Technische Universität München
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Characteristics of EEG Burst Suppression pattern during general anesthesia

- Substance-Specific Differences in Human Electroencephalographic Burst Suppression Patterns
- Always Assess the Raw Electroencephalogram: Why Automated Burst Suppression Detection May Not Detect All Episodes

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1. Introduction:

The application of intraoperative electroencephalographic (EEG) patient monitoring has received increasing attention over the last few years. One of the main focal points is the identification of EEG Burst Suppression (BSupp). This rhythm can be observed under various conditions, such as hypothermia [1], coma [2] and very deep levels of anesthesia [3, 4]. The association between anesthetic-induced BSupp and the occurrence of postoperative neurocognitive dysfunction (pNCD), such as postoperative delirium (POD), has been widely discussed [5-8].

The BSupp pattern is defined as an alternation of very low voltage activity, the suppression, and sharp high voltage bursts. [3, 9] However, the architecture of the anesthetic-induced rhythm seems to vary depending on various reasons, for instance the patient's age [10]. In addition, observations made in animal studies suggested substance-specific differences of the BSupp pattern [11-14].

For the intraoperative BSupp detection EEG-based patient monitoring systems, such as the Bispectral Index (BIS, Medtronic, Dublin Ireland), the SedLine Patient State Index (PSI, Masimo, Irvine, Ca, USA), the Cerebral State Monitor (CSM, Danmeter, Odense, Denmark) and the Entropy Module (GE Healthcare, Helsinki, Finland), are used. All monitors calculate index values based on a processed EEG. The indices are designed to reflect the patient's "depth" of anesthesia, i.e. the hypnotic component of anesthesia, as well as the probability of BSupp being present. Different studies suggest that these modules may not work as accurately in predicting the patient's anesthetic level as suggested by the manufacturers [15-18]. Muhlhofer and colleagues [16] evaluated the performance of the SedLine PSI monitor and found that the calculated burst suppression ratio (BSR) significantly underestimates the actual duration of BSupp in the unprocessed EEG. Eagleman and others [19] found that the offline accuracy of the modules also varies between the different commonly used monitors. Since no evaluation on the Entropy Module's performance had been done so far, we analyzed the module's BSupp detection accuracy. Furthermore, we provide insights about possible architectural features that could compromise the module's detection ability.

One of the aims of our investigations was to gather more information about the anesthetic-induced BSupp pattern, that could be used to adapt the detection algorithms. A more precise automated BSupp identification and thus improved anesthetic monitoring could reduce the number of patients with unnecessarily excessive anesthesia and help prevent postoperative sequelae or side effects, such as pNCD.

But more than anything, we want to emphasize the importance of the visual BSupp identification by the anesthesiologist. We believe that the most accurate monitoring of the brain

effects of anesthesia is provided by a combination of index value interpretation and visual EEG analysis.

1.1. The electroencephalogram:

EEG monitoring is a very sensitive method to reflect the status of the central nervous system and the pharmacological effects of anesthetics on the brain. It reflects neuronal ionic currents that lead to electrical currents which can be recorded via surface electrodes [3]. Due to the heterogeneity of the cortex the EEG activity is generally derived from several electrode locations on the scalp for a global overview. The electrodes are usually installed using the international 10-20 system [20]. Depending on the location of the electrodes the channels can be traced back to certain cortical regions; the frontal, the central, the parietal and the occipital region. The voltage is measured by the potential difference between two electrodes [3]. The EEG is very sensitive and thus vulnerable to various external factors, e.g., the heart rate, muscular activity and eye movement, which can result in serious artefacts.
The classification of the basic EEG rhythms is based on the EEG frequency. Anesthetic-induced EEG patterns can best be understood with some general knowledge of the EEG during sleep or coma [4].

1.1.1. During sleep:

The EEG of awake adults is described as desynchronized. It is dominated by a relatively low amplitude and high frequency activity (13-30 Hz), mostly β-activity (**Table 1**). In a relaxation state with closed eyes, highly symmetrical α-activity (8-12 Hz) becomes predominant. This α-oscillatory activity is usually completely ablated by eyes opening. During drowsiness α-activity disappears and slower synchronized ϕ-activity (4-7 Hz) can be present. The very slow δ-activity (<4 Hz) is a common finding in deeper levels of sleep in adults. [9]

EEG rhythm	**Frequency range**	**Clinical manifestation**
β - beta	13-30 Hz	awake, eyes closed
α - alpha	8-12 Hz	awake, eyes open
ϕ - theta	4-7 Hz	during sleep

δ - delta	<4 Hz	during sleep

Table 1: The four fundamental EEG rhythms. [9]

There are different stages of sleep (**Table 2**) defined by specific EEG features. Stage I is characterized by drowsiness and slow eye movement, as well as slower δ- and ϕ-waves. With stage II δ-frequencies begin to emerge, k-complexes, posterior occipital sharp transients of sleep (POSTS) and sleep spindles are seen. K-complexes are biphasic waveforms that usually last >500 ms and represent a nonspecific arousal response. POSTS are sharp positive transients that can occur individual or in clusters. Sleep spindles are usually symmetrical and synchronous and have a frequency of 12-14 Hz. In stage III, the slow wave sleep, high voltage δ-activity emerges even more, k-complexes and sleep spindles fade. Another feature is the rapid eye movement stage of sleep, the REM sleep. It was described as paradoxical sleep, with a predominance in desynchronized low-voltage activity and similarities to an awake EEG pattern with eyes open. Rhythmic saw-toothed waves may be associated with REM sleep as well. [9, 21]

