only two electrodes and one minute of recording, large differences can be found between patients with and without delirium.

Two previous studies found that delirium can be detected with two electrodes, using T5-O1 (parietal to occipital) or C3-A1 (central to left ear) derivations in combination with EEG frequency analyses. However, the observed differences in these studies were much smaller than the differences found in our investigation.[13, 22] Our study contrasts with previous investigations as we determined, in a systematic fashion, which combination of bipolar electrode derivation and EEG characteristic showed the largest differences between patients with and without delirium. Unlike previous quantitative EEG studies in delirium, we did not observe that relative theta power is an important characteristic to distinguish delirious patients from those without delirium.[15] These previous studies often stratified the theta frequency band in an upper and a lower part, in which only the lower part proved to be significantly different between delirium and non-delirium.[23, 24] We did not use further division of the theta band, as this would have further increased the number of possible combinations to study.

Some limitations of the present study should be acknowledged. This study describes only the first step towards an objective delirium detection tool. Due to the study design, in which doubtful cases of delirium were excluded, we cannot derive the incidence of delirium in this population. Therefore, parameters as the area under the receiver operating curve, sensitivity and specificity should be interpreted with caution. In our study, artifact-free data was manually selected for analysis and not automatically chosen. Automatic artifact detection programs are available and already implemented

in single channel sleep EEG analysis programs.[25] A comparable automatic detection algorithm needs to be implemented in a future objective delirium detection tool. The homogenous study population of post-cardiothoracic surgery patients did not have residual sedation, which may be an issue in delirium detection in a general population of ICU patients. Besides, the etiology of delirium after cardiothoracic surgery differs from the etiology of ICU delirium.[26] It is therefore unclear whether our findings can be extrapolated to a general ICU population. Another possible limitation of this study may be that differences in haloperidol use between the delirium and the non-delirium group could have affected the results. It is, however, unlikely that this explains our findings, as we found no differences between users and non-users of haloperidol within the group of delirium patients. As delirium is caused by an underlying disease, unsurprisingly, there was a difference in APACHE IV score and Charlson comorbidity index between patients with and without delirium.

Future prospective studies should validate our results, and investigate whether our findings can be generalized to an unselected population of ICU patients and to a general population of postoperative patients. The effects of residual sedation and automatic data selection should also be considered in these future studies.

In conclusion, we showed that with two electrodes and one minute of EEG data, delirium can be discriminated from non-delirium. This opens the prospect of EEG-based detection of delirium.

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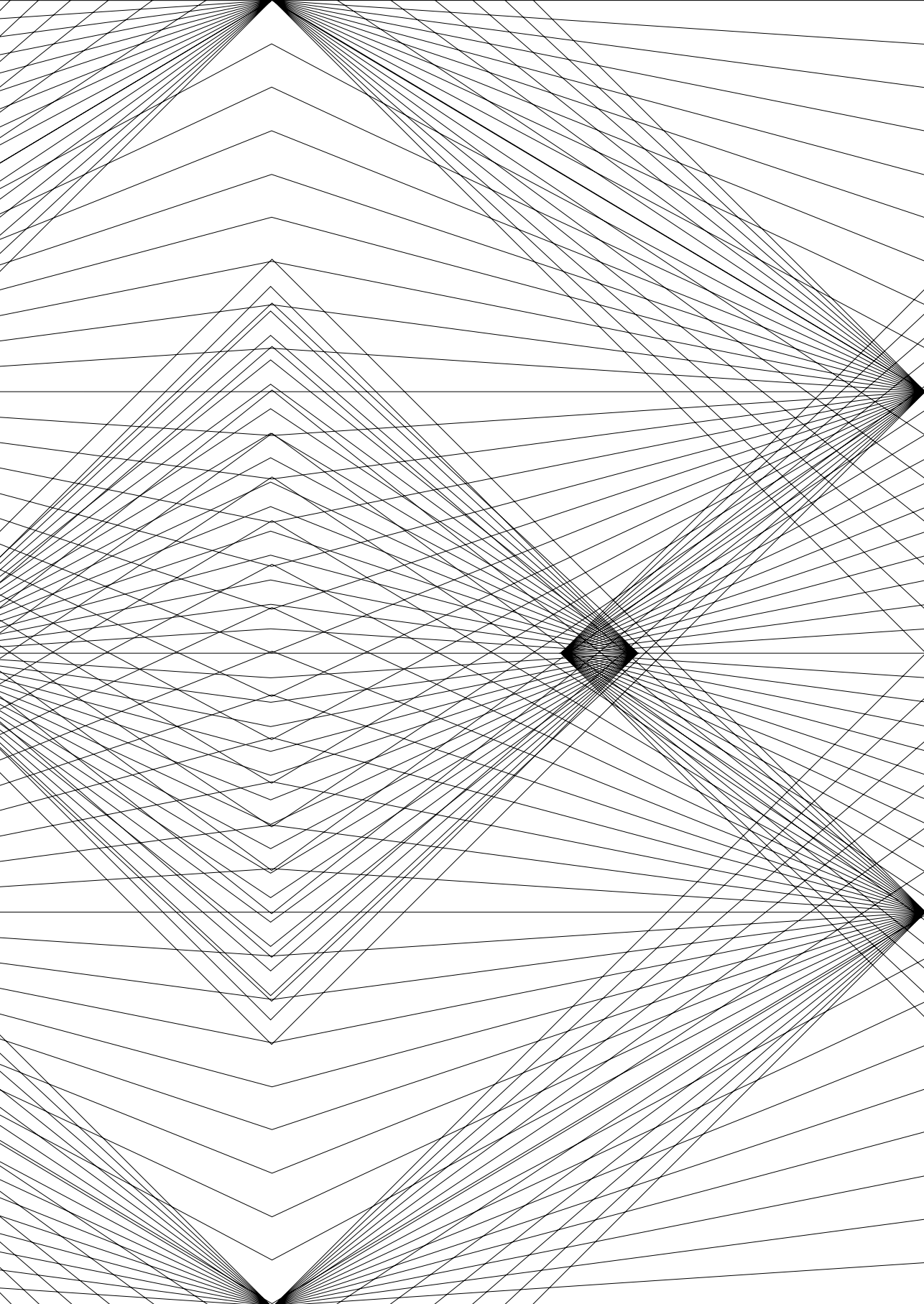

◆ CHAPTER 7 ◆

DELIRIUM DETECTION BASED ON MONITORING OF BLINKS AND EYE MOVEMENTS

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AM J GERIATR PSYCHIATRY 2014

ABSTRACT

OBJECTIVE To investigate whether delirious patients differ from non-delirious patients with regard to blinks and eye movements, in order to explore opportunities for delirium detection.

DESIGN Single-center, observational study.

SETTING Tertiary hospital in the Netherlands.

PARTICIPANTS 28 delirious- and 28 age- and gender-matched (group level) non-delirious elderly, postoperative cardiac surgery patients.

INTERVENTION None.

MEASUREMENTS Patients were evaluated for delirium by a geriatrician, psychiatrist or neurologist using the Diagnostic and Statistical Manual of mental disorders IV criteria. Blinks were automatically extracted from electro-oculograms and eye movements from electroencephalography recordings using independent component analysis. The number and duration of eye movements and blinks were compared between patients with and without delirium, based on the classification of the delirium experts described above.

RESULTS During eyes open registrations, delirious patients showed, compared to non-delirious patients, a significant decrease in the number of blinks per minute (median 12 (interquartile range (IQR) 5-18) versus 18 (IQR 8-25); $p = 0.02$) and number of vertical eye movements per minute (median 1 (IQR 0-13) versus 15 (IQR 2-54); $p = 0.01$), as well as an increase in the average duration of blinks (median 0.5 (IQR 0.36-0.95) seconds versus 0.34 (IQR 0.23-0.53) seconds; $p<0.01$). During eyes closed, the average duration of horizontal eye movements was significantly increased in delirious patients compared to patients without delirium (median 0.41 (IQR 0.15-0.75 seconds) versus 0.08 (IQR 0.06-0.22) seconds; $p<0.01$).

CONCLUSIONS Spontaneous eye movements and particularly blinks appear to be affected in delirious patients, which holds promise for delirium detection.

INTRODUCTION AND OBJECTIVE

Delirium is common in elderly postoperative- and critically ill patients. It is associated with increased morbidity and mortality, prolonged hospitalization and functional decline.[1-4] Nevertheless, delirium is poorly recognized.[5] Therefore, several delirium assessment tools have become available. The Nursing Delirium Symptom Checklist (Nu-DeSC) is a delirium assessment tool with the highest sensitivity in postoperative patients,[6, 7] whereas the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) has the highest sensitivity in Intensive Care Unit (ICU) patients.[5, 8-10]

It should however be noted that the studies mentioned above were done in a research setting, in which the performance of a limited number of research nurses was investigated. In daily practice, delirium screening is performed by numerous bedside nurses as part of routine clinical care. The sensitivity of the Nu-DeSC has never been investigated in a real-life, postoperative setting,[6] whereas the sensitivity of the CAM-ICU appeared to be much lower in a real-life ICU setting than in a research setting.[11] The largest study in routine, clinical practice was performed in 10 different ICUs and used teams of three delirium experts as gold standard. These included psychiatrists, geriatricians, and neurologists, who evaluated together all patients. In this investigation, the sensitivity of the CAM-ICU in routine, daily practice was not more than 47%, and only 31% for the hypoactive form of delirium,[11] the subtype that is most difficult to recognize.[5] The specificity in this study was high (98%), but this is of minor importance, as the CAM-ICU is used for screening and not for diagnosis. The only other study on the performance of the CAM-ICU in daily practice showed a higher sensitivity (81%), but was a single-center study from the same institution where the CAM-ICU was developed, where research nurses acted as reference standard.[12]

Unfortunately, the Nu-DeSC and the CAM-ICU have more limitations as these screenings tool may not fit well in the culture of the recovery room and ICU, which is primarily orientated on monitoring of physiological alterations. Moreover, delirium severity cannot be quantified with the CAM-ICU. The consequence of impaired recognition of delirium is that treatment is delayed, which may impair outcome.[13]

Numerous studies have shown that delirium is associated with a change in motor activity level, and that changes can already be noticed in a very early stage.[14-16] An alternative approach to detect delirium, could be based on altered motor activity.[15, 16] Using actigraphy, a decrease of overall activity was observed during delirium.[15] However, actigraphy requires the patient to move the limbs spontaneously, which may be difficult in postoperative- and critically ill patients because of pain, weakness, and the use of physical restraint. Blinks and eye movements are less affected by these issues,[17] and a decrease in eye movement velocity has been associated with a decrease of the level of consciousness.[18]

As the level of consciousness [19] and motor activity [20] can be affected in delirium, we hypothesized that monitoring of blinks and eye movements could provide a new approach for delirium detection. The objective of this study was to investigate whether blinks and eye movements are different in delirious patients compared to non-delirious patients.

METHODS

STUDY DESIGN AND PATIENT SAMPLE

This observational single-center study was approved by the medical-ethics committee of the University Medical Center Utrecht (protocol number 11-073). The sample consisted of a homogeneous group of elderly cardiothoracic surgery patients. Patients presenting at the pre-operative out-patient clinic, or at the in-patient clinic the day before surgery, were asked for written informed consent. Inclusion criteria were age above 50 years and written informed consent prior to cardiac surgery. Exclusion criteria were a history of neurological or psychiatric disease as these may influence eye movement parameters.[21, 22] Patients with a previous cerebrovascular event were not excluded, unless the event resulted in electro-encephalography (EEG) asymmetry. In that case the patient was excluded after EEG recording. A sample of 28 non-delirious cardiothoracic surgery patients were matched (on group level) for age and gender to the group of 28 delirious cardiothoracic surgery patients. Sample size calculation could not be performed as there were no prior data with this analysis method and outcome variables available for delirium patients.

