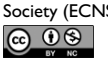
Clinical EEG and Neuroscience
2019, Vol. 50(6) 436–443



DOI: 10.1177/1550059419838938
journals.sagepub.com/home/eeg


Resting State EEG Characteristics During Sedation With Midazolam or Propofol in Older Subjects

Tianne Numan[1], Edwin van Dellen[2,3], Frank P. Vleggaar[4], Paul van Vlieberghe[4], Cornelis J. Stam[5], and Arjen J. C. Slooter[1]

Abstract

Background. Despite widespread application, little is known about the neurophysiological effects of light sedation with midazolam or propofol, particularly in older subjects. The aim of this study was to assess the effects of light sedation with midazolam or propofol on a variety of EEG measures in older subjects. *Methods*. In patients (≥60 years without neuropsychiatric disease such as delirium), 2 EEG recordings were performed, before and after administration of either midazolam (n = 22) or propofol (n = 26) to facilitate an endoscopic procedure. Power spectrum, functional connectivity, and network topology based on the minimum spanning tree (MST) were compared within subjects. *Results*. Midazolam and propofol administration resulted in Richmond Agitation and Sedation Scale levels between 0 and −4 and between −2 and −4, respectively. Both agents altered the power spectra with increased delta (0.5-4 Hz) and decreased alpha (8-13 Hz) power. Only propofol was found to significantly reduce functional connectivity. In the beta frequency band, the MST was more integrated during midazolam sedation. Propofol sedation resulted in a less integrated network in the alpha frequency band. *Conclusion*. Despite the different levels of light sedation with midazolam and propofol, similar changes in power were found. Functional connectivity and network topology showed differences between midazolam and propofol sedation. Future research should establish if these differences are caused by the different levels of sedation or the mechanism of action of these agents.

Keywords

midazolam, propofol, electroencephalography, functional connectivity, minimum spanning tree (MST)

Received June 2, 2018; revised January 24, 2019; accepted February 16, 2019.

Introduction

Every day, midazolam and propofol are administered to numerous individuals for general anesthesia, procedural sedation, or for comfort in the intensive care unit (ICU). Yet, little is known about the neurophysiological effects of both sedatives, particularly in elderly individuals. In a healthy, awake subject, electroencephalography (EEG) shows an alpha rhythm (8-13 Hz) in posterior derivations when the eyes are closed. Moreover, in a resting state, brain areas are functionally connected with a dominant posterior to anterior flow of information.[1-5] Sedative agents alter these characteristics, and these alterations coincide with alterations in the level of consciousness.[2]

Previous studies using EEG coherence suggested that light sedation with benzodiazepines results in functional uncoupling of frontal brain regions.[6] However, EEG coherence is difficult to interpret as connectivity measure because it can be influenced by the signal power and the effect of volume conduction.[7,8] Functional magnetic resonance imaging (fMRI) studies on midazolam-induced light levels of sedation showed disruption of networks related to higher order brain functions with preservation of lower-order networks,[9] and reduced functional connectivity within the default mode network.[10] Propofol-induced loss of consciousness showed similar effects: decreased cortico-cortical and thalamo-cortical connectivity[11,12] was found using fMRI, and EEG studies showed reduced functional

[1]Department of Intensive Care Medicine and Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[2]Department of Psychiatry and Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[3]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Victoria, Australia
[4]Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[5]Department of Clinical Neurophysiology and MEG Center, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands

Corresponding Author:
Tianne Numan, Department of Intensive Care Medicine, University Medical Center Utrecht F06.149, PO box 85500, Utrecht, 3508 GA, the Netherlands.
Email: tiannenuman@gmail.com

Full-color figures are available online at journals.sagepub.com/home/eeg

connectivity, a less efficient brain network, and disruption of the directed feedforward connectivity.[1,2,12]

Connectivity effects have mostly been studied for propofol,[11,13] while literature on other sedatives, such as midazolam and other benzodiazepines, is relatively scarce. Moreover, these studies were performed in healthy younger subjects, whereas in clinical practice, mainly older patients receive sedation, for example for endoscopic procedures.[14,15] In general, older subjects show reduced resting state functional connectivity and less efficient brain network topology compared with younger adults.[16] We therefore aimed to replicate the previous findings of sedation on EEG connectivity and network topology in a population of 60 years and older. We hypothesized that light levels of sedation in these older patients result in an altered power spectrum, reduced functional connectivity, and altered network topology. This was assessed in 2 datasets: subjects receiving midazolam and subjects receiving propofol during an endoscopic procedure.