Sleep stages	**EEG activity**	**Additional EEG phenomena**
Stage I	δ and ϕ activity	slow eye movement
Stage II	δ activity predominant	k-complexes, POSTS, spindles
Stage III	δ activity predominant	slow wave sleep
REM sleep	desynchronized low-voltage activity	rhythmic saw-toothed waves

Table 2: The stages of sleep and their EEG phenomena. [9, 21]

The EEG activities may also be influenced by age. People of older age show a reduction of the amplitude in all frequencies, as well as a local increase of delta activity while awake [22].

1.1.2. During anesthesia:

Gibbs et al. [23] and Kiersey et al. [24] were among the first to describe the EEG during anesthesia as an increase in low frequency and high amplitude activity (Stage I). With an increasing anesthetic depth (**Table 3**), a decrease in the high frequency/low amplitude β-band

and an increase in the low frequency/high amplitude α- and δ-activity, especially in the anterior EEG leads (Stage II), is seen [4, 25]. During this intermediate state, the EEG looks similar to slow wave sleep. In very deep levels of anesthesia (Stage III) the EEG amplitudes get flatter and transition into suppression [4]. These suppression phases are interrupted by periods of high amplitude and high frequency alpha and beta waves, the bursts. This rhythm with an alternation of burst and suppression phases, is called BSupp [4, 26, 27]. Even deeper anesthesia may also result in an isoelectrical EEG, as seen in comatose or brain dead patients [4].

Stages of anesthesia	**clinical manifestation**	**EEG activity**	**Additional information**
Stage I	light anesthesia	β decrease, α and δ increase	
Stage II	intermediate anesthesia	β decrease, α and δ increase with anteriorization	similarity to slow wave sleep
Stage III – BSupp	very deep anesthesia	flat EEG periods with intermittent α and β bursts	
Stage IV	overly deep anesthesia	isoelectric EEG	can also be seen in comatose or brain-dead patients

Table 3: The stages of anesthesia and their EEG phenomena. [4]

1.2. Burst Suppression:

The BSupp rhythm was first described by Derbyshire et al. [28] in 1936, who researched EEG characteristics during anesthesia in cats. The first investigation of BSupp in humans was made by Henry and others [29] who described suppression-burst in the EEG of man after prefrontal lobotomy. The cellular mechanism behind BSupp in general is still not fully understood. Steriade et al. [30] describe it as synchronized pace making of thalamocortical discharges to a widely unresponsive cortex. An important hint on the pathological origin of the rhythm, is its possible presence during coma and its unquestionable absence during normal physiological sleep EEG [4]. Rampil [3] also described it as an indicator for a non-specific reduction of the cerebral metabolic activity.

A number of risk factors for the appearance of anesthetic-induced BSupp have been outlined, such being advanced age, past medical history of coronary artery disease and male gender [31]. The exact pathophysiological mechanisms behind intraoperative BSupp are not fully understood, however there are two main hypotheses for its appearance: an individual

anesthetic overdose (MAC, minimum alveolar concentration) [32] and low mean arterial pressure (MAP) [33]. Most anesthetic agents work as GABA agonists, thus depress the cellular excitability in the central nervous system [34]. Low blood pressure can result in a critically reduced brain blood flow, leading to an ischemic suppression of the brain metabolism. Sessler et al. described the triple low theory [33] and determined low MAP, low MAC and low BIS (index for deep anesthesia, also with BSupp) to be strongly associated with increased postoperative mortality.

Even though anesthetic induced BSupp has been an object of research for years, there still exists no explicit definition for it, nor is there a standardized method to detect it in the raw EEG. Various authors described the rhythm in different ways: Rampil [3] for example gave the suppression a set duration of >0.5 seconds with an amplitude of +/- <5 µV, while Daube et al. [9] did not further specify duration or amplitude cut offs. What the authors describe in common, is the alternation of very low voltage suppression phases and high voltage bursts [3, 4, 9]. Many of those criteria are linked to BSupp in general and are difficult to project on BSupp during anesthesia. **Figure 1** represents an episode of anesthetic-induced BSupp.

Furthermore, the pattern does not always totally look alike; it can vary in its duration [35] as well as in its burst architecture [10, 36]. Age related differences, as seen in normal EEG, are also present during BSupp. Kratzer et al. [10] described a significant decrease in alpha power, amplitude and slope in older patients. Another factor influencing the BSupp pattern is the used anesthetic agent. Animal studies showed significant higher amplitudes in BSupp derived from volatile anesthetics compared to BSupp derived from propofol [13, 14].