DATA COLLECTION

Daily mental status was assessed by research nurses and -physicians with the CAM-ICU during the first five post-operative days, or when surgery was complicated, the first five days that the patient was not in a comatose state. A comatose state was defined as a Richmond Agitation and Sedation Scale (RASS) score lower than -3 or a Glasgow Coma Score lower than 9.[23, 24]

When the CAM-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 (DSM) IV criteria for delirium.[25] The evaluation included assessment of the level of consciousness, attention, language, thinking, memory, psychomotor behavior and perception. The neuropsychiatric evaluation was conducted as soon as possible before or after the EEG recording, but always within two hours before or after the EEG recording. When this neuropsychiatric evaluation indicated delirium, the EEG recording of the patient was included for the study. When it was equivocal, the EEG recording of the patient was excluded.

When a patient was CAM-ICU negative, his or her age and sex were compared to already included delirious patients. When age and sex corresponded with the delirious patients group, the patient received a neuropsychiatric evaluation by a psychiatrist, geriatrician or neurologist using the DSM IV criteria for delirium.[25] 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 non-delirious patient, the EEG recording of the patient was included for the study. When the neuropsychiatric evaluation was equivocal, the EEG recording of the patient was excluded.

For every patient various characteristics were registered, including the Acute Physiology and Chronic Health Evaluation (APACHE) IV score (score for disease severity at ICU admission),[26] Charlson Comorbidity index (measure of prognostic comorbidity),[27] Euroscore (score for predicted mortality for cardiac surgery patients),[28] type of surgery, bypass time, medication use in the 24 hours prior to EEG recording and motoric subtype of delirium (based on RASS scores during EEG recording).

EEG measurements were conducted according to the international 10/20 system extended with an electro-oculography (EOG) electrode below the right eye and recorded with Micromed (Micromed, Trevisio, Italy), using a sample frequency of 512 Hz. Thirty minute EEGs were recorded, in which patients were asked to keep their eyes open for 15 minutes and close them for the last 15 minutes of the recording. Patients were not allowed to sleep during the measurement and the purpose was to record resting state EEG and EOG. To ensure that patients stayed awake, they were asked to conduct tasks like squeezing their hands at several time points during the recording. We selected EEG and EOG epochs at least 30 seconds after the arousal stimulus. When delirious patients had difficulty with eyes open and eyes closed instructions, they received multiple reminders to keep their eyes closed or eyes open. After digital storage, the data was pre-processed by band pass filtering (0.5-30 Hz) using the signal processing toolbox EEGlab (Version 9.0.4.5s, Swartz Center for Computational Neuroscience, San Diego, California, USA) in combination with MATLAB (Matlab, version 7.10.0.499, The MathWorks Inc, Natick, U.S.A). For quantitative analysis, the first 60 seconds of artefact free data with eyes open and first 60 seconds of artefact free data with eyes closed were selected.

DATA ANALYSIS

Based on the EEG and EOG, we investigated eye blinks (during eyes open), horizontal eye movements (during eyes open and during eyes closed) and vertical eye movements (during eyes open and during eyes closed), using the ADJUST algorithm.[29] The Adjust algorithm is a completely automatic independent component analysis (ICA) based

algorithm for identification of artifact-related components in EEG recordings, such as eye movements. In order to accomplish this artifact recognition, each of the components found during the ICA is analyzed for its topographical distribution (spatial features) and distribution in time (temporal features). If a component fulfills the criteria set for a certain artifact based on spatial and temporal features, it is recognized as an artifact. Various criteria were set to differentiate between artifacts of horizontal- and vertical eye movements. The independent components that met the criteria of eye movements based on spatial and temporal features,[29] were selected from the EEG and other components were eliminated. Since eye blinks cause a high amplitude electrical signal, the EOG signal could be used for the analysis of eye blinks without the need for the ADJUST algorithm. The EOG and reconstructed EEG were further analyzed in the time domain. For all five features, described above, we determined per minute the number of eye movements and their average duration. To detect an eye movement, both negative and positive peaks were used, representing movements to left and right or up and down. Eye movement duration was determined by the time interval between the maximal (negative or positive) amplitude and the next point of zero amplitude.

STATISTICAL ANALYSIS

Categorical variables were compared using the Chi-square test or Fisher exact test (when categories contained 5 cases or less). Continuous variables were screened for normal distribution. Normally distributed, continuous variables were compared between two groups using the student's T-test, and between more than two groups with an analysis of variance (ANOVA). Not normal, continuous distributed variables were studied with the Mann-Whitney U test or the Kruskal Wallis test, where appropriate. For all eye movement variables a receiver operating characteristic and corresponding area under the curve (AUC) were determined, in order to estimate the diagnostic value. A p-value smaller than 0.05 was assumed to be statistically significant. For eye movement variables that showed statistical significant differences between delirium and non-delirium patients, additional analyses were conducted. These analyses included comparisons between delirium patients with and without haloperidol, and between delirium patients with different motoric subtypes. Statistical analyses were performed with SPSS (IBM SPSS, version 20, New York, U.S.A.).

RESULTS

The sample included 28 delirious and 28 non-delirious cardiac surgery patients (Table I). Of the 28 patients with delirium, 14 had a hypoactive motoric subtype, seven a hyperactive, and seven a mixed type. Delirious patients had higher APACHE IV and Charlson Comorbidity scores compared to non-delirious patients, and used more often haloperidol in the 24 hours prior to the EEG recording (Table I). Two non-delirious patients used haloperidol in the 24 hours previous to the EEG, because of delirium two days before the EEG recording and tapering of the haloperidol medication.

The number and duration of blinks and eye movements are shown in Table II for patients with and without delirium. During eyes open, delirious patients showed less blinks and vertical eye movements, and an increased duration of blinks, when compared to patients without delirium. During eyes closed, delirious patients showed an increased duration of horizontal eye movements compared to non-delirious patients. In Table II, the AUC for these variables is also shown.

When we further compared delirious patients with and without haloperidol, there was no difference in the number or duration of blinks and eye movements. In addition, we found no differences in the blinks or eye movement variables between motoric subtypes of delirium (Table III).

TABLE I *Patient characteristics*

	DELIRIOUS PATIENTS (N=28)	NON-DELIRIOUS PATIENTS (N=28)	P-VALUE	DF
Age, mean (Standard Deviation)	77 (5.6)	74 (8.6)	0.16[a]	54
Gender: male, n (%)	16 (57%)	16 (57%)	1[b]	1
APACHE IV score, median (IQR) [26]	58 (45-65)	43 (35-51)	<0.01[c]	
Charlson comorbidity index, median (IQR) [27]	2 (1-3)	1 (0-1)	0.02[c]	
EuroSCORE, median (IQR) [28]	7 (6-9)	7 (5-8)	0.17[c]	
Surgery type			0.49 [d]	
- CABG, n (%)	3 (11%)	5 (18%)		
- Valve, n (%)	8 (28%)	11 (39%)		
- Other, n (%)	17 (61%)	12 (43%)		
Bypass time, median (IQR)	129 (95-158)	108 (77-168)	0.07[c]	
Medication past 24 hours				
- Morphine, n (%)	10 (36%)	10 (36%)	1[b]	1
- Benzodiazepines, n (%)	7 (25%)	6 (21%)	0.75[b]	1
- Alpha-2-agonist, n (%)	4 (14%)	0 (0%)	0.11[d]	
- Haloperidol, n (%)	17 (61%)	2 (7%)	<0.01[d]	
Postsurgical day of EEG recording, mean (Standard Deviation)	3 (2-5)	3 (2-4)	0.78[c]	

Abbreviations: Apache IV = Acute Physiology and Chronic Health Evaluation IV; CABG = Coronary Artery Bypass Graft; DF = Degrees of freedom; EEG = Electroencephalography; IQR = Interquartile Range; N = number. Other surgery type refers to cardiothoracic surgery that includes two or more of the following procedures: Coronary Artery Bypass Graft, Valve surgery or Maze procedure. Type of test used: [a] = Unpaired T-test (equal variances); [b] = Chi-square test; [c] = Mann-Whitney U test; [d] = Fisher exact test.

TABLE II *Eye movements in patients with and without delirium*

EYES	VARIABLE	DELIRIUM MEDIAN (IQR)	NON-DELIRIUM MEDIAN (IQR)	P-VALUE	AUC (95% CI)
Open	Number of eye movements				
	Horizontal	6 (0-51) n=23	26 (0-55) n=28	0.54[a]	0.55 (0.39-0.71)
	Vertical	1 (0-13) n=23	15 (2-54) n=28	0.01[a]	0.70 (0.55-0.85)
	Blinks	12 (5-18) n=23	18 (8-25) n=27	0.02[b] df=40	0.65 (0.50-0.80)
Open	Duration of eye movements (s)				
	Horizontal	0.24 (0.10-0.56) n=14	0.14 (0.04-0.27) n=17	0.14[a]	0.66 (0.47-0.85)
	Vertical	0.14 (0.06-0.49) n=10	0.07 (0.04-0.60) n=18	0.46[a]	0.59 (0.37-0.81)
	Blinks	0.50 (0.36-0.96) n=20	0.34 (0.23-0.53) n=27	<0.01[b] df=34	0.74 (0.59-0.88)
Closed	Number of eye movements				
	Horizontal	0 (0-42) n=27	0 (0-51) n=27	0.37[a]	0.57 (0.41-0.72)
	Vertical	5 (0-47) n=27	10 (0-52) n=27	0.40[a]	0.56 (0.41-0.72)
Closed	Duration of eye movements (s)				
	Horizontal	0.41 (0.15-0.75) n=12	0.08 (0.06-0.22) n=13	<0.01[a]	0.81 (0.64-0.99)
	Vertical	0.15 (0.07-0.29) n=15	0.07 (0.03-0.27) n=17	0.19[a]	0.64 (0.44-0.84)

Abbreviations: AUC = Area Under the Curve; CI = Confidence Interval; df = degrees of freedom; IQR = Interquartile Range; N = Number of patients for which variable could be determined. The number of patients differs per variable, due to the impossibility of determining the duration of eye movements when patients had no eye movements and exclusion of patients for specific conditions. Five delirious patients were unable to keep their eyes open during the registration and excluded for eyes open analysis. One delirious patient would not close his eyes and excluded for eyes closed analysis. The T8 electrode was defect during eyes closed registration in one non-delirious patient and therefore excluded from eyes closed analysis. The electro-oculography channel of one non-delirious patient was defect and therefore, excluded for the analysis of blinks. Type of test used: [a] = Mann-Whitney U test; [b] = Unpaired T-test (unequal variances).

TABLE III *Specific eye movements in delirious patients: effects of haloperidol and motoric subtypes*

	DELIRIUM WITH HALO-PERIDOL	DELIRIUM WITHOUT HALO-PERIDOL	P-VALUE	HYPO-ACTIVE DELIRIUM	HYPER-ACTIVE DELIRIUM	MIXED TYPE DELIRIUM	P-VALUE
Number of vertical movements, Eyes Open: Median (IQR)	2 (0-17) n=14	0 (0-17) n=9	0.69[a]	1 (1-21) n=11	2 (0-8) n=6	1 (0-58) n=6	0.89[c] df=2
Number of blinks, Eyes open: Median (IQR)	12 (4-19) n=14	12 (6-17) n=9	0.87[b] df=21	11 (4-18) n=11	11 (4-21) n=6	13 (5-19) n=6	0.95[d] df=2,20
Duration of blinks, Eyes open (s): Median (IQR)	0.49 (0.39-1.01) n=12	0.52 (0.34-0.93) n=9	0.81[a]	0.47 (0.36-0.69) n=10	0.50 (0.37-1.01) n=5	0.96 (0.32-1.08) n=6	0.63[c] df=2
Duration of horizontal movements, Eyes closed, (s): Median (IQR)	0.59 (0.23-1.40) n=6	0.27 (0.13-0.69) n=6	0.19[b] df=10	0.15 (0.11-0.60) n=5	0.52 (0.12-1.33) n=4	0.68 (0.38-1.02) n=3	0.36[c] df=2

Abbreviations: df = degrees of freedom; IQR = Interquartile Range; N = Number of patients for which variable could be determined.; S = seconds. The number of patients differs per variable, due to the impossibility of determining the duration of eye movements when patients had no eye movements and exclusion of patients for specific conditions. Type of test used: [a] = Mann-Whitney U test; [b] = Unpaired T-test (equal variances); [c] = Kruskal Wallis test; [d] = ANOVA.