Method

Study Population

This study was performed from December 2014 to December 2016 in patients scheduled for a gastrointestinal endoscopic procedure in the University Medical Center Utrecht (UMCU). The ethical committee of UMCU waived the need for informed consent (number 14-466), although included subjects signed approval for participation, after being informed about the study procedure according to the Helsinki declaration. Inclusion criteria were age >60 years and planned endoscopy with light sedation with either midazolam or propofol. Exclusion criteria were previous stroke, epilepsy, and any psychiatric disease.

Study Procedures and Data Collection

The following patient and procedural characteristics were collected: age, sex, type and duration of endoscopy, type of sedation, and type of analgesia. The type sedative was chosen by the gastroenterologist performing the endoscopy based on physical state (ie, American Society of Anesthesiologists [ASA] classification), invasiveness and risk of the procedure, the need of lying still by the patient, and previous experiences of the patient. In general, in case of higher ASA classification or invasive procedure propofol was chosen. One hour prior to the endoscopic procedure, patients arrived at the endoscopy unit, a room with 10 beds for preparation of the patients for endoscopy and recovery afterward, for the preparation of the setup. An EEG cap with 32 electrodes (Brain products GmbH, Munich, Germany) was placed according to the 10-20 system. The EEG measurement during sedation was performed in a separate room for the endoscopic procedure. A reference electrode was located between Fz and Cz. Electrode impedances were kept below 20 kohm, sample frequency was 5000 Hz, and the hardware high pass filter was 0.1 Hz. During registration a 50 Hz notch-filter was used for visualization, although raw data were obtained for analyses.

For the baseline EEG recording, patients were lying on their back and were instructed to relax and keep their eyes closed for 5 minutes, while the researcher ensured that the patient was not falling asleep. The patient was subsequently transported to the endoscopy room where impedances were checked again, and the EEG cap was adjusted when necessary.

Midazolam was administered intravenously as a bolus of 2 to 5 mg depending on body weight and health status (such as alcohol use) by the physician performing the endoscopic procedure, and additional boluses could be given to make the endoscopic procedure possible, but without standardized assessment of the level of consciousness. The majority of patients receiving midazolam also received 50 μg fentanyl intravenously. Saturation and blood pressure were monitored during the procedure, and none of these patients were ventilated. Propofol was administered by a nurse anesthetist, starting with a bolus of 5 mg/kg and followed by continuous infusion with 4 mg/kg/h. The dose of propofol was adjusted based on response to voice or a physical stimulus to make the endoscopic procedure possible. In addition, 50 to 200 μg alfentanil was administered, depending on the body weight, health status, and procedure. Saturation, blood pressure, and electrocardiogram were monitored. These patients received some additional oxygen dependent on oxygen saturation, but were not ventilated.

The sedation EEG recording was started, and the level of consciousness was assessed using the Richmond Agitation and Sedation Scale (RASS) every 10 minutes by the researcher[17] during the entire endoscopic procedure. A RASS score of 0 indicates an alert and calm state, −1 indicates drowsiness where the patient is able to have eye contact for more than 10 seconds, −2 indicates light sedation with eye contact <10 seconds, −3 indicates moderate sedation with movement or eye opening to voice but without eye contact, −4 indicates deep sedation where the patient only moves or opens the eyes after physical stimulation but not to voice, and −5 indicates an unarousable state without response to voice or physical stimulation. Patients were requested to keep their eyes closed. During the EEG recording, the patients were observed, and any eye opening was documented to facilitate epoch selection afterward.

EEG Analysis

Raw data were down sampled using spline interpolation to 512 Hz with the Brain Vision Analyzer software (version 2.0.4.368 Brain Products GmbH, Munich, Germany) to enable comparison with previous studies.[18] From all baseline recordings, the first 4 artifact-free epochs of 8 seconds were selected, as this was previously shown to be sufficient for stable results.[18,19] From each sedation recording (with either midazolam or propofol), 4 epochs of 8 seconds artifact-free EEG with eyes closed were selected within 3 minutes after the first determination of the reduced level of consciousness using the RASS score, in a time frame in which no additional sedatives or analgesics were administered. We assumed stable levels of consciousness within

these 3 minutes as the administration of sedatives was unchanged in this time frame. For all analyses, the following 17 channels were included; F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2 to enable comparison with previous literature.[8,20] A source reference was used for connectivity and topology analysis, as approximation of the Laplacian[21] eliminating the influence of active reference in the analysis.