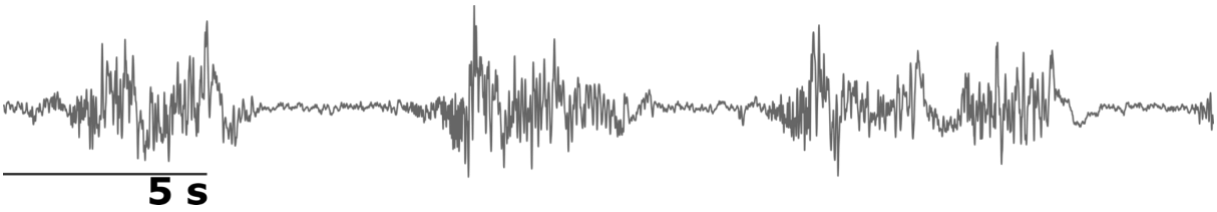

Figure 1: Example of BSupp during general anesthesia.

1.3. Automated anesthetic depth monitoring:

The use of automated anesthetic depth monitoring during surgery has increased over the past few years and it has almost become an indispensable part on the intraoperative anesthetic monitoring. The monitors calculate their index parameters based on a processed single channel EEG. The algorithms behind the value calculation is substantially different between

the modules of different manufacturers. As the Cerebral State Index (CSI) and the Entropy Module were the two monitors used in my analyses, I set my focus on these two.

1.3.1. The Cerebral State Monitor:

The CSM calculates a total of four indexes; the CSI, the burst suppression ratio (BS%), the Electromyographic Activity (EMG%) and the Signal Quality Indicator (SQI%).
The CSI processing algorithm is fuzzy logic based. The module gains four sub-parameters for this. Three of them (α-ratio, β-ratio and β-α) are gained by a spectral analysis of the processed EEG and one, the BS%, is calculated directly by the monitor. These four parameters are used as an input to a fuzzy logic classifier system that calculates the CSI. This Adaptive Neuro Fuzzy Interference System was trained on pre-recorded EEG data and helps implementing very complex processes, where using a simple mathematical procedure alone would not suffice. [37, 38]
The CSI is a unit-less index from 0 to 100 that inversely correlates to the patient's level of consciousness. A CSI of 0 indicates a totally suppressed isoelectric EEG, while CSI of 90-100 corresponds to an awake patient. The manufacturer suggests a CSI of 40-60 as an adequate "depth" of anesthesia for standard surgical procedures. A CSI<40 is in most cases accompanied by BSupp. The BS% indicates periods of suppressed and flat EEG. It reflects the percentage of BSupp over the last 30 seconds. [38]
The other two indexes give an insight on the signal's cleanliness. The EMG% reflects the percentage of muscular electromyographic (EMG) interference on the EEG signal. The SQI% measures the EEG signal quality, based on the number of artefacts during the last minute. It is presented as percentage (0-100%). The CSM applies an artefact- and EMG-filter on the raw EEG trace to prevent potential contamination. [38]

1.3.2. The GE Entropy module:

The GE Entropy Module calculates three parameters; the BSR, the response (RE) and the state entropy (SE). The exact algorithm for the index calculation has not been disclosed by the manufacturer. The Entropy calculates the SE and RE by using the Shannon entropy [39] and applying it to the EEG power spectrum. With increasing "depth" of anesthesia slow EEG oscillations become predominant. This shift of the spectral dominance towards the lower frequencies induces a decrease of the RE and SE. The RE includes a frequency range of 0.8-47 Hz and shows fast reactions. Due to the wider frequency range, it also reacts to EMG

components, potentially indicating reaction to pain. The SE, on the other hand, is a more stable parameter. It includes a frequency range of 0.8-32 Hz and was designed to primarily reflect the patients' cortical status. Similar to the CSI the SE and RE inversely correlate to the patient's level of consciousness. A RE or SE of 0 indicates a totally suppressed EEG, while a maximal value of 100 in RE and 91 in SE stands for a fully awake and conscious patient. The manufacturer suggests a RE or SE of 40-60 as adequate hypnotic level of anesthesia for standard surgeries. [40-42]

During the presence of BSupp the Entropy module switches to another mode of the algorithm. This suppression algorithm is based on a nonlinear energy operator (NLEO) and leads to a BSR elevation. To differentiate a totally suppressed EEG from the EEG of an awake patient, an amplitude cut-off is needed. Such amplitude cut-offs were revealed for other monitors, but not for the Entropy module. The BSR is the relative amount of suppression within the last minute of EEG. Therefore, a BSR=1 equals a suppression of at least 0.6 seconds. [40, 41]

Table 4 compares the index values of the CSM and Entropy Module during different stages of anesthesia.