DISCUSSION AND CONCLUSIONS

In summary, we found in delirium less blinks and vertical eye movements, and an increased duration of blinks during eyes open registrations, as well as an increased duration of horizontal eye movements during eyes closed registrations. These observations could not be explained by differences in the use of haloperidol, and were not related to different motoric subtypes of delirium.

The only previous study on eye movements in delirium, defined by current criteria, described an increased number of rapid eye movements.[30] In that study, the number of rapid eye movements (duration from baseline to peak less than 250 msec) increased with the level of anxiety, while slow eye movements (duration from baseline to peak more than 250 msec) increased with the level of consciousness.[30] We did not assess the level of anxiety. However, we did not find an association between motoric subtypes of delirium and the duration of blinks or eye movements. Our findings are consistent with previous literature using limb actigraphy that described less motor activity during delirium.[15] Some actigraphy studies also suggested that motor subtypes could be identified with limb actigraphy.[31] However, others observed no differences in motor subtypes, which corresponds with our results.[15, 16]

Blinks are accompanied by a downward, nasal eye movement.[32] Therefore, it is not surprising that similar findings were obtained with regard to both vertical eye movements and blinks in relation to delirium. The number of vertical movements was less than the number of blinks, because not all vertical eye moments during blinks were above the threshold and thereby large enough to qualify as eye movements. Central dopaminergic mechanisms are thought to play a role in the rate of spontaneous blinks.[33] Extremely low blink rates have been found in parkinsonism, which were associated with decreased dopaminergic activity, while increased blink rates have been found in schizophrenia, that were related to increased dopaminergic activity.[21, 22] The low blink rate that we observed in delirious patients may thus suggest dopamine hypoactivity. However, this would be in contrast with other studies that suggest increased activity of the dopaminergic system in delirium.[34-36] It should be noted that there are numerous hypotheses on the pathogenesis of delirium, and it seems unlikely that one specific neurotransmitter alteration explains the whole delirium syndrome. Most likely, several neurotransmitter alterations are involved in a multifactorial pathophysiology.[36]

This study has several strengths. It is the first study that suggests that an objective tool for delirium detection could be based on monitoring of blinks and eye movements, as these could be automatically analyzed. Further, there was a good gold standard for the diagnosis of delirium as all patients in this study were evaluated for delirium by a

psychiatrist, geriatrician or neurologist, who was blinded to the EEG and EOG recordings. EEG and EOG are non-invasive methods and can determine eye movements with as limited as several minutes of data, while other methods such as actigraphy need at least several hours of data.[15] Moreover, limb actigraphy measurements proved to be difficult in critical ill patients probably due to pain or muscle weakness.[37] While eye movements are rarely affected by muscle weakness, detection of delirium by eye movements instead of limb actigraphy seems to be more promising.[17]

This study has also some limitations. A limitation of our eye movement detection method is that 22 electrodes are needed, due to the ADJUST algorithm and the ICA. However, blinks can be measured with only two electrodes, because blinks cause electrical signals of a large amplitude and particular shape. Therefore, no ADJUST algorithm or ICA was necessary for extracting these features from the EOG channel (that was referenced to FzCz). Blinks appeared to be very informative, which makes them very feasible for monitoring purposes. Furthermore, there were differences in Apache IV score and Charlson comorbidity index between patients with and without delirium. This is not surprising as both the Charlson comorbidity index and Apache score are risk factors for delirium,[38, 39] but not directly associated with eye movements. Although, no differences between delirious patients with and without haloperidol were found, we cannot totally exclude an effect of haloperidol on eye movements due to the relatively small sample size. In addition, no differences between delirious patients with different levels of consciousness, as assessed with the RASS score, were found, but due to small sample sizes we cannot exclude an effect of these on eye movements and blinks. In this study the RASS score was used to identify motoric subtypes. More specific measures for motoric subtype identification exist, but were unfortunately not used in this study. Due to the small sample and the problem that some delirious patients could not open or close their eyes for 1 minute, we could not investigate whether a combination of eye movement variables (for example number of blinks and duration of blinks, during eyes open and closed) could result in a more robust delirium detection method. Moreover, we could not correct for confounders using a multivariable model, due to the small sample. However, the sample was large enough to show significant differences in eye movements, thereby providing the answer on our research question. Because of multiple testing, it should be considered that there is a high chance of type I error. Besides, no EEG's were recorded after patients recovered from delirium. Therefore, we cannot exclude that differences in blinks and eye movements that we detected between patients with and without delirium are related to pre-existing factors. The only previous study on eye movements in delirium, showed that changes in eye movement variables increased when the delirium episode started and decreased when delirium resolved.[30]

Future, larger studies should establish whether eye movements can discriminate delirium from non-delirium in a general sample of postoperative- and critically ill patients, and whether it can recognize delirium at an early stage. Furthermore, eye movement detection could be combined with other types of physiological monitoring to improve the discriminative power, for example temperature variability or EEG.[40]

In conclusion, this is the first study with automatic eye movement detection in delirious patients. We found that spontaneous eye movements, in particular blinks, were affected in delirious patients, which holds promise for the development of an objective tool to detect delirium.

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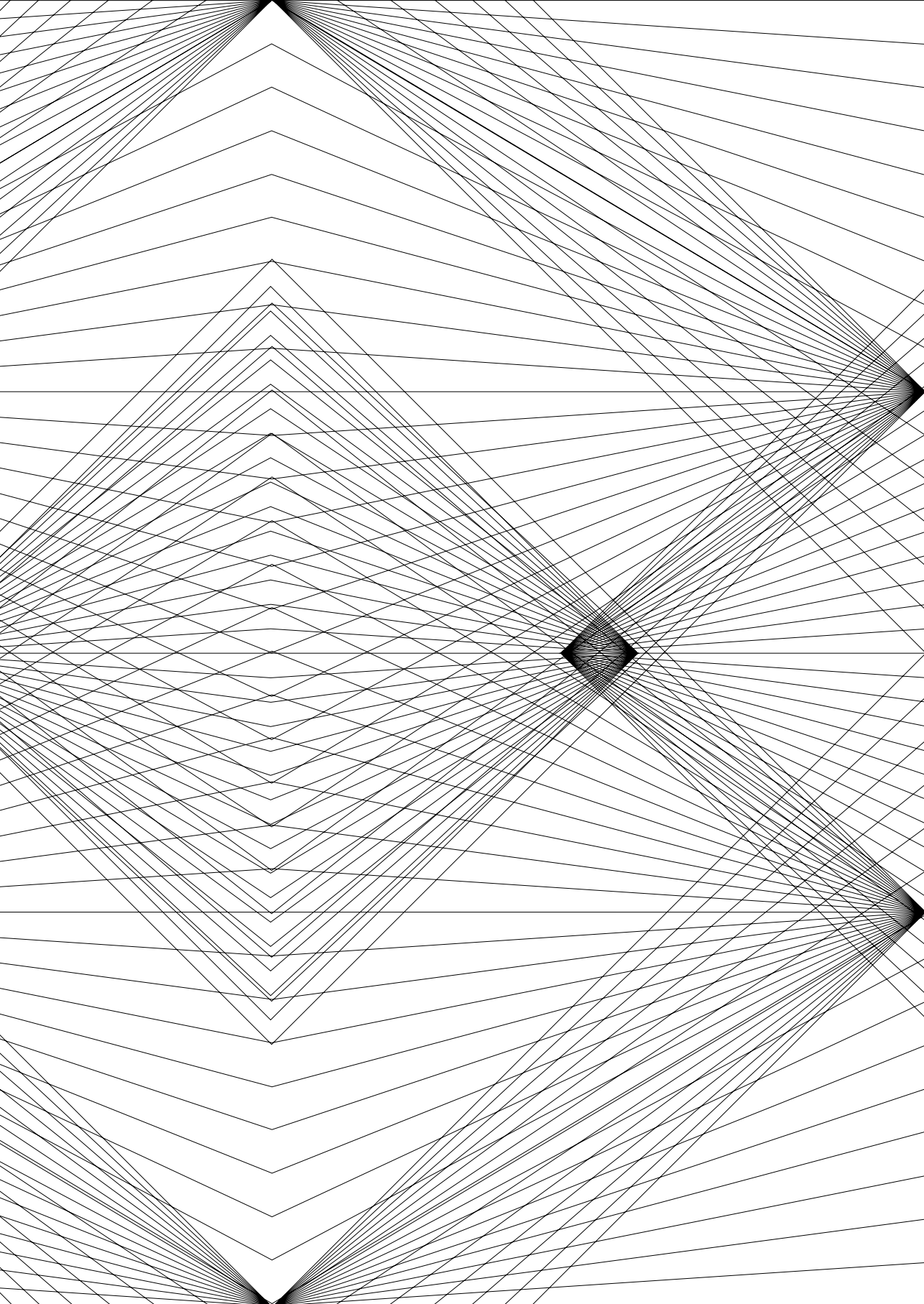

◆ CHAPTER 8 ◆

TEMPERATURE VARIABILITY DURING DELIRIUM IN ICU PATIENTS: AN OBSERVATIONAL STUDY

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ABSTRACT

INTRODUCTION Delirium is an acute disturbance of consciousness and cognition. It is a common disorder in the intensive care unit (ICU) and associated with impaired long-term outcome. Despite its frequency and impact, delirium is poorly recognized by ICU-physicians and –nurses using delirium screening tools. A completely new approach to detect delirium is to use monitoring of physiological alterations. Temperature variability, a measure for temperature regulation, could be an interesting component to monitor delirium, but whether temperature regulation is different during ICU delirium has not yet been investigated. The aim of this study was to investigate whether ICU delirium is related to temperature variability. Furthermore, we investigated whether ICU delirium is related to absolute body temperature.

METHODS We included patients who experienced both delirium and delirium free days during ICU stay, based on the Confusion Assessment Method for the ICU conducted by a research- physician or –nurse, in combination with inspection of medical records. We excluded patients with conditions affecting thermal regulation or therapies affecting body temperature. Daily temperature variability was determined by computing the mean absolute second derivative of the temperature signal. Temperature variability (primary outcome) and absolute body temperature (secondary outcome) were compared between delirium- and non-delirium days with a linear mixed model and adjusted for daily mean Richmond Agitation and Sedation Scale scores and daily maximum Sequential Organ Failure Assessment scores.

RESULTS Temperature variability was increased during delirium-days compared to days without delirium ($\beta_{unadjusted}$ = 0.007, 95% Confidence Interval (CI) = 0.004 to 0.011, p<0.001). Adjustment for confounders did not alter this result ($\beta_{adjusted}$ = 0.005, 95% CI=0.002 to 0.008, p<0.001). Delirium was not associated with absolute body temperature ($\beta_{unadjusted}$ = -0.03, 95% CI = -0.17 to 0.10, p = 0.61). This did not change after adjusting for confounders ($\beta_{adjusted}$ = -0.03, 95% CI = -0.17 to 0.10, p = 0.63).

CONCLUSIONS Our study suggests that temperature variability is increased during ICU delirium.