Spectral Analysis. First, the data were filtered using a Butterworth high-pass filter of 0.5 Hz and low-pass filter of 50 Hz, both with an order of 2 and in a forward and backward arrangement to exclude phase distortion by filtering. Subsequently, for each epoch the power spectral density was calculated with the Welch method and normalized according to the power between 0.5 and 20 Hz. For visualization, the power spectra were averaged over the 4 epochs for each patient. Relative delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-20 Hz) were calculated for each epoch and averaged over the 4 epochs. Frequencies >20 Hz were excluded, as these represented particularly muscle activity due to the clinical procedures.[22,23]

Functional Connectivity Analysis. The phase lag index (PLI) was calculated to assess functional connectivity, a measure of synchronization between electrode time series as follows[24]:

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

For each sample (t) the instantaneous phase was obtained using the Hilbert transformation, and the instantaneous phase difference between 2 times series ($\Delta\varphi$) was calculated, ranging between $-\pi$ and π. The sign-function is 1 for all positive phase differences and -1 for all negative phase differences, which are averaged over the epoch. Calculating the absolute value results in the PLI, a value ranging between 0 (no phase synchronization or zero lag phase synchronization) and 1 (complete, nonzero phase-locking over the epoch). The PLI was averaged over all combinations of electrodes.

Network Analysis. The topology of the functional network was assessed using the minimum spanning tree (MST). Based on the PLI connectivity matrix, the MST was obtained using Kruskal's algorithm, including the strongest connections without forming loops.[25] This resulted in a network of 17 nodes (ie, channels) and 16 connections (ie, PLI values).

First, to assess overall differences in topology, an MST reference was calculated for each subject. Using a leave-one-out method (ie, excluding the PLI matrix of this subject), an averaged PLI matrix was calculated based on all other baseline recordings. An MST reference was calculated based on that averaged PLI matrix, as an approximation of the averaged baseline topology. The number of overlapping connections of the MST of each epoch with the MST reference was counted. The ratio of overlap (MST overlap) was calculated by dividing the number of overlapping connections by the total number of connections within the MST (ie, 16 connections). Functional connectivity and MST overlap were calculated for each frequency band for each of the 4 selected epochs and averaged. Subsequently, the MST overlap was averaged over the 4 epochs. MST measures were calculated when a significant difference in MST overlap was found on a group level. Degree, diameter, and leaf fraction were calculated to characterize global integration of information, betweenness centrality, and eccentricity quantified the centrality of nodes, and tree hierarchy was used as a global measure of hierarchical organization of the MST topology (see Table 1).

Connectivity and network analysis were performed in Brainwave (Version 0.9.152.4.1 freely available on http://home.kpn.nl/stam7883/brainwave.html) and Matlab (Version 2015a, The MathWorks, Inc) using the connectivity toolbox.[26]

Statistical Analysis

Patient characteristics were tested for normality and presented as mean with standard deviation (SD), median with interquartile range (IQR), or number (%) as appropriate. Patient characteristics were compared between the midazolam and propofol groups, using t test, Mann-Whitney U test, or chi-square test where appropriate.

To study the difference in EEG characteristics between baseline and sedation with either midazolam or propofol, Student's paired t test was used in case of a normal distribution, and a Wilcoxon signed rank test was used for a skewed distribution. The Bonferroni correction was applied to correct for multiple testing in the 4 frequency bands, therefore statistical significance was defined as $P < .0125$. MST measures were only calculated for a frequency band when the MST overlap was significantly different. Therefore, these comparisons using the Wilcoxon signed rank test were assumed post hoc analyses and not corrected for multiple testing. P values <.05 were statistically significant for post hoc analyses. Statistical analyses were performed with SPSS, version 21 (IBM, Armonk, NY).

Results

Study Population

In total, 85 patients participated in this study. Thirty-seven patients were excluded because of the following reasons: no sedation during endoscopy (n = 1), meningioma, or stroke in the medical history (n = 2), no EEG recording possible due to logistic reasons (n = 4), no eyes closed segments (n = 1), no EEG signal on one or more of the included channels (n = 6), or no artifact-free epochs due to the noisy environment of the experimental setup (n = 23). In the remaining 48 patients, 22 received midazolam sedation and 26 propofol sedation. The patient characteristics are described in Table 2.