	CSM Module		**Entropy Module**		
Clinical State	**CSI**	**BS%**	**RE**	**SE**	**BSR**
Awake	90-100		100	90	
Light anesthesia	60-80		60-80	60-80	
Anesthetic level appropriate for standard surgery	40-60		40-60	40-60	
Burst Suppression	<40	>0	<40	<40	>0
Total Suppression	0-10	>75	0	0	>0

Table 4: Index values of the CSM and Entropy module and the equivalent clinical state. [38, 42]

1.3.3. Weaknesses of intraoperative EEG monitors:

Various investigations have shown possible inaccuracies of the processed EEG monitoring. Palanca et al. [15] were under the first to question the detection capability and the clinical implication of the modules. Muhlhofer and colleagues [16] evaluated the BSupp detection precision of the Sedline PSI module. They used a technique dividing the EEG trace into 30 second epochs and scoring each epoch using the Kruger grading system. This method focuses on the presence of suppression, rather than the presence of alternating bursts and

suppressions, but resembles the monitor's algorithm. They were able to show that the BSR significantly underestimates the absolute minutes of EEG suppression compared to the visual EEG evaluation. They also found the number of minutes of visual suppression to be significantly associated with the occurrence of POD, while the number of minutes recognized by the Sedline was not associated with POD. [16]

Such an accuracy evaluation had not been done for the Entropy module. The performance of the different modules is quite difficult to compare. An offline comparison of monitors by various manufacturers shows, that their BSupp detection performance is very unequal [19]. Hence, we cannot make any assumption on the detection ability of the Entropy module.

A case report by Hart and colleagues [17] shows an example were the Entropy module totally misinterprets the EEG of a patient with extreme BSupp and falsely presents high RE and SE values indicating an awake patient. Another problem of the Entropy module is the display of contradictory high RE and SE values at the same time as elevated BSR [18]. These findings suggest that the RE/SE and the BSR are not interconnected. Nevertheless, neither an analysis on RE/SE values during unrecognized BSupp phases, nor an analysis on the architecture of these had been done yet.

1.4. Clinical reasons for intraoperative neuromonitoring:

The rating of the patient's level of anesthesia is of great importance. On one hand, we want to prevent the occurrence of intraoperative awareness and the consequential damages it may cause. On the other hand, unnecessarily deep levels of anesthesia and associated pNCD should be avoided as well.

POD was first described as postoperative insanity back in the 19th century [43]. Its symptoms are very variable; for one thing, it can appear as aggressiveness, agitation and hallucination, then again also as depression, stupor and cognitive impairments. Depending on the clinical manifestation it can be divided into a hyper- and hypoactive delirium, as well as in a mixed form and is sometimes quite difficult to diagnose [44].

There are 4 classes of risk factors for POD: demographics, comorbidities, surgery and anesthesia [45]. Some of them, such as age, surgery type and duration, cardiovascular and central nervous comorbidities, are non-influenceable [46, 47]. One important influenceable risk factor is the level of anesthesia, more precisely the prevention of unnecessarily deep anesthesia and BSupp. Various studies have shown a correlation between intraoperative BSupp and POD [5, 8, 48]. An intraoperative BSupp identification may identify patients at risk for POD even though the casual relationship remains unknown. That's why intraoperative

depth of anesthesia monitoring might reduce the number of patients with POD [49, 50]. Though the impact on healthy and young patients has not yet been completely clarified [6, 7].

2. Aims of the dissertation:

The correct interpretation of BSupp during anesthesia is of great importance, especially in patients of mature age and with a variety of co-morbidities. Yet again, the automated detection modules do not work as precisely as one would hope. Therefore, it is necessary to gain as much new information regarding BSupp and its detection as possible. Every new information on the BSupp pattern may be of great value to improve the intraoperative patient monitoring.

The effects of different anesthetics on the central nervous system are an important topic of research. Yet, investigations on the BSupp pattern produced by different anesthetics are of limited quantity and only conducted in animal studies, which are not easily transferable on humans. A study on substance-specific difference in the BSupp pattern in humans had not been done before. Hence, the aim of the first publication was to outline distinct architectural differences between three commonly used anesthetics.

An evaluation of the Sedline's BSupp detection performance showed a significant underestimation of the actual BSupp duration. Similar investigation on the accuracy of the Entropy module were missing. With the second publication we were the first to determine the Entropy's BSupp detection precision. Furthermore, we wanted to understand why some BSupp phases are not correctly classified by the module. Even though the architecture might be of great importance regarding the detection reliability, we were missing an EEG analysis of unrecognized BSupp phases in previous studies. Our investigation highlights differences of correctly recognized and falsely unrecognized BSupp episodes. A secondary end point of the study was to evaluate how the Entropy classifies unrecognized BSupp, e.g. the RE and SE values during these phases.

We think that our additional knowledge may be a valuable contribution to the field and that our results can help optimize EEG-based patient monitoring in the future. In addition, we also want to highlight the importance of a correct raw EEG trace interpretation by the anesthesiologist.

3. Methods

3.1. Paper I:

Substance-Specific Differences in Human Electroencephalographic Burst Suppression Patterns

3.1.1. Study design:

We performed a retrospective analysis on a previously recorded EEG data set. This data set was recorded at the Klinikum rechts der Isar from February 2005 until May 2006. The protocol was approved by the Ethics Committee of the Technische Universität München (Chairman Prof. A. Schömig, Ethical Committee N° 1239/05). [51]
After written consent, 45 patients undergoing elective surgery under general anesthesia, were included in the study. The patients were divided into three groups (sevoflurane group, desflurane group and propofol group; **Figure 2**), based on the substance being used for anesthetic maintenance. The assignment to the used anesthetic was performed by the anesthesiologist in charge. To reflect the clinical daily routine, randomization was deliberately avoided. Each group consisted of 15 patients.
Inclusion criteria (**Table 5**) were patients undergoing elective surgery in general anesthesia, who were ≥18 years and classified as American Society of Anesthesiologists (ASA) status 1-3. Excluded were patients with psychiatric and neurological diseases, medications with central nervous effects, alcohol or drug abuse and indication for rapid sequence induction, e.g. emergencies or pregnancy.