INTRODUCTION

Delirium is an acute disturbance of attention, consciousness and cognition that usually fluctuates over time.[1] It is a common disorder in the intensive care unit (ICU), with three different subtypes based on psychomotor behavior: hypoactive, hyperactive and mixed-type delirium.[2] Delirium is associated with higher mortality, longer hospital stay, long-term cognitive impairment and increased costs.[3-6]

Despite its frequency and impact, recognition of delirium by ICU-physicians is poor (overall sensitivity 29%).[2] In order to improve early diagnosis and treatment, the Society of Critical Care Medicine and the American Psychiatric Association recommend daily monitoring of delirium in ICU patients.[7, 8] Various delirium assessment tools have been developed. Of these, the Confusion Assessment Method for the ICU (CAM-ICU) has the highest sensitivity (80% in meta-analysis).[2, 9, 10] In contrast to results from a research setting, the sensitivity of the CAM-ICU showed to be low in routine, daily practice (overall 47%).[11] This hinders early detection of delirium, and the subsequent delay in treatment may worsen patient outcome.[12]

A completely new approach to detect delirium is to use monitoring of physiological alterations.[13] Delirium is a manifestation of encephalopathy which may also affect thermoregulation. In delirium tremens, Wernicke encephalopathy, as well as schizophrenia, temperature regulation is disturbed.[14-16] However, temperature variability has never been investigated in ICU patients with and without delirium. The primary aim of this study was to investigate whether ICU delirium is related to temperature variability. We hypothesized that delirium is associated with increased temperature variability. Secondary, we investigated whether ICU delirium is related to absolute body temperature.

MATERIALS AND METHODS

STUDY DESIGN

In this single-center retrospective cohort study, patients were selected from three prospective studies conducted at the ICU of the University Medical Centre Utrecht (UMCU) between March 2009 and May 2012. These three prospective studies included: the control group of the randomized clinical trial on Rivastigmine,[17] the ICU Environment Study [18] and the Epidemiology of ICU Delirium Study (unpublished data, but study results were presented at the European Delirium Association 7th annual meeting, 2012, Bielefeld, Germany). All three studies were approved by the UMCU medical ethics committee. For the trial on Rivastigmine patients gave written informed consent (UMCU medical ethics committee number 08-077), whereas for the latter two studies, the UMCU medical ethics committee waived the need to obtain informed consent (UMCU medical ethics committee number 11-450 and 12-421 respectively). From these three studies patient characteristics and prospective delirium and RASS assessments were obtained. In addition, temperature data was extracted retrospectively from the patient data management system. The local medical ethics committee approved the retrospective study Delirium and Temperature Variability (UMCU medical ethics committee number 11-567).

PATIENTS

All medical records of patients included in the three prospective studies mentioned above were re-evaluated for possible inclusion in the present study. All adult patients with at least one delirious and one delirious-free episode during an ICU admission of at least 24 hours were included, except for the following five exclusion criteria: (1) disturbed regulation of body temperature: renal replacement therapy, extra corporal membrane oxygenation, therapeutic hypothermia or admission because of an intoxication; (2) no temperature data in the medical record; (3) persistent delirium or comatose state during the whole ICU admission, which makes comparison of delirium- with non-delirium days impossible; (4) admission because of a neurological- or neurosurgical disease, as it may be difficult to diagnose delirium in these patients; or (5) impossibility to be tested with the CAM-ICU, for example because of an inability to understand Dutch or English. A comatose state was defined as a Glasgow Coma Score lower than 9 or a Richmond Agitation and Sedation Scale (RASS) score lower than minus 3.[19, 20] Furthermore, we excluded patients with sepsis throughout their whole ICU admission as well as days with sepsis in other patients. Sepsis was defined as two or more systemic inflammatory response syndrome criteria together with a suspected or proven infection described in the medical record.[21] All included patients were treated with paracetamol 1000 mg 4 times daily, both on days with delirium,

as on days without. None of the patients were receiving dexemedatomidine during their ICU admission.

DATA COLLECTION

In all three original studies, patient data was collected per day and baseline parameters, sepsis parameters, as well as RASS and Sequential Organ Failure Assessment (SOFA) scores were extracted from the medical records.[22]

Because of suboptimal sensitivity of the CAM-ICU in daily practice,[11] delirium was assessed in all three original studies, prospectively, seven days a week, by a research-nurse or –physician. This delirium assessment included the scoring of the CAM-ICU by the research-nurse or –physician prospectively, review of medical records and review of nursing charts including CAM-ICU scores performed twice-daily by bedside nurses. Based on this assessment, the research-nurse or –physician made a daily classification of the mental status of patients as either: (1) awake and non-delirious, (2) delirious or (3) comatose, as defined above. In doubtful cases, a neurologist-intensivist (AJCS) was consulted, who made the final classification. Temperature in the ICU was automatically controlled in every room to be constantly 18 degrees Celsius using a thermostat.

Temperature data was measured every minute in the inguinal crease or rectum with a temperature probe (Respectively YSI 403 or YSI 409B, YSI temperature, Dayon, Ohio, U.S.A.). Measured temperature data was filtered and sampled by the Spacelabs Medical Ultraview® Command Module (Spacelabs healthcare, LLC, Issaquah, WA, U.S.A.). Temperature data was stored at 1 sample per minute in the patient data monitoring system (Metavision, version 5.45.62, iMDsoft, Needham, Massachusetts, U.S.A.). Data analysis and artifact detection was conducted in Matlab (Matlab, version 7.9.0.529, The MathWorks Inc, Natick, Massachusetts U.S.A.). For artifact detection, temperature measurements below 35 degrees were excluded, together with data from the preceding and following 20 minutes, in order to overcome decreases in temperature due to a removed thermometer. Per measurement day at least 144 temperature measurements (10%) had to be available after artifact removal, otherwise that day was excluded for temperature variability analysis.

OUTCOME

The primary outcome was temperature variability. Temperature variability was defined as the daily mean absolute second derivative (i.e. acceleration) of the body temperature signal. The secondary outcome was absolute body temperature and this was defined as the daily mean of the body temperature signal.

STATISTICAL ANALYSIS

Temperature variability data as well as absolute body temperature data were averaged per day. Data of a particular day was excluded from analysis, when that day a patient was comatose, had only less than 10% of the 24 hour temperature data available, suffered from sepsis or died.

All variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed variables were presented using mean and standard deviation (Std), non-normally distributed variables with median and interquartile range (IQR).

Patients with and without delirium were compared for differences in temperature variability and absolute body temperature, and additionally adjusted for level of activity (mean RASS) and disease severity (maximal SOFA score). Linear mixed models were used to account for clustering of multiple, daily measurement averages per patient. Delirium scores, as well as possible confounders, mean RASS and maximal SOFA scores, were included as fixed effects. All models included a random intercept. Random slopes for the fixed effects were included when the Akaike Information Criterion of that particular model was five points lower than the Akaike Information Criterion of the same model with only a random intercept. The used covariance type for models with only a random intercept was 'identity'; in all other cases it was 'unstructured'. Statistical analyses were performed with Statistical Package for the Social Sciences (IBM SPSS Statistics, version 20, Armonk, New York, U.S.A.). A two-tailed p-value less than 0.05 was considered to be statistically significant.

RESULTS

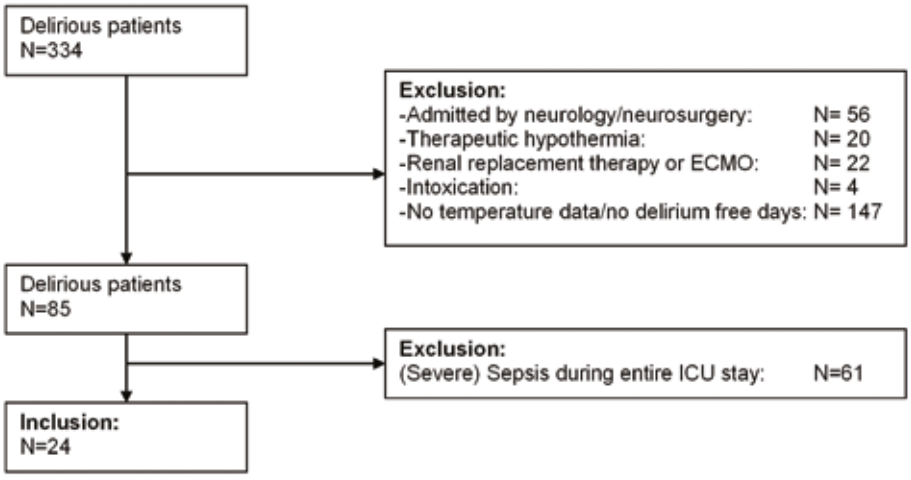
In total, 334 delirious patients were evaluated of whom 24 patients were included (Figure I). Characteristics of the included patients are described in Table I. Nine patients were female. The mean age was 68 years old (Std = 14) and mean Acute Physiology and Chronic Health Evaluation IV score was 52 (Std = 21). Median length of ICU stay in these patients was 5 days (IQR 3.3 to 9.8). The median number of delirium days in the study population was 2 (IQR 1.0 to 2.0) and the median number of non-delirium days 1 (IQR 1.0 to 2.8).

Overall, the median (interquartile range) of the number of samples per measurement day was 755 (506-1027). In Figure II, the determination of temperature variability is explained for one patient. The differences per patient for temperature variability are shown in Figure III. Of the 24 patients, 21 patients (88%) showed increased temperature variability during delirium when compared to non-delirium. The mean temperature variability on delirium days was 0.021 (Std = 0.008) and non-delirium days 0.015 (Std = 0.010).

The best unadjusted and adjusted linear mixed models for temperature variability included only a random intercept and no random slopes. Both the unadjusted and adjusted linear mixed models showed that temperature variability is increased during delirium ($\beta_{unadjusted}$ = 0.005, 95% CI = 0.003 to 0.008, p<0.001 and $\beta_{adjusted}$ = 0.005, 95% CI = 0.002 to 0.008, p<0.001).

The mean absolute body temperature on delirium days was 36.9 °C (Std = 0.50) and on non-delirium days 36.9 °C (Std = 0.58). Of the 24 patients, 13 patients (54%) showed decreased temperature during delirium when compared to non-delirium. The best unadjusted and adjusted linear mixed models for absolute body temperature also included only a random intercept and no random variables. Both the unadjusted and adjusted linear mixed models showed that delirium is not associated with absolute body temperature ($\beta_{unadjusted}$ = -0.03, 95% CI = -0.17 to 0.10, p = 0.61 and $\beta_{adjusted}$ = -0.03, 95% CI = -0.17 to 0.10, p = 0.63).

FIGURE I *Screening and enrolment*



Abbreviation in Figure I: ECMO = Extra Corporal Membrane Oxygenation.