Spectral Analysis

The relative power in the 4 frequency bands are presented for baseline and sedation conditions in Figure 1 and Table 3. Midazolam resulted in an increase in delta and beta power,

Table 1. Definitions of the Different Minimum Spanning Tree (MST) Measures.

MST Measure	Definition
Degree	The degree of each node is calculated as the number of connections, which is normalized by dividing by the maximum number of connections (ie, 16 connections). The global degree is defined as the highest normalized degree within the MST.
Leaf fraction (Lf)	The leaf fraction is a global measure defined as the number of leaf nodes (ie, nodes with only 1 connection) divided by the maximum number of nodes within the MST (ie, 17 nodes).
Diameter (D)	The diameter is a global measure and defined as the longest distance between any 2 nodes in the network.
Betweenness centrality (BC)	The number of paths crossing this node, divided by the total number of paths within the MST. The maximum BC is used as global MST measure. BC value of 0 indicates a leaf node, maximum BC is 1 which is the central node in a star-like network
Eccentricity (Ecc)	The maximum distance between a node an any other node in the MST network. The global eccentricity is the range between the highest Ecc and lowest Ecc.
Tree hierarchy (T_h)	The tree hierarchy is a global measure and calculated by $T_h = L / 2mBC_{max}$ and describes the extent of hierarchical organization of the MST. A star-like tree has an T_h of 0.5, for a path-like tree the T_h value decreases toward 0. MST structures with an hierarchical organization can have a Th value up to 1. m is the number of paths in MST (ie, 16 connections)

Table 2. Patient Characteristics.

Characteristic	Midazolam (n = 22)	Propofol (n = 26)
Age, years, mean (SD)	72.7 (5.9)	71.5 (6.4)
Male sex, n (%)	13 (59.1)	17 (65.4)
Endoscopic procedure, n (%)		
Coloscopy	11 (50.0)	9 (34.6)
Gastroscopy	11 (50.0)	17 (65.4)
Planned duration of endoscopic procedure, minutes, median (IQR)	33.0 (23.8-41.3)	35.0 (25.0-77.5)
Analgesia, n (%)		
None	5 (22.7)	—
Alfentanil	1 (4.5)	25 (96.2)
Fentanyl	16 (72.7)	—
Remifentanil	—	1 (3.8)
RASS score, n (%)		
0	2 (9.1)	—
−1	5 (22.7)	—
−2	10 (45.5)	4 (15.4)
−3	4 (18.2)	5 (19.2)
−4	1 (4.5)	17 (65.4)

Abbreviations: IQR, interquartile range; RASS, Richmond Agitation and Sedation Scale; SD, standard deviation.

whereas alpha power was significantly lower compared with the baseline condition. Sedation with propofol significantly increased the delta power, with a reduction of theta and alpha power.

Functional connectivity

Midazolam sedation did not result in changes in the PLI (Table 4), whereas propofol sedation resulted in a significantly increased PLI in the delta and beta frequency bands, and a significantly decreased PLI in the alpha frequency band.

Topology of the Functional Brain Networks

To study network topology, MST references were created and MST overlap was calculated and compared between the baseline and sedation recordings. Midazolam sedation altered network topology in the beta frequency band as indicated by a significantly reduced MST overlap (baseline, median 0.172 [IQR 0.156-0.320]; sedation, median 0.125 [IQR 0.106-0.156]; $P = .001$). In contrast, sedation with propofol resulted in topological changes in the alpha frequency band, with a significant reduction of MST overlap (baseline, median 0.156 [IQR 0.125-0.172]; sedation, median 0.125 [IQR 0.110-0.141]; $P = .005$, see Table 5). No differences were found in the other frequency bands. Therefore, the MST measures in the beta frequency band and alpha frequency band were calculated for the midazolam and propofol group, respectively.

Leaf fraction and tree hierarchy were significantly higher during sedation with midazolam compared to baseline (Table 6), indicating a more integrated topology in the beta band. Propofol sedation resulted in an increased diameter and eccentricity in the alpha band compared with baseline, suggesting a less integrated topology in the alpha frequency band.