Inclusion criteria	**Exclusion criteria**
Elective surgery under general anesthesia	Psychiatric and neurological disorders
Age ≥18 years	Alcohol or drug abuse
ASA classification 1-3	Medication with central nervous effects
Written informed consent	Emergency surgeries, rapid sequence induction

Table 5: Inclusion and exclusion criteria for study on substance-specific differences.

Anesthesia was induced by slow intravenous propofol injection in all three groups. During the induction the patients were ask to squeeze the researchers hand every 15 seconds. Thus, the

exact time of loss of responsiveness could be documented. Atracurium or mivacurium were used for neuromuscular blocking. In the propofol group remifentanil and in the other two groups sufentanil was applied as analgesic. After intubation the assigned anesthetic agent was used for anesthetic maintenance according to clinical practice. After surgical skin incision, the anesthetic depth was increased until BSupp rhythms appeared in the EEG. After at least 3 seconds of BSupp, the anesthetic dosage was reduced to a level of anesthesia adequate for surgery. [36]

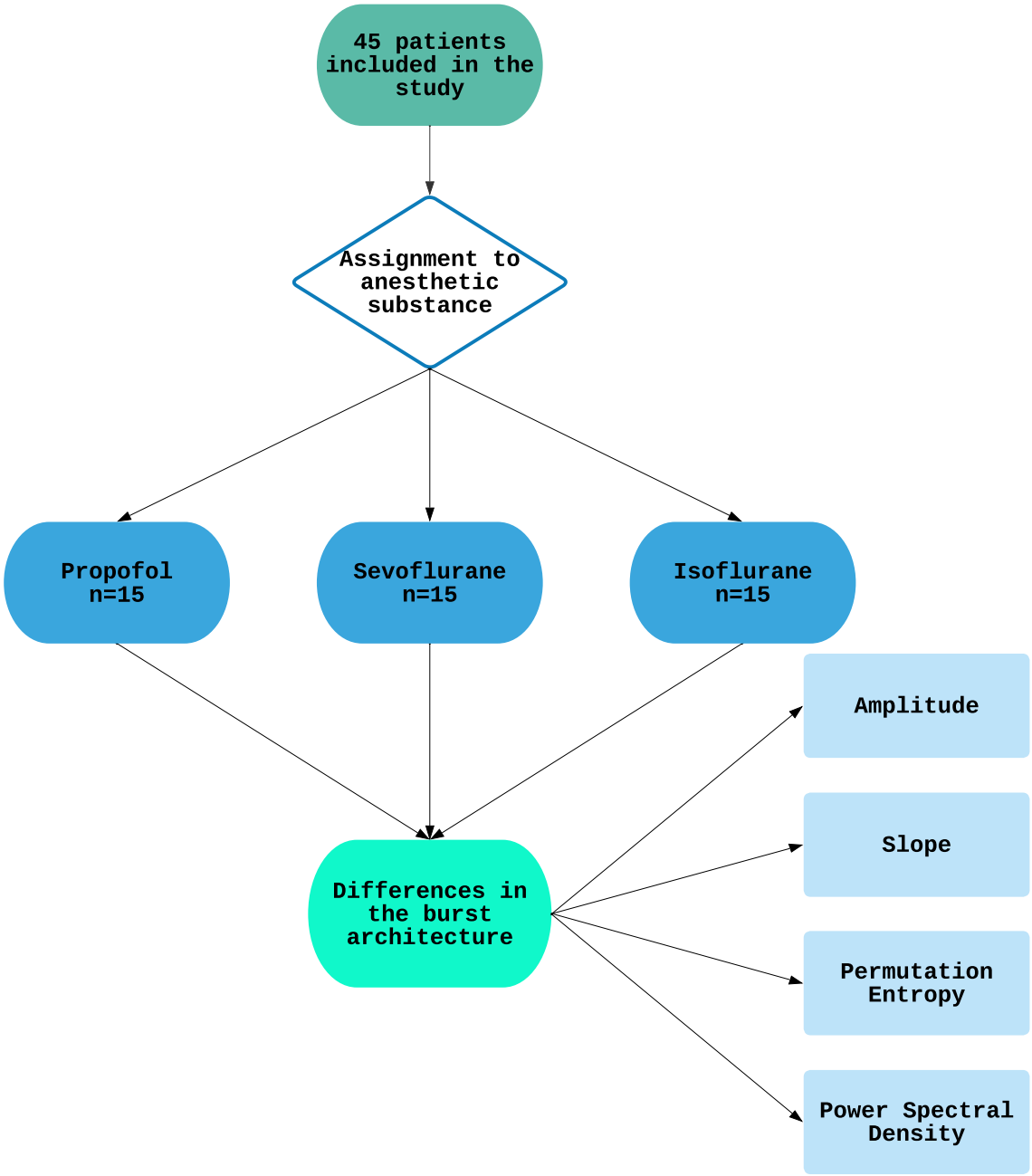

Figure 2: Flowchart for study on substance-specific BSupp differences.