TABLE I *Patient characteristics*

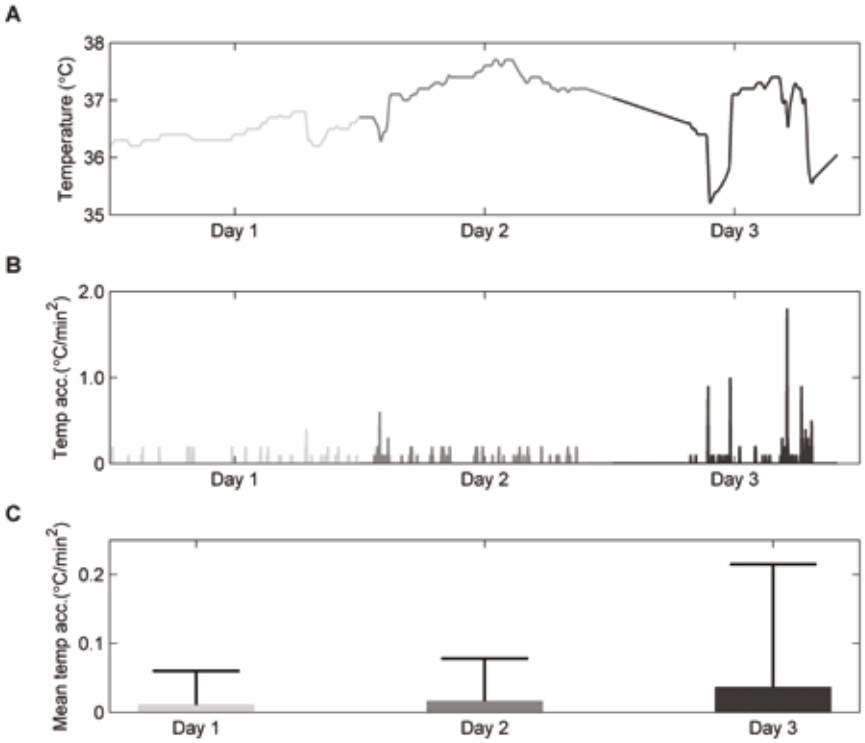
CASE	AGE	GENDER	ADMITTING DISCIPLINE	APACHE IV	DELIRIUM TYPE
1	37	M	Gen. Surg.	49	Mixed
2	75	M	Int. Med	94	Mixed
3	53	F	Card. Surg.	26	Mixed
4	69	M	Card. Surg.	48	Hypo
5	68	M	Int. Med	85	Mixed
6	73	M	Gen. Surg.	41	Mixed
7	78	M	Gen. Surg.	100	Mixed
8	82	M	Gen. Surg.	72	Hypo
9	71	M	Gen. Surg.	61	Mixed
10	65	M	Gen. Surg.	36	Hypo
11	80	M	Card. Surg.	60	Mixed
12	75	M	Card. Surg.	76	Mixed
13	79	F	Card. Surg.	63	Mixed
14	53	M	Card. Surg.	81	Mixed
15	55	F	Int. Med	38	Mixed
16	74	F	Gen. Surg.	62	Hypo
17	58	F	Card. Surg.	30	Mixed
18	84	M	Card. Surg.	69	Mixed
19	75	F	Card. Surg.	62	Mixed
20	72	F	Card. Surg.	38	Hypo
21	35	F	Card. Surg.	58	Hypo
22	67	M	Gen. Surg.	47	Mixed
23	79	M	Gen. Surg.	88	Mixed
24	44	F	Gen. Surg.	38	Mixed

Abbreviations in Table I: Apache IV = Acute Physiology and Chronic Health Evaluation IV score; Card. Surg. = Cardiology and cardiac surgery; D = Delirium; Gen. Surg. = General surgery; Hyper = Hyper active delirium; Hypo = Hypo active delirium; Int. Med. = Internal medicine; Mixed = Mixed type delirium;

TEMPERATURE (MEAN±Std)		TEMPERATURE VARIABILITY (MEAN±Std) 10^{-2} $^{o}C/MIN^{2}$		NUMBER OF ANALYSED DAYS (N)	
D	ND	D	ND	D	ND
37.4±0.2	37.6±0.3	1.2±0.4	0.8±0.3	2	7
36.9±0	37.3±0	1.8± 0.1	0.4± 0	2	1
37.9±0	37.8±0	1.6±0	0.8±0	1	1
36.3±0	36.0±0	1.6±0	1.3±0	1	1
36.3±0.4	36.1±0.4	1.5± 1.1	1.0±0.4	4	4
37.0±0.3	36.9±0.2	2.2±0.6	2.0±0.6	9	6
36.6±0.4	36.8±0.3	1.5±0.5	1.7±0.6	4	6
36.4±0	37.0±0.1	1.6±0	0.9±0.5	1	2
37.3±0.3	37.9±0	2.5±1.5	0.3±0	2	1
36.7±0	37.4±0	3±0	2.6±0	1	1
37.1±0	36.3±0	2±0	1.9±0	1	1
37.7±0.6	37.4±0	2.9±0.6	0.8±0	2	1
36.7±0.1	36.8±0	2.5±0.4	1.5±0.4	2	1
37.2±0.2	37.5±0	2.6±0.2	1.4±0	2	1
37.1±0.1	37.3±0.1	2.4±0.6	2.7±0.1	2	2
37.4±0	36.3±0	1.7±0	1.3±0	1	1
36.0±0.2	36.4±0.2	2.2±0.6	2.1±0.1	3	3
36.9±0	36.8±0	3.1±0	1.8±0	1	1
36.6±0	36.2±0	3.6±0	3.4±0	1	1
36.5±0.1	37.0±0	3.9±1.3	1.0±0	3	1
35.9±0	35.8±0	1.0±0	1.3±0	1	1
36.9±0	37.0±0	1.3±0.5	0.8±0	2	1
37.0±0.2	36.9±0.4	2.0±1.0	1.9±0	2	3
36.7±0	37.2±0	3.6±0	1.6±0	1	1

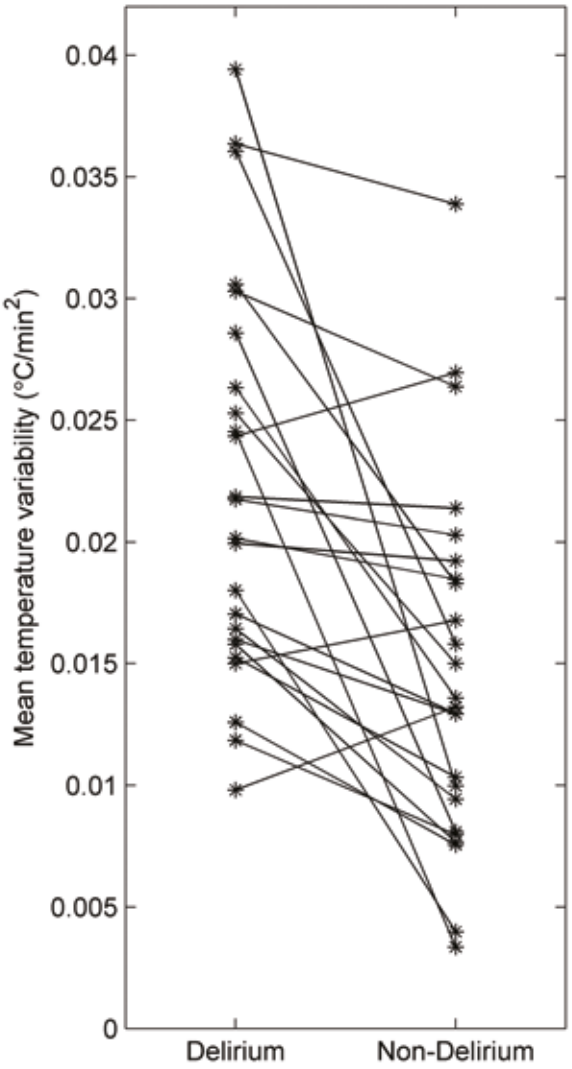
ND = Non-Delirium; Std = Standard deviation. Type of delirium was based on Richmond agitation and sedation scale (RASS) during delirium days: Hyper = always RASS > 0, Hypo = always RASS score < 1, Mixed = not always RASS > 0 or RASS <1.

FIGURE II *Example of temperature variability determination*



Panel A shows the temperature curve, which was corrected for artifacts using linear interpolation. Panel B shows the normalized temperature acceleration and panel C the mean normalized temperature acceleration per day with corresponding standard deviations. Periods of coma are depicted in light grey, periods of no delirium in dark grey, and periods of delirium in black. The whiskers represent the standard deviation.

FIGURE III *Temperature variability per patient*



Per patient the mean temperature variability is depicted for delirium and non-delirium days. The majority of patients (21/24) shows higher mean temperature variability during delirium.

DISCUSSION

In summary, temperature variability was found to be increased in ICU patients during delirium-days when compared to days without delirium. When we adjusted for level of activity and disease severity, temperature variability remained increased during delirium. Absolute body temperature was not related to delirium.

Increased temperature variability during delirium can be a manifestation of the encephalopathy that underlies delirium. Using electroencephalography, it has been shown that during delirium the brain is suffering from an encephalopathy.[23] Body temperature is mainly controlled by the hypothalamus. Encephalopathic changes may affect the thermoregulation network of the hypothalamus, which impairs the capability to keep body temperature constant. In addition, the underlying etiology of delirium could also be a source for increased temperature variability. In Wernicke encephalopathy, delirium tremens and schizophrenia, thermal dysregulation has been described.[14-16] In ICU delirium, this has never been studied before.

This is the first study on temperature variability in ICU delirium. Previously, temperature variability has been investigated with approximate entropy, detrended fluctuation analysis and wavelet properties.[24-26] However, these variables are more complex to compute than the mean absolute second derivative of the temperature signal that was used in the present study. To investigate temperature curve complexity, a continuous temperature signal is needed, with minimal artifacts. In patients with hyperactive or mixed type delirium it can be difficult to establish continuous temperature measurements for several days, due to an increased amount of movements which may result in artifacts. Therefore, a less complex time based analysis method, which is less vulnerable for artifacts, was used in this study to investigate whether the temperature curve differs between delirium days and non-delirious days in the same patient. This time based analysis method can be easily implemented in a monitoring device.

Other strengths of this study are that delirium diagnoses were prospectively obtained per day by research-nurses and –physicians with a combination of the CAM-ICU and review of medical and nursing charts. Although in daily practice the sensitivity of the CAM-ICU for detecting delirium may be disappointing, in research setting the CAM-ICU proves to be a sensitive tool for detecting delirium with sensitivities of 64 to 100% and specificities of 88 to 100%.[9, 11, 27] Although, we excluded all patients with characteristics that may affect temperature variability, we still found increased temperature variability during delirium.

A limitation of this study was that temperature data was obtained retrospectively. To minimize artifacts one could argue to obtain the data prospectively

in order to control the environment of the measurement. The measurement in the inguinal crease may have been biased due to influence of sedative medication on skin perfusion. We excluded deeply sedated and comatose patients and thereby the effects of deep sedation. In addition, we adjusted for the level of sedation (RASS) in our linear mixed model analysis, to minimize the effect of sedation on temperature variability. Correcting for this confounder did not alter our results. Moreover, delirious patients may be more likely to remove thermometers which could have affected our results. By using the RASS score as a variable in the linear mixed model, we aimed to adjust for the fact that awake patients will move more and are more likely to remove thermometers. Correction for this variable did not alter the results. Therefore, the effect seems minimal. A future prospective design could resolve this problem.

As a first step to evaluate whether temperature variability could be used for delirium monitoring, we excluded patients with conditions affecting thermal regulation or therapies affecting body temperature as well as data of days on which the patient suffered from sepsis. One could argue to exclude several days before sepsis as well, as previous literature showed that delirium preceded the development of overt sepsis by at least 48 hours in 31% of all patients.[28] By using a linear mixed model and correcting for the Sequential Organ Failure Assessment score (also known as Sepsis-related Organ Failure Assessment) we corrected for organ faillure prior to possibly upcoming sepsis. Correcting for this confounder did not alter our results. In this study, we did not investigate whether individuals in the ICU who never developed delirium have the same temperature variability. Instead, to increase statistical power, we compared delirium days with days without delirium, where patients were their own controls. Of note, 15 of the 24 patients included in this study were treated with haloperidol. We cannot exclude that the administration of pharmacological substances has a certain influence on our findings. However, such an influence of haloperidol on temperature variability has never been described.

The natural circadian rhythm of body temperature also gives rise to a temperature variability which is on average $1.2*10^{-5}$ °C/min^2 for a cosines with an amplitude of 1 degree Celsius.[29] Removal of time periods with signal containing artifacts could have influenced our findings. However, the circadian temperature variability was approximately a thousand times smaller than the temperature variability measured in this study. Therefore, this could only have a minimal effect on the difference in temperature variability between delirium- and non-delirium days.

Future prospective diagnostic studies should explore whether temperature variability can be used as a diagnostic parameter in an unselected population of ICU patients for delirium monitoring. These studies should also consider blood stream temperature

measurement (via central line or artery), because this might lead to more reliable data. In this first explorative study, we could only investigate if there are any opportunities to use temperature variability for monitoring. When our findings are confirmed, temperature variability could be incorporated together with other physiological parameters into an objective monitoring device for delirium. Electroencephalography (EEG) shows generalized slowing of background activity during delirium.[13] Temperature variability together with EEG, with a limited number of electrodes and automatic processing, could provide the input for an objective tool to monitor delirium.