Discussion

Similar changes in EEG power were found with either midazolam or propofol sedation. During midazolam sedation no changes in functional connectivity were found, but network topology showed higher integration in the beta frequency band. During propofol sedation, the functional connectivity was changed compared to baseline and a less integrated network topology in the alpha frequency band was found, indicating loss of network efficiency.

Our findings on the effects of midazolam and propofol on relative power are consistent with most previous studies in younger subjects,[27-29] which described slowing of background activity for midazolam and propofol, and a specific

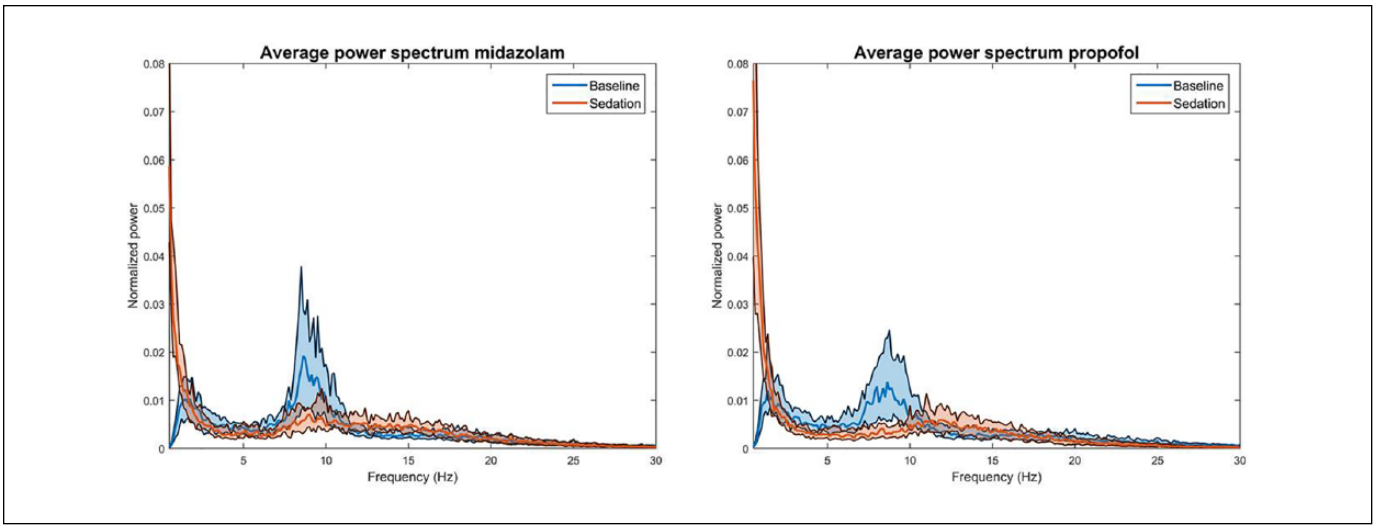


Figure 1. Average power spectrum of the effect of midazolam (left) and propofol (right). Thick line represents the median, shaded color gives the first to third quartile range.

Table 3. Relative Power for All Frequency Bands During Baseline and Sedation Condition.

Frequency Band	Baseline	Sedation	z	P
Midazolam (n = 22)				
Delta	0.188 (0.107-0.264)	0.365 (0.274-0.429)	−3.815	<.001[a]
Theta	0.176 (0.130-0.213)	0.127 (0.106-0.156)	−2.094	.036
Alpha	0.484 (0.312-0.575)	0.235 (0.194-0.324)	−4.074	<.001[a]
Beta	0.160 (0.118-0.226)	0.245 (0.164-0.289)	−2.938	.003[a]
Propofol (n = 26)				
Delta	0.205 (0.159-0.300)	0.443 (0.296-0.640)	−4.076	<.001[a]
Theta	0.206 (0.164-0.282)	0.104 (0.079-0.128)	−4.229	<.001[a]
Alpha	0.330 (0.218-0.501)	0.208 (0.140-0.292)	−3.899	<.001[a]
Beta	0.157 (0.115-0.191)	0.188 (0.107-0.251)	−0.673	.501

[a]Statistically significant after Bonferroni correction.

Table 4. Functional Connectivity for All Frequency Bands During Baseline and Sedation Condition.