3.1.2. Intraoperative patient monitoring:

All patients were intraoperatively monitored according to the usual clinical standards with a Datex® AS/3 (GE Healthcare, Chalfont St Giles, United Kingdom) monitor and the data was saved with the NeuMonD [52] program. Non-invasive arterial blood pressure was measured with an upper arm cuff every few minutes. Electrocardiogram and heart rate were continuously derived through thoracic adhesive electrodes. Blood oxygen saturation percentage and pulse frequency were measured by a finger clip sensor. Ventilation parameters, e.g. inspiratory oxygen, oxygen saturation, end-tidal carbon dioxide, and volatile anesthetic concentrations were monitored as well. Demographic data (age, sex, body mass index, ASA classification), comorbidities, intraoperative events, time point for loss and return of responsiveness, and type of premedication were also saved in the NeuMonD.
The NeuMonD (neuromonitoring device) is an online signal processing module that can be used for data acquisition, signal processing, online visualization and interpretation, clinical event recording and offline data analysis. It allows a synchronized and simultaneous recording of different monitors with several device channels (e.g. blood pressure, oxygen saturation, heart rate), as well as the recording of EEG signals and processed EEG parameters. [52]

3.1.3. EEG recordings:

The CSM monitor (Danmeter, Odense, Denmark) was used for the EEG recording. The positioning of the electrodes with one electrode on the center of the forehead, the second on the left mastoid and the reference electrode on the left side of the forehead (**Figure 3**) was according to the manufacturer's recommendation [38]. The CSI, the BSR, the signal quality data and the one-channel EEG trace of the CSM were stored in .csv files every second. The stored EEG had a sample rate of 100 Hz and a frequency range from 6–42 Hz.

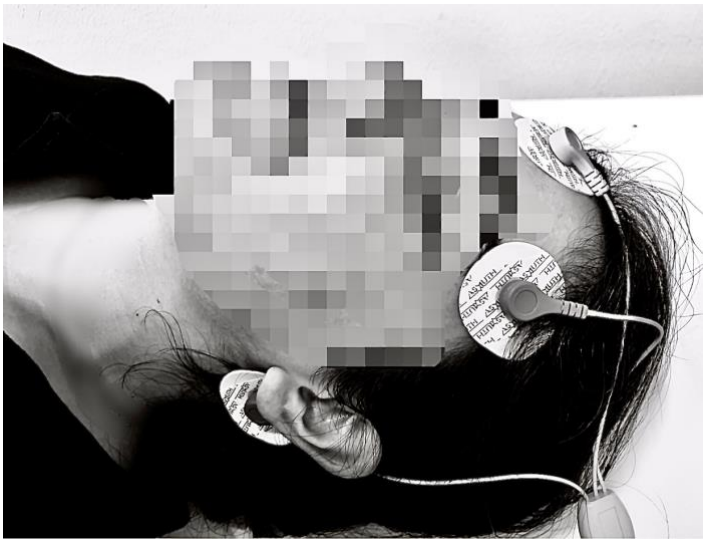

Figure 3: Electrode positioning of the CSM Module.

3.1.4. BSupp selection:

The selection of the BSupp phases was made by offline visual inspection of the EEG trace. During the selection the researcher was blinded to the applied anesthetic agent. We defined BSupp based on the silent second strategy [53], i.e. a suppression of >1 second followed by a strong and prompt increase of oscillatory activity, the burst. We focused our analysis on the first 2 seconds of the first burst, to closely examine the onset of BSupp, i.e. the switch from non-BSupp to BSupp, and to facilitate comparability between patients. With this method we were able to minimize bias based on different burst lengths, changing dynamics with ongoing burst duration and changing EEG features due to different anesthetic concentrations. [36]

3.2. Paper II:

Always Assess the Raw Electroencephalogram: Why Automated Burst Suppression Detection May Not Detect All Episodes

3.2.1. Study design:

We did a retrospective analysis of a previously recorded dataset. This dataset was recorded in a randomized monocentric interventional study that was designed to determine whether an intraoperative intervention can reduce BSupp during general anesthesia. It was conducted at the Klinikum rechts der Isar from January 2019 until December 2020 and was approved by the ethics committee of the medical faculty at the Technical University of Munich (Chairperson Prof. Dr. Georg Schmidt) on Aug/13 2018 (246/18S). [54]
The inclusion criteria (**Table 6**) were age ≥60 years, surgery under general anesthesia (volatile and intravenous), a planned surgery duration over one hour and written patient's consent to participate in the study. Criteria such as central nervous or psychiatric diseases, deafness, cranial or otolaryngologic surgery, pregnancy and planned postoperative ventilation, resulted in an exclusion from the study.