Temperature variability is increased during delirium in ICU patients. Opportunities for delirium monitoring using temperature variability should be further explored. Particularly, in combination with EEG, it could provide the input for an objective tool to monitor delirium in ICU patients.

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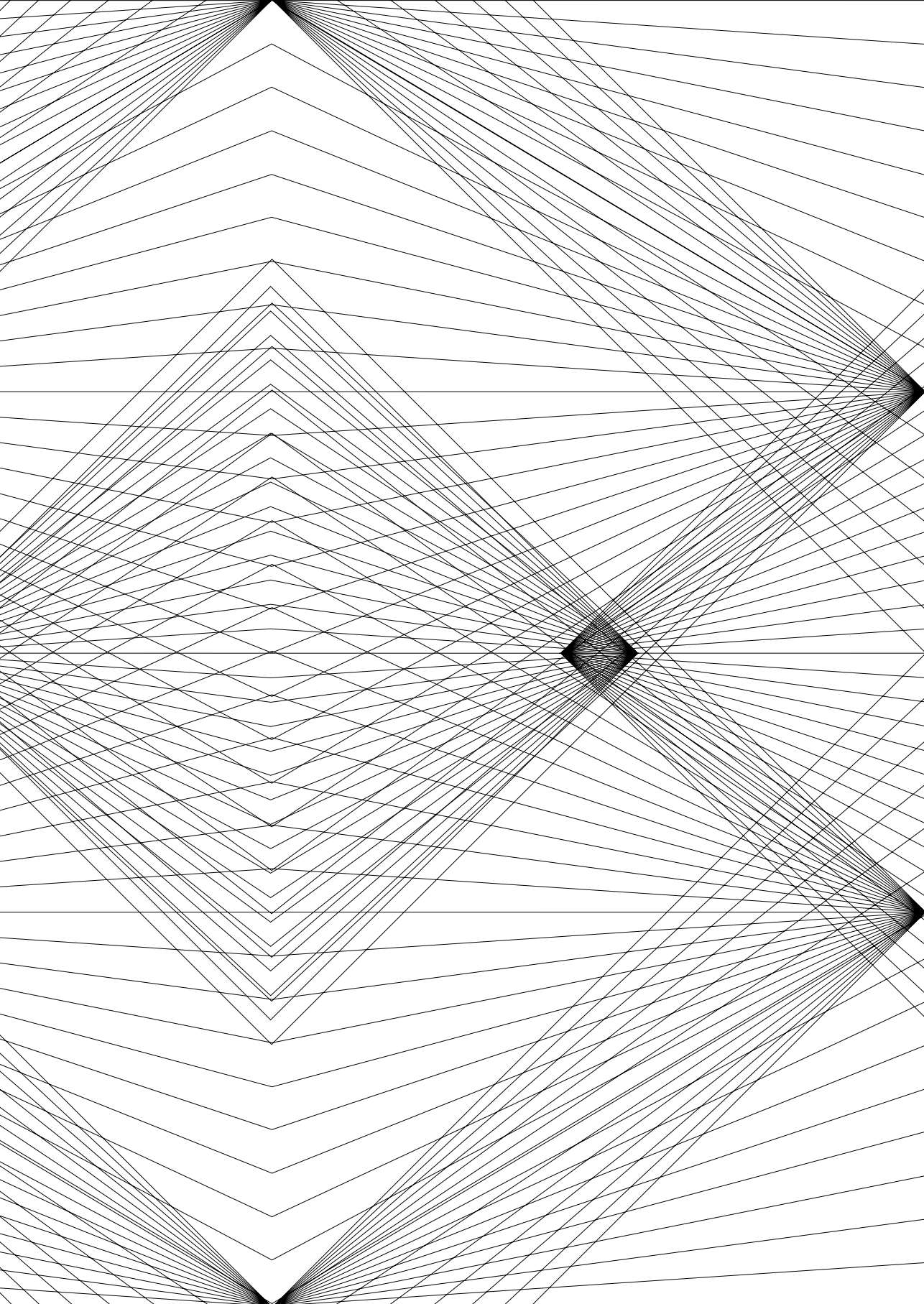

◆ CHAPTER 9 ◆

GENERAL DISCUSSION

GENERAL DISCUSSION

The objective of this thesis was to characterize the neurophysiology of delirium and to assess whether alterations in the neurophysiology of delirium, could provide opportunities for delirium detection. In the first part of this thesis, we showed that by the analysis of the electroencephalogram (EEG) and electrocardiogram (ECG) we can expand our knowledge of the neurophysiological characteristics of delirium. Patients with delirium suffer from decreased functional connectivity and loss of small world topology in their EEG when compared to patients without delirium. These findings are consistent with altered functional connectivity and network topology in other diseases that affect cognitive functioning, such as schizophrenia and Alzheimer's disease. In addition, delirious patients have less complex EEG signals with increased spectral variability. The reduced complexity corresponds with results in Alzheimer's disease. The analysis of heart rate variability (HRV) derived from the ECG, revealed that that the balance between parasympathetic and sympathetic activity (sympathovagal balance) may not be altered during Intensive Care Unit (ICU) delirium.

In the second part of this thesis, we presented the results of studies assessing the opportunities for delirium detection using EEG, eye movements and body temperature. It was described that several EEG parameters were significantly different during delirium compared to non-delirium even when these were measured by only two electrodes and over a short period of time. Furthermore, the number of eye movements, especially blinks, were significantly decreased during delirium and had a longer duration. Moreover, temperature variability was increased in ICU patients with delirium, when compared to ICU patients without delirium.

CHARACTERIZATION OF DELIRIUM

Delirium has a highly heterogeneous pathophysiology that is not well understood. Instead of searching for a common causal pathway to increase our understanding of delirium, one could also focus on the characterization of the neurophysiology to expend our comprehension. Clinically, delirium is characterized by an acute change in cognition.[1] The mechanism by which this acute change in cognition occurs is unclear. In this thesis it was demonstrated that during delirium the functional connectivity and network topology determined using EEG are altered in a similar manner to other diseases that affect cognitive functioning. Thereby delirium may be seen as a disconnection syndrome. This is supported by results from an fMRI study in which it was described that functional connectivity alterations caused by delirium largely resolve after the episode of delirium has ended. Furthermore, the extent of the

functional connectivity alterations was correlated to delirium severity.[2] The cause of the functional connectivity alterations is still unclear, but current progress in neural network models could provide answers. Recently, a first attempt was made to use neural mass models to elucidate EEG phenomena as seen in encephalopathy such as polymorphic delta activity. An encephalopathy usually manifests as delirium and, in severe cases, as coma. The results indicated that EEG phenomena characteristic for encephalopathy may be caused by imbalances between inhibitory and excitatory activity and increased fluctuations in subcortical input combined with an altered shape of the excitatory postsynaptic potential.[3] These results suggest that neural mass models may improve our understanding of delirium characteristics.

While delirium may be considered as a reversible syndrome, current evidence reveals that there is a strong association between delirium and long term cognitive decline. In a recent multicenter, prospective cohort study the incidence of long term cognitive impairment after critical illness was estimated and related to the duration of delirium. ICU patients were at high risk for long-term cognitive impairment. Even more interesting, the duration of delirium was independently associated with worse global cognition at 3 and 12 months after hospital discharge.[4] Because this study was conducted in an ICU population with limited information on the pre-ICU cognitive trajectory of patients, it was unclear whether the delirium caused an absolute decrease in long term cognition or accelerated the pre-existing cognitive deterioration associated with aging. Population studies could resolve this issue, as subjects are already monitored before hospital admission. In a cohort study of 533 Finnish subjects aged 85 years or older at baseline, delirium was a strong risk factor for dementia.[5] For individuals with existing dementia, delirium was associated with an acceleration of cognitive decline. Whether functional connectivity and network topology display also long term alterations caused by delirium, has not been studied yet. When we assume that delirium leads to a (temporary) disconnection syndrome, delirium could make the brain more prone for future disconnections which possibly results in other non-temporary disconnection syndromes like Alzheimer's disease. Future neural network studies could provide more insights into this hypothesis and explain the mechanism by which delirium accelerates cognitive impairment.

APPROACHES FOR DELIRIUM DETECTION

To enhance the quality of future research in delirium and more importantly, the daily care for patients with delirium, we need an optimal diagnostic tool for monitoring of delirium. Current delirium tools need intense training as well as dedication to provide a reasonable sensitivity.[6] As we cannot expect that every nurse has a natural dedication

to cognitive screening methods, these tools appear to lack sensitivity in daily clinical care.[7] Thereby, the recognition of delirium in daily care is low and current options for delirium severity monitoring are sparse.[8] This current situation makes it difficult to find new prevention and treatment strategies. The optimal diagnostic tool should ideally have a high sensitivity and specificity for delirium detection. Furthermore, this tool should be practical and easy to use by all kinds of medical staff from nurses to physicians without the need for intense training and educations programs. The tool should fit in the clinical setting where it will be used. By providing an indication of the delirium severity, the delirium monitoring tool should make it possible to monitor and titrate the impact of treatment strategies on the delirium severity.

In this thesis we show that there are other opportunities for delirium screening besides cognitive screening. During delirium several neurophysiological parameters as number and duration of eye movements, temperature variability and EEG parameters are affected. Measuring these parameters can help us distinguishing delirium from non-delirium. However, some neurophysiological parameters are more promising than others.

The number and duration of eye movements, especially blinks, are different during delirium. Blinks can be measured by use of only two electrodes, but monitoring of blinks requires the patient to keep the eyes open for at least one minute. Temperature variability is easy to measure, as continuous temperature measurements are already conducted in almost all ICU patients. However, it remains unknown whether temperature variability in a general population of ICU patients is a sensitive measure for delirium monitoring, as many patients suffer from conditions or undergo treatment that affect body temperature. Moreover, outside the ICU temperature monitoring is much more difficult, as body temperature is not continuously, but only intermittently monitored, which is not suitable for temperature variability determination. EEG measured with only two electrodes and one minute of data with eyes closed, could easily distinguish delirium from non-delirium. The use of only two electrodes makes EEG detection of delirium much more feasible for use in daily practice. However, these results should be validated in another study and also the association between EEG and delirium severity should be investigated. The delirium monitoring device should be designed in concordance with nurses in order to develop a device that is simple and practical for clinical use. The monitor should display the results in an easy to interpret scale that indicates the risk and severity of delirium. To increase the robustness of the delirium measurement, one could add a reliability scale, that indicates whether the measurement results can be trusted or should be interpreted with caution (when the measurements was not performed well).

One of the important issues that remains to be solved for delirium detection in ICU patients is the confounding of light levels of sedation. Most commonly used sedative and analgesic agents have prolonged effects, especially after long-term exposure.[9] It is very difficult to predict the duration of this prolonged effect, particularly in patients with multi-organ failure.[9] In recent years it has been established that light levels of sedation in adult ICU patients improves clinical outcomes when compared to deep sedation.[10] The new pain, sedation and agitation guidelines of the Society of Critical Care Medicine endorse this light sedation regimen.[11] During light levels of sedation or residual sedation, patients may show similar features as during delirium, for example reduced level of consciousness and psychomotor slowing.[12] However, these features can also be caused by delirium or a combination of delirium and sedation. One study showed that patients with delirium have lower Bispectral Index (BIS) values, an EEG measure for the level of sedation measured by a limited number of electrodes.[13] This could be caused by difficulty of distinguishing sedation from delirium.[12] Whether residual sedation needs treatment is unclear. However, when the patient suffers from delirium, it is desirable to provide an intervention in order to limit the negative influences of delirium on patient outcome.[14] Choices for analgesics and sedatives should then be carefully evaluated and early mobility and exercise should be initiated. With current cognitive screening methods for ICU delirium it is impossible to make the distinction between sedation and delirium.[12] Sedation monitors on the other hand are not designed for light sedation monitoring in ICU patients. It was already shown that BIS has a correlation with light sedation levels and not specifically with delirium in ICU patients.[15] If sedation monitors could be further developed so that these are suitable for light sedation monitoring and additionally be combined with delirium monitoring, one could have an optimal monitor. First a study should be conducted in non-delirious ICU patient's to determine whether BIS is suitable for light sedation monitoring and to evaluate the accuracy of the BIS monitor for light levels of sedation. In addition, these study results can be used to develop an objective light sedation scale. A second study in which an EEG is recorded in delirious and non-delirious ICU patients using an F8-Pz derivation combined with BIS monitor electrodes multiple times per day and correlated to delirium and sedation levels (using the Richmond agitation sedation scale scores and plasma levels of sedatives), could provide us the answer whether delirium can be distinguished from light sedation. One could first focus on a homogenous ICU subgroup of post cardiac surgery patients and when results show clear correlations expand to a general population of ICU patients.