Frequency Band	Phase Lag Index		z	P
	Baseline	Sedation		
Midazolam (n = 22)				
Delta	0.158 (0.147-0.170)	0.175 (0.157-0.182)	−1.786	.074
Theta	0.133 (0.117-0.142)	0.132 (0.121-0.146)	−0.016	.987
Alpha	0.168 (0.136-0.214)	0.135 (0.115-0.187)	−2.127	.033
Beta	0.102 (0.093-0.106)	0.104 (0.098-0.110)	−0.763	.445
Propofol (n = 26)				
Delta	0.160 (0.152-0.180)	0.191 (0.173-0.211)	−3.010	.003[a]
Theta	0.136 (0.121-0.153)	0.124 (0.119-0.136)	−2.324	.020
Alpha	0.160 (0.131-0.210)	0.128 (0.118-0.138)	−3.302	.001[a]
Beta	0.099 (0.096-0.105)	0.101 (0.093-0.109)	−0.546	.001[a]

[a]Statistically significant after Bonferroni correction.

Table 5. Minimum Spanning Tree (MST) Overlap With Reference MST for All Frequency Bands During Baseline and Sedation.

Frequency Band	MST Overlap		z	P
	Baseline	Sedation		
Midazolam (n = 22)				
Delta	0.156 (0.121-0.191)	0.125 (0.109-0.141)	−2.429	.015
Theta	0.141 (0.109-0.156)	0.125 (0.090-0.156)	−1.084	.278
Alpha	0.180 (0.125-0.254)	0.188 (0.168-0.223)	−0.637	.524
Beta	0.172 (0.156-0.320)	0.125 (0.106-0.156)	−3.479	.001[a]
Propofol (n = 26)				
Delta	0.141 (0.109-0.191)	0.125 (0.106-0.141)	−2.138	.033
Theta	0.156 (0.106-0.191)	0.141 (0.106-0.156)	−1.650	.099
Alpha	0.156 (0.125-0.172)	0.125 (0.110-0.141)	−2.803	.005[a]
Beta	0.164 (0.109-0.188)	0.125 (0.078-0.172)	−1.838	.066

[a]Statistically significant after Bonferroni correction.

increase in beta power due to midazolam. Lee et al[2] showed an increase in delta frequency band PLI and a decrease in alpha band PLI during regaining of consciousness after propofol sedation in younger individuals. Interestingly, the propofol group of the current study showed a similar decrease in the alpha frequency band PLI; however, the PLI in the delta frequency band was reduced during propofol sedation. This could be explained by the difference in age (ie, younger adults vs older subjects in the current study) or the difference in sedation trajectory (ie, regaining consciousness after loss of consciousness vs light levels of sedation without loss of consciousness). In our previous study on functional connectivity during recovery from anesthesia after surgery, the PLI in the alpha frequency band was decreased compared with control subjects, while delta band PLI was not significantly different.[30] Thus reduction of functional connectivity in the

Table 6. Minimum Spanning Tree (MST) Measures in Beta Frequency Band for Midazolam Group and Alpha Frequency Band From Propofol Group.

MST Measure	Baseline	Sedation	z	P
Midazolam (n = 22) Beta frequency band				
Degree	0.297 (0.281-0.317)	0.313 (0.278-0.344)	−1.308	.191
Leaf fraction	0.500 (0.485-0.547)	0.547 (0.532-0.578)	−2.453	.014[a]
Diameter	0.508 (0.469-0.531)	0.492 (0.453-0.500)	−1.170	.242
Betweenness centrality	0.708 (0.669-0.733)	0.701 (0.681-0.728)	−0.520	.603
Eccentricity	0.401 (0.371-0.420)	0.391 (0.367-0.401)	−1.104	.270
Tree hierarchy	0.367 (0.339-0.388)	0.396 (0.371-0.412)	−2.646	.008[a]
Propofol (n = 26) Alpha frequency band				
Degree	0.344 (0.297-0.379)	0.313 (0.309-0.344)	−1.131	.258
Leaf fraction	0.586 (0.547-0.625)	0.555 (0.516-0.582)	−1.742	.082
Diameter	0.453 (0.407-0.485)	0.469 (0.438-0.500)	−1.993	.046[a]
Betweenness centrality	0.746 (0.702-0.762)	0.721 (0.709-0.751)	−0.780	.436
Eccentricity	0.357 (0.333-0.377)	0.374 (0.355-0.393)	−2.146	.032[a]
Tree hierarchy	0.397 (0.379-0.423)	0.379 (0.356-0.408)	−1.651	.099

[a]Statistically significant.

alpha frequency band is characteristic for sedation in both younger and elderly subjects.[2,30] It is not clear if this is a specific propofol effect because we found a nonsignificant trend in alpha frequency band PLI during midazolam sedation. However, direct comparisons between effects of midazolam and propofol in our study are hampered by differences in sedation level.