Inclusion criteria	**Exclusion criteria**
Elective surgery under general anesthesia	Psychiatric and central nervous disorders
Age ≥60 years	Deafness, pregnancy
Planned surgery duration >1 hour	Emergency, cranial or otolaryngologic surgery
Written informed consent	Planned postoperative ventilation

Table 6: Inclusion and exclusion criteria for evaluation on Entropy BSupp detection.

The 110 participating patients were randomly assigned to one of two groups, group A and B. All patients underwent routine blood pressure measuring in different situations, e.g. during pre-anesthetic consultation, in the hospital ward or in the preoperative anesthetic preparation room. The lowest measured blood pressure defined the baseline MAP. Group A formed the control group, leaving the anesthesiologist blinded to the BSR and raw EEG. In this group the anesthesia was conducted according to the usual clinical standards and monitoring methods. Group B was the interventional group. In this group the anesthesiologist was able to see the BSR and Entropy values and had to follow an interventional protocol at BSR>0. The intervention consisted of an elevation of the MAP, if it was lower than baseline MAP. If the

MAP was above the baseline, the applied anesthetic was reduced, until BSR=0 was displayed by the Entropy module. The exact details of the interventional procedure and the primary results of the study have been published. [54]

Out of the 110 patients included, 4 could not participate due to screening failure, 2 had incomplete anesthetic protocol and 14 unfortunately had damaged EEG recordings, leaving 90 patients for our EEG analysis (**Figure 4**). [55]

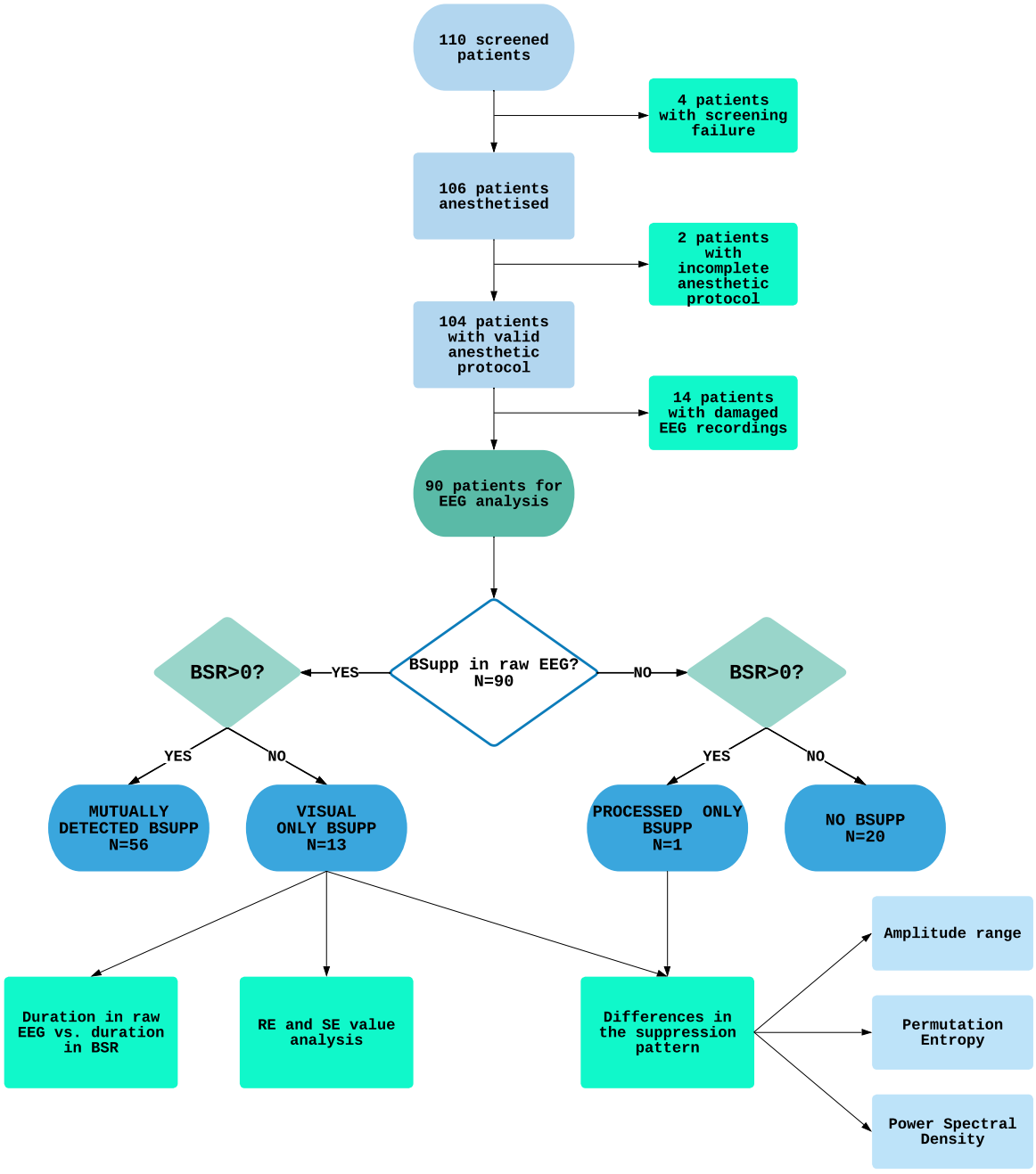

Figure 4: Flowchart for study on Entropy module accuracy evaluation.

3.2.2. Intraoperative patient data:

All patients were monitored by the standard clinical parameters including non-invasive or invasive arterial blood pressure, oxygen saturation, heart and pulse frequency, electrocardiogram, and respiratory and ventilation parameters. All intraoperative data were stored in .csv format in our patient data management system (PDMS). The trend data were recorded every 10 seconds.

The PDMS is an online system that is used by the department of anesthesiology and intensive care at the Klinikum rechts der Isar. It is a tool for electronic documentation that can be used in the operating room and on the PACU (post-anesthesia care unit). All information regarding the patient, including all parameters of the intraoperative monitors, applied medication, medical incidents, laboratory parameters and important timepoints, are saved here. This tool allows a continuous and real time data collection of each patient, that can later be accessed for data evaluation and follow-ups.

Furthermore, a study protocol documented all intraoperative information, e.g. demographics (age, sex, body mass index, ASA classification), comorbidities, timepoints during surgery (beginning of induction, endotracheal intubation, skin incision, suture finish), type and length of surgery, applied anesthetic dosages, analgesic method and interventional procedures.

3.2.3. EEG recordings:

In addition to the standard perioperative monitoring, all patients were monitored with a GE Healthcare Entropy Sensor and a 10-channel EEG.

The 3 Entropy sensor electrodes were placed on the forehead and temple with a fronto-temporal montage (**Figure 5**), as specified in the manufacturers' instruction guide [42]. This positioning creates an average one channel recording of an approximate Fp1 and F7 or Fp2 and F8 EEG placement. All Entropy index values were stored in .csv format with a resolution of 10 seconds in the PDMS.

Further we placed scalp EEG electrodes using the Medtronic NIM Eclipse System. The electrodes were placed using the 10-20 method [20], attached with an EEG cap and connected to the scalp by conductive gel. EEG data were stored in .eeg format and converted into .mat files for the EEG data analysis.

To gain a broad EEG database, which can be used for other future investigation, we recorded a baseline EEG before the first drug application in a calm setting outside the operational room. This recording involved documented periods with eyes opened and closed. During the full

length of the surgery, the Entropy module and Eclipse system were recording the patients' neuronal brain activity. After surgery, when the patient was already in the recovery room, the baseline recording with eyes opened and closed was repeated.

Figure 5: Electrode positioning of the Entropy module.

3.2.4. BSupp selection:

All index values of the Entropy module were blinded during the process of the BSupp selection. BSupp again was defined using the silent second method [53]. In comparison to the first paper where we used the first identified burst for further investigation, we focused the analysis of this paper on the suppression phases instead. We chose this approach, because the automated BSupp index calculations are most likely based on suppression phases. [55]

3.3. BSupp analysis:

We used very similar methods for the BSupp analysis in both papers. For the first paper we compared (a) absolute amplitude, (b) slope, (c) Permutation Entropy (PeEn) and (d) Power Spectral Density (PSD) of the very first burst between the groups of different anesthetics.
In the second paper, we analyzed suppression periods from the beginning, the center and the end of a BSupp episode, and calculated medians of those three. We did the comparison between the group of mutually detected and visual only BSupp. Again, we calculated (c) PeEn and (d) PSD, but instead of absolute amplitude and slope, we calculated the (e) amplitude range.

(a) Absolute amplitude:

We evaluated the 99th percentile of the absolute amplitude of the burst. The percentile approach was used to add some robustness to the analysis.

(b) Slope:

The slope is the amplitude change over time. We calculated the first derivative of the EEG and again defined the 99th percentile.

(c) Permutation Entropy:

The PeEn is an ordinal time-domain parameter and can be considered as a measure of signal complexity[56]. It evaluates the probability distribution of ordinal rank patterns of length m. PeEn has been widely used to evaluate different levels of anesthesia. We used the embedding dimensions m=3 and the shift tau=1, to allow a direct comparison between PeEn and the spectral information [57].

(d) Power Spectral Density:

We calculated the PSD using the MATLAB pwelch function with standard settings. To get the normalized PSD we divided the power of each frequency by the cumulative power of the used frequency range.

(e) Amplitude range:

The amplitude range is the difference between the maximal and minimal EEG amplitude within the suppression.

3.4. Statistical analysis:

Due to the retrospective nature of both studies, no sample size estimations were made. All statistical analyses were made in MATLAB (The Mathworks, Natick, Massachusetts, USA).
For the calculation of absolute amplitude, amplitude range, slope and PeEn we used non-parametric approaches. For analysis of differences between the three anesthetic agents we applied the Kruskal-Wallis test with a post hoc Dunn's test [58]. For the comparison between the visual only and mutually detected BSupp groups, we used the Mann-Whitney U test. P-values $p<0.05$ were considered significant. We present the precise p-values for interpretation, as we did not correct for multiple