CONCLUSION

The causal pathways to delirium are heterogeneous and multifactorial and may include an ensemble of neuro-inflammation and neurotransmitter imbalances. By focusing on the neurophysiological characteristics, one can increase the understanding of delirium. Neural network analysis could be a valuable tool for these purposes.

For the detection of delirium, EEG with a limited number of electrodes seems the most promising method. Unfortunately, this method is not suitable for ICU patients due to interference of sedation. A combination of EEG based sedation monitoring and EEG based delirium monitoring may provide future solutions for delirium monitoring on the ICU.

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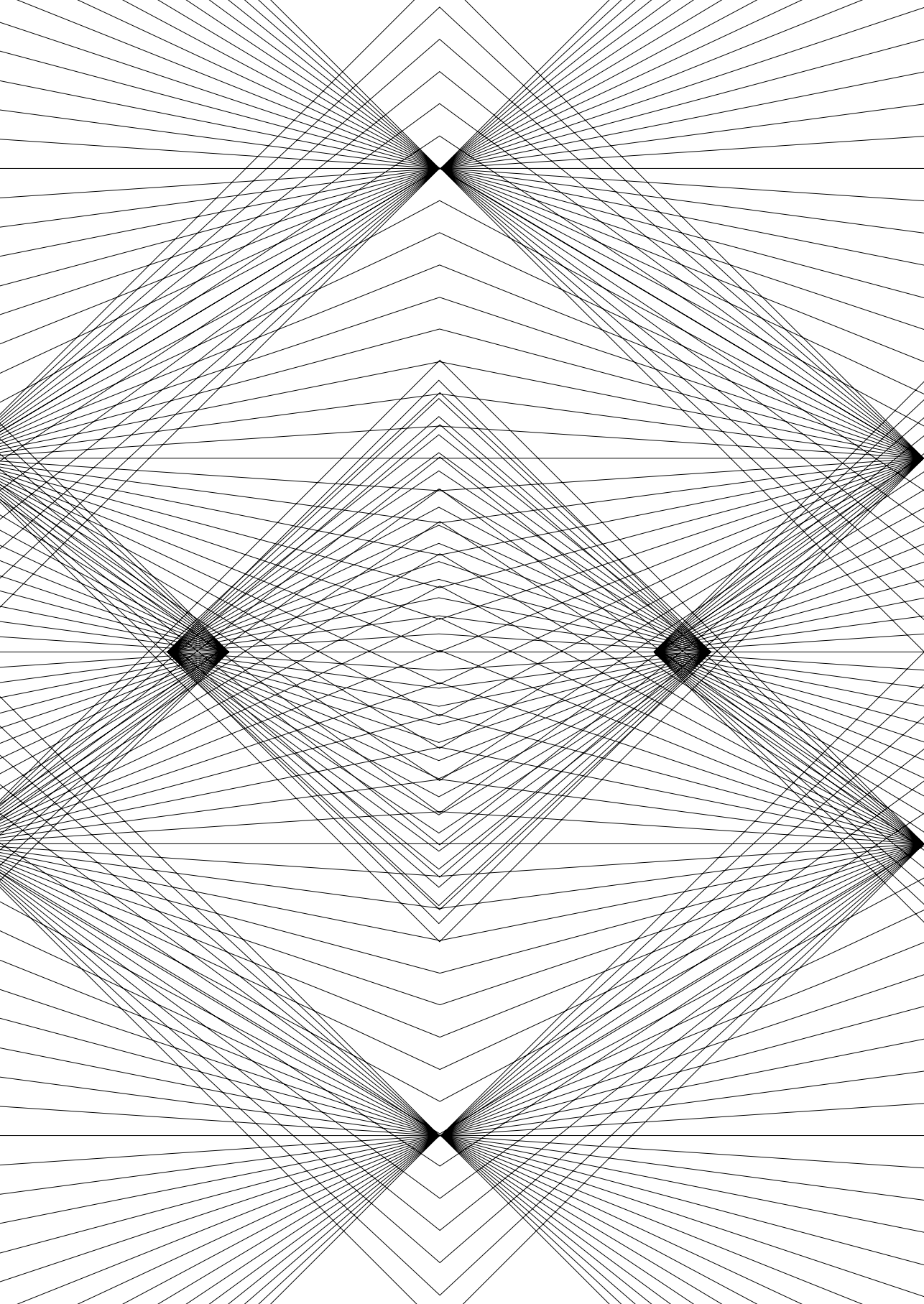


DUTCH SUMMARY

NEDERLANDSE SAMENVATTING

NEDERLANDSE SAMENVATTING

Delirium is een acute verstoring van bewustzijn, aandacht en cognitie. In *hoofdstuk 1* wordt een korte introductie op delirium gegeven. Delirium is een veel voorkomende aandoening die wordt geassocieerd met een verhoogde mortaliteit, langere ziekenhuis opname, cognitieve achteruitgang en verhoogde ziekenhuis kosten. De pathofysiologie van delirium is nog onduidelijk. Er zijn verscheidene hypothesen gesuggereerd in de richting van neuro-inflammatie en verstoringen van neurotransmitter systemen. Hoewel in de afgelopen decennia veranderingen in het elektro-encefalogram (EEG) tijdens delirium zijn beschreven, blijken andere neurofysiologische veranderingen maar minimaal bestudeerd te zijn. Op de intensive care (IC) wordt momenteel gebruik gemaakt van vragenlijsten om dagelijks de aanwezigheid van delirium te evalueren. De CAM-ICU is een van de meest gebruikte vragenlijsten voor dit doeleinde. Echter, in de dagelijkse praktijk zijn er veel meer vals-negatieve CAM-ICU beoordelingen dan verwacht op basis van de literatuur, waardoor delirium op de IC nog steeds wordt onder gediagnosticeerd. Een nieuwe methode om delirium te herkennen zou kunnen voortkomen uit het monitoren van neurofysiologische afwijkingen gerelateerd aan delirium, zoals bijvoorbeeld met EEG. Het doel van dit proefschrift is om de neurofysiologie van delirium te karakteriseren om hiermee opties voor delirium detectie te exploreren.

Met behulp van de Phase Lag Index (PLI) is de netwerk topologie en connectiviteit in het EEG geanalyseerd om zo de neurofysiologie van delirium beter te kunnen karakteriseren. De hypothese was dat verstoringen in aandacht en bewustzijn gerelateerd zijn aan veranderingen in functionele connectiviteit. Bij 28 patiënten met en 28 patiënten zonder delirium na hartchirurgie zijn EEG's gemaakt. Vanwege de noodzaak van 36 seconden artefact vrije data met ogen dicht konden uiteindelijk 25 delirante en 24 niet-delirante patiënten geïncludeerd worden. In *hoofdstuk 2* wordt beschreven dat de gemiddelde PLI lager was in de alfa frequentie band (8–13 Hz) in patiënten met delirium dan in patiënten zonder delirium ($p<0.01$). Patiënten met delirium lieten een lagere genormaliseerd gewogen kortste pad lengte zien (maat voor globale integratie) in de alfa frequentie band ten opzichte van patiënten zonder delirium ($p<0.01$). De lokale clustering (maat voor lokale segregatie) liet geen verschil zien tussen beide groepen. Delirium patiënten worden daarmee gekarakteriseerd door lagere functionele connectiviteit en een meer willekeurige (random) netwerk topologie. Dit kan zou kunnen verklaren waarom het verwerken van informatie minder efficiënt is tijdens delirium.

Hoewel delirium vaak gepaard gaat met fluctuatie van symptomen over de tijd, was er nog niet eerder beschreven of er ook meer fluctuaties in het EEG gekwantificeerd kunnen worden in patiënten met delirium dan in patiënten zonder delirium. De

EEG's van de eerder genoemde 28 patiënten met en 28 patiënten zonder delirium na hartchirurgie werden nader geanalyseerd in het tijds- en frequentiedomein. In het frequentiedomein werd gekeken naar variabiliteit van de verscheidene frequentiebanden en in het tijdsdomein naar complexiteit van het signaal. In *hoofdstuk 3* wordt beschreven dat delirium wordt gekenmerkt door een afname van complexiteit in het tijdsdomein, en door een toename van variabiliteit in het frequentiedomein. Er is dus meer fluctuatie in het frequentiedomein in de EEG's van patiënten met delirium, maar de EEG signalen zijn wel minder complex dan in patiënten zonder delirium. Een afname in complexiteit is kenmerkend voor een verstoorde cognitie, een symptoom van delirium.

Sommige symptomen van delirium, zoals tachycardie en tremoren, suggereren een verhoogde sympathische activiteit tijdens Intensive Care delirium. De mate van hart ritme variabiliteit (HRV) kan een indicatie geven van de sympatho-vagale balans, de balans tussen sympathische en parasympathische activiteit. In *hoofdstuk 4* wordt beschreven dat in 15 IC patiënten met en 15 IC patiënten zonder delirium de HRV is bepaald. De HRV indicatoren werden gemeten in het frequentiedomein over ECG segmenten van 5 minuten. De lage frequentie (LF = 0.04-0.15Hz) component van HRV weerspiegelt zowel sympathische als parasympathische activiteit, terwijl de hoge frequentie (HF = 0.15-0.40 Hz) component alleen de parasympathische activiteit weerspiegelt. De verhouding LF:HF is dan ook een maat voor sympathische activiteit. De resultaten lieten geen statistisch significant verschil zien tussen patiënten met en zonder delirium voor de genormaliseerde LF, HF en de LF:HF ratio. Deze resultaten suggereren dat autonome functie misschien niet verschilt tussen IC patiënten met en zonder delirium.

Zoal eerder genoemd, wordt delirium maar matig herkend in IC patiënten en postoperatieve patiënten. Een EEG met een beperkt aantal electroden zou mogelijk een sensitievere methode voor delirium detectie kunnen zijn. Daarom wordt in *hoofdstuk 5* een systematisch literatuur onderzoek beschreven naar EEG kenmerken van delirium. Er werden 14 studies gevonden, welke voornamelijk waren uitgevoerd in oudere, bejaarde patiënten. De relatieve power in de thèta en alfa frequentie banden lieten het vaakst (7 van de 14 studies) een significant verschil zien tussen patiënten met en zonder delirium. Omdat continue EEG monitoring al mogelijk is op de IC, lijkt EEG monitoring van delirium een veelbelovende methode te zijn.

Zoals in hoofdstuk 5 al was geconcludeerd, kan met behulp van EEG een delirium worden gediagnosticeerd. Dit is wel een lastige en onpraktische methode die ongeschikt is voor dagelijkse delirium screening. In *hoofdstuk 6* wordt daarom een studie beschreven die als doel heeft te bepalen of delirium te detecteren is met een beperkt aantal EEG electroden en zo ja, wat hiervoor dan de beste combinatie van EEG afleiding en parameter is. Standaard EEG's werden gemaakt in 28 delirante en 28 niet

delirante postoperatieve cardiochirurgie patiënten, zoals eerder beschreven in hoofdstuk 2 en 3, welke op groepsniveau overeenkomen qua leeftijd en geslacht. Delirium werd vastgesteld door een expert met behulp van de 'Diagnostic and Statistical Manual of Mental disorders-IV' criteria voor delirium. De eerste minuut artefact vrije data voor zowel ogen open als ogen dicht werd geselecteerd voor analyse. Voor ogen dicht werden alle mogelijke bipolaire afleidingen geanalyseerd, terwijl voor ogen open alleen occipitale en pariëtale electroden voor analyse werden gebruikt. Per bipolaire afleiding werden zes parameters berekend: de relatieve power in de delta, thèta, alfa en bèta frequentie band, de piek frequentie en de langzaam/snel ratio. Alle combinaties van bipolaire afleiding en EEG parameter werden vergeleken met de Mann-Whitney U-test en de bijbehorende p-waardes werden gerangschikt. Het grootste verschil tussen patiënten met en zonder delirium werd gevonden tijdens ogen dicht, op bipolaire afleiding F8-Pz (frontaal-pariëtaal) en relatieve power in de delta band ($p = 1.8*10^{-12}$). Hierdoor kan geconcludeerd worden dat de relatieve power in de delta band in een ogen dicht EEG opname met maar 2 elektrodes goed onderscheid kan maken tussen post cardiochirurgie patiënten met en zonder delirium.

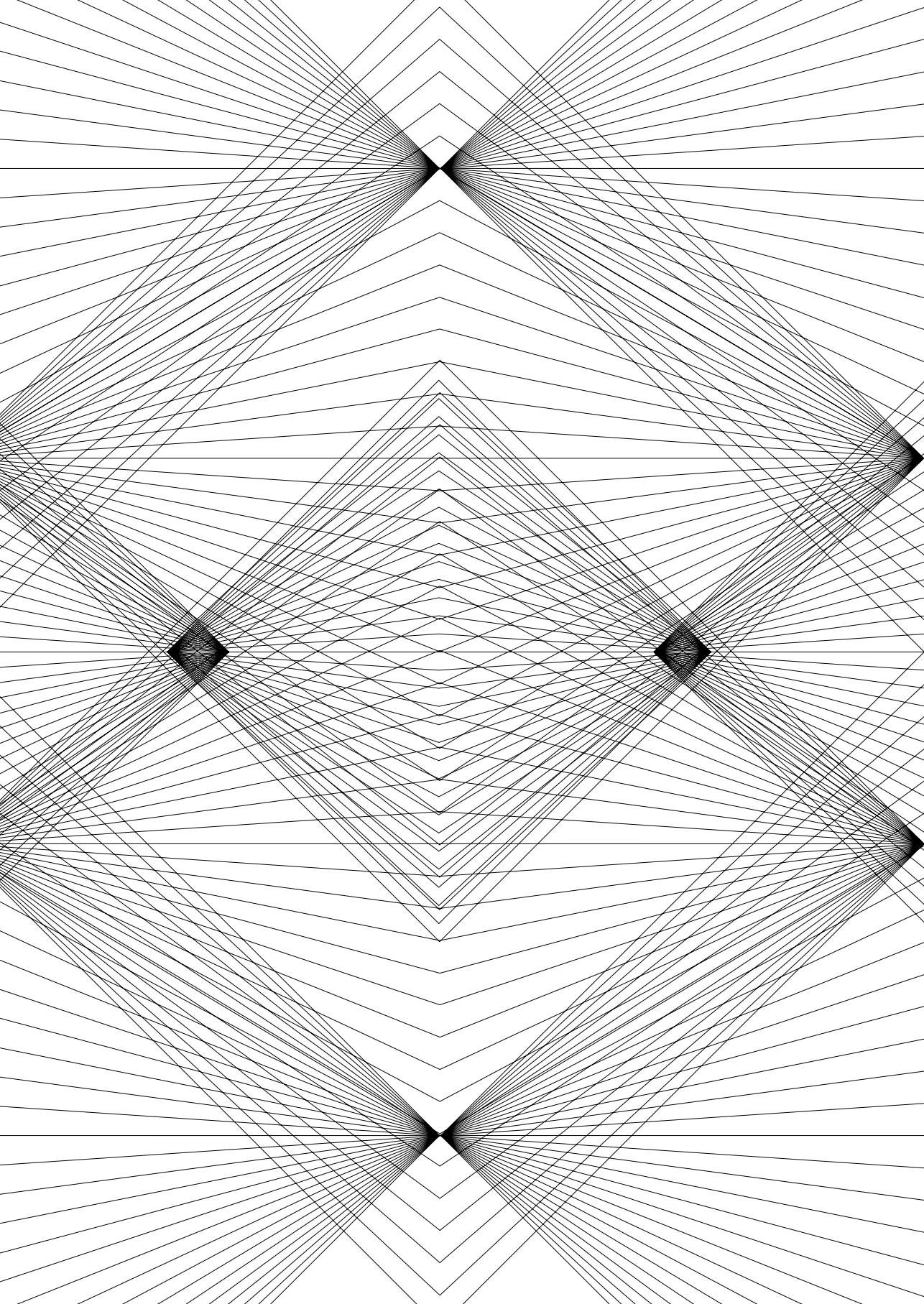
Met als doel de detectie van delirium te verbeteren is er naast EEG ook gekeken of oogknippers en oogbewegingen verschillen tussen patiënten met en zonder delirium. Deze studie die beschreven staat in *hoofdstuk 7*, was uitgevoerd op dezelfde patiënten populatie en EEG's als eerder beschreven in hoofdstuk 2, 3 en 6. De eerste minuut artefact vrije data voor zowel ogen open als ogen dicht werd geselecteerd voor analyse. Oogknippers werden automatisch geëxtraheerd uit het electro-oculogram en oogbewegingen werden met behulp van een onafhankelijke componenten analyse (independant component analyses) automatisch geëxtraheerd uit het EEG. Het aantal oogbewegingen en knippers per minuut en de gemiddelde duur van de oogbeweging en knippers in seconden werd vergeleken tussen patiënten met en zonder delirium. Tijdens ogen open lieten delirante patiënten significant minder oogknippers ($p = 0.02$) en verticale oogbewegingen ($p = 0.01$) per minuut zien ten opzichte van niet delirante patiënten. Ook lieten delirante patiënten een langere duur van oogknippers zien ($p = 0.01$) ten opzichte van niet delirante patiënten. Tijdens ogen dicht, hadden patiënten met delirium minder horizontale oogbewegingen dan patiënten zonder delirium ($p<0.01$). Deze resultaten laten zien dat oogbewegingen en knippers zijn aangedaan tijdens delirium, wat interessant kan zijn voor toekomstige delirium detectie.

In *hoofdstuk 8* zijn lichaamstemperatuur en temperatuurvariabiliteit, een maat voor temperatuur regulatie, bestudeerd als componenten voor een mogelijke delirium detectie methode. Het effect van delirium op de lichaamstemperatuur regulatie was nog nooit onderzocht. Daarom was het doel van de studie om uit te zoeken of

lichaamstemperatuur en temperatuurvariabiliteit gerelateerd zijn aan IC delirium. Voor deze studie werden patiënten geïncludeerd die tijdens verblijf op de IC dagen hadden met delirium en dagen hadden zonder delirium, gebaseerd op screening met de CAM-ICU (delirium screenings methode) uitgevoerd door onderzoeks- verpleegkundige of arts in combinatie met het bestuderen van de patiëntendossiers. Alle patiënten met aandoeningen of therapieën die de temperatuur regulatie mogelijk konden verstoren, werden geëxcludeerd. Lichaamstemperatuur werd continu per minuut gemeten in alle IC patiënten en per dag werd de gemiddelde lichaamstemperatuur bepaald. De dagelijkse temperatuurvariabiliteit werd bepaald door het per dag berekenen van de gemiddelde, absolute, tweede afgeleide van het lichaamstemperatuur signaal. Temperatuurvariabiliteit (primaire uitkomst) en lichaamstemperatuur (secundaire uitkomst) werden vergeleken tussen delirium en niet- delirium met behulp van een lineair mixed model, gecorrigeerd voor dagelijkse 'Richmond Agitation and Sedation scale' scores (maat voor agitatie en sedatie) en 'Sequential Organ Failure Assessment' scores (maat voor ernst van ziekte). In totaal werden 334 patiënten geëvalueerd waarvan 24 patiënten werden geïncludeerd. Temperatuurvariabiliteit was toegenomen tijdens delirium dagen ten opzichte van niet-delirium dagen ($p<0.001$) en correctie voor confounders veranderde dit resultaat niet. Delirium was niet geassocieerd met absolute lichaamstemperatuur ($p = 0.61$) en correctie voor confounders had geen effect op dit resultaat. Hieruit kan worden geconcludeerd dat temperatuurvariabiliteit lijkt toegenomen tijdens IC delirium.

Ten slotte wordt in *hoofdstuk 9* een visie op de resultaten uit dit proefschrift gegeven. Om delirium beter te kunnen begrijpen kan men zich focussen op de pathofysiologie, maar deze is nog onduidelijk en complex. Door te focussen op de neurofysiologische kenmerken van delirium kunnen we mogelijk ons begrip over delirium ook vergroten. Delirium wordt gekenmerkt door een afname van de complexiteit van het EEG, maar ook door een relatieve verandering van neurale netwerken in een meer random type. Deze kenmerken worden beide gerelateerd aan een verslechtering van cognitie. Dit lijkt overeen te komen met één van de klinische symptomen van delirium, namelijk een verandering van cognitie. Toekomstige studies moeten uitzoeken of ook de lange termijn cognitieve problemen na delirium gerelateerd zijn aan neurale netwerk veranderingen.

Naast meer begrip over delirium kan er ook worden gekeken of neurofysiologische kenmerken van delirium interessant zijn voor nieuwe delirium detectiemethoden. EEG met een beperkt aantal electroden lijkt hiervoor de meest veelbelovende methode. Helaas is deze methode op dit moment nog niet geschikt voor alle IC patiënten, doordat rest-sedatie bij IC patiënten het EEG kan verstoren. Het combineren van een op EEG gebaseerde sedatie monitor en een op EEG gebaseerde delirium monitor zou hier mogelijk in de toekomst een oplossing voor kunnen bieden.



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CURRICULUM VITAE

Arendina Wilhelmina van der Kooi was born in Winterswijk on September 10th 1986 and grew up in Aalten, the Netherlands. After graduating from secondary school in 2004 (Christelijk college Schaersvoorde, Aalten), she started her bachelor 'Clinical Technology' at the University of Twente, Enschede. During the second year of the bachelor program, she was invited to participate in a research master class at the department of Pathology of the Radboud University Nijmegen Medical Center. Here she made her first contact with academic scientific research. In 2007 she graduated (cum laude) for her bachelor 'Clinical Technology'. She chose to start her master's in 'Technical Medicine' with a specialization in medical signaling. During her master's she performed medical internships at the department of Intensive Care Medicine, Clinical Neurophysiology, Cardiology and Thoracic Surgery and received her radiation expertise level three diploma and article nine certificate. She graduated in 2010 (cum laude) after conducting a research project on myotonia congenita at the Clinical Neurophysiology Department of the Radboud University Nijmegen Medical Center.

In 2011 she began her research in the field of delirium and electroencephalography as PhD candidate at the Department of Intensive Care Medicine of the University Medical Center Utrecht under the supervision of dr. A.J.C.Slooter and prof.dr. J.Kesecioglu. As a result of this research project she and dr. A.J.C. Slooter hold a patent (pending) through the University Medical Center of Utrecht entitled "Method and system for determining a parameter which is indicative for whether a patients is delirious" (Application No.: PCT/EP2013/069521, Filed September 19, 2013).

From January 2014, she is working for the department of Medical Technology and Clinical Physics of the University Medical Center Utrecht in the field of ventricular assist devices.