Still, midazolam and propofol had opposite effects on network topology. During midazolam sedation a more integrated network was found in the beta frequency band. A more integrated network has shorter communication paths between all nodes[4] and is therefore more efficient. Interestingly, the network topology was only affected in the beta frequency band, and an increase in power of the beta frequency band was specific for benzodiazepines like midazolam.[27-29] Since subjects who received propofol had lower RASS scores compared with those who received midazolam, this more integrated network in the beta frequency band during midazolam sedation may be more specific for the working mechanism of midazolam than the depth of sedation level. However, how this relates to the different working mechanisms between midazolam and propofol on the $GABA_A$ receptor is unclear.

Propofol sedation resulted in a different topology in the alpha frequency band, a more integrated network was found. Previously, small-world measures path length and clustering coefficient were found to be increased in young subjects during propofol sedation, without changing the small-world index (the ratio of these measures).[2] The diameter of the MST is highly correlated with the small-world measure path length (ie, higher diameter correlates with longer path length),[4] and the results in the current study in elderly patients are therefore consistent with the previous study in younger subjects.[2]

This is the first study on EEG characteristics of light levels of sedation with midazolam or propofol in older subjects. Furthermore, this is the first investigation on this topic using advanced topological analysis with MST. MST provides unbiased estimates of the backbone of the brain network and is not dependent on arbitrary choices regarding thresholding of the network strength. However, some limitations of the current study need to be addressed. Several patients were excluded due to the clinical setting of this study for logistic and technical reasons such as environmental artifacts, which is unlikely to have affected our findings. Second, because we performed observations during otherwise care-as-usual, the level of consciousness was not strictly targeted, and administered analgesics differed per patient. This resulted not only in clinically realistic alterations in EEG characteristics but also in different levels of consciousness between the midazolam group and propofol group, hampering direct comparison. Both fentanyl and alfentanil are known to have a slowing effect of the EEG, with fentanyl having a higher potency and longer life-time compared with alfentanil.[31,32] However, the additional effects on top of midazolam or propofol sedation are unclear and could not be assessed based on the current data. Therefore, in our study it is impossible to disentangle the different effects of level of consciousness, type of analgesia, and type of sedation.

In conclusion, despite the different levels of light sedation between midazolam and propofol, overlapping results were found in the power spectra. However, only propofol sedation showed a reduction of functional connectivity in the alpha frequency band, which was previously found in younger subjects who had received propofol.[2] The opposite effects in network topology found during midazolam and propofol sedation may suggest a difference in mechanism of action. However, future research should establish if our results are related to the type of sedation or the level of consciousness and how these relate to age effects.

Author Contributions

TN contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. EvD contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. FPV contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. PvV contributed to conception; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. CJS contributed to conception; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. AJCS contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Support was provided solely from institutional and/or departmental sources.

References

1. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA. Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. *Anesthesiology*. 2013;118:1264-1275.
2. Lee H, Mashour GA, Noh GJ, Kim S, Lee U. Reconfiguration of network hub structure after propofol-induced unconsciousness. *Anesthesiology*. 2013;119:1347-1359.
3. Vecchio F, Miraglia F, Bramanti P, Rossini PM. Human brain networks in physiological aging: a graph theoretical analysis of cortical connectivity from EEG data. *J Alzheimers Dis*. 2014;41:1239-1249.
4. Stam CJ, Tewarie P, Van Dellen E, van Straaten EC, Hillebrand A, Van Mieghem P. The trees and the forest: characterization of complex brain networks with minimum spanning trees. *Int J Psychophysiol*. 2014;92:129-138.
5. Moon JY, Kim J, Ko TW, et al. Structure shapes dynamics and directionality in diverse brain networks: mathematical principles and empirical confirmation in three species. *Sci Rep*. 2017;7:46606.
6. Alonso JF, Mañanas MA, Romero S, Rojas-Martínez M, Riba J. Cross-conditional entropy and coherence analysis of pharmaco-EEG changes induced by alprazolam. *Psychopharmacology (Berl)*. 2012;221:397-406.
7. Numan T, Stam CJ, Slooter AJC, van Dellen E. Being conscious of methodological pitfalls in functional brain network analysis. *Anesthesiology*. 2015;123:484-485.
8. van Diessen E, Numan T, van Dellen E, et al. Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. *Clin Neurophysiol*. 2015;126:1468-1481.
9. Liang P, Zhang H, Xu Y, Jia W, Zang Y, Li K. Disruption of cortical integration during midazolam-induced light sedation. *Hum Brain Mapp*. 2015;36:4247-4261.
10. Greicius MD, Kiviniemi V, Tervonen O, et al. Persistent default-mode network connectivity during light sedation. *Hum Brain Mapp*. 2008;29:839-847.
11. Tang CY, Ramani R. Functional connectivity and anesthesia. *Int Anesthesiol Clin*. 2016;54:143-155.
12. Jordan D, Ilg R, Riedl V, et al. Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. *Anesthesiology*. 2013;119:1031-1042.
13. Hudetz AG. General anesthesia and human brain connectivity. *Brain Connect*. 2012;2:291-302.
14. Travis AC, Pievsky D, Saltzman JR. Endoscopy in the elderly. *Am J Gastroenterol*. 2012;107:1495-1501.
15. Triantafillidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol*. 2013;19:463-481.
16. Smit DJ, de Geus EJ, Boersma M, Boomsma DI, Stam CJ. Life-span development of brain network integration assessed with Phase Lag Index connectivity and minimum spanning tree graphs. *Brain Connect*. 2016;6:312-325.
17. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166:1338-1344.
18. van Dellen E, van der Kooi AW, Numan T, et al. Decreased functional connectivity and disturbed directionality of information flow in the electroencephalography of intensive care unit patients with delirium after cardiac surgery. *Anesthesiology*. 2014;121:328-335.
19. Fraschini M, Demuru M, Crobe A, Marrosu F, Stam C, Hillebrand A. The effect of epoch length on estimated EEG functional connectivity and brain network organisation. *J Neural Eng*. 2016;13:036015.
20. van Wijk BC, Stam CJ, Daffertshofer A. Comparing brain networks of different size and connectivity density using graph theory. *PLoS One*. 2010;5:e13701.
21. Hjorth B. An on-line transformation of EEG scalp potentials into orthogonal source derivations. *Electroencephalogr Clin Neurophysiol*. 1975;39:526-530.
22. Whitham EM, Pope KJ, Fitzgibbon SP, et al. Scalp electrical recording during paralysis: quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG. *Clin Neurophysiol*. 2007;118:1877-1888.
23. Pope KJ, Fitzgibbon SP, Lewis TW, Whitham EM, Willoughby JO. Relation of gamma oscillations in scalp recordings to muscular activity. *Brain Topogr*. 2009;22:13-17.
24. Stam CJ, Nolte G, Daffertshofer A. Phase Lag Index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. *Hum Brain Mapp*. 2007;28:1178-1193.
25. Kruskal JB. On the shortest spanning subtree of a graph and the traveling salesman problem. *Am Math Soc*. 1956;7:48-50.
26. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*. 2010;52:1059-1069.
27. Hotz MA, Ritz R, Linder L, Scollo-Lavizzari G, Haefeli WE. Auditory and electroencephalographic effects of midazolam and

α-hydroxy-midazolam in healthy subjects. *Br J Clin Pharmacol*. 2000;49:72-79.
28. Nishida M, Zestos MM, Asano E. Spatial-temporal patterns of electrocorticographic spectral changes during midazolam sedation. *Clin Neurophysiol*. 2016;127:1223-1232.
29. Breimer LT, Hennis PJ, Burm AG, et al. Quantification of the EEG Effect of Midazolam by Aperiodic Analysis in Volunteers. Pharmacokinetic/pharmacodynamic modelling. *Clin Pharmacokinet*. 1990;18:245-253.
30. Numan T, Slooter AJC, van der Kooi AW, et al. Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. *Clin Neurophysiol*. 2017;128:914-924.
31. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology*. 1985;62:234-241.
32. Sebel PS, Bovill JG, Wauquier A, Rog P. Effects of high-dose fentanyl anesthesia on the electroencephalogram. *Anesthesiology*. 1981;55:203-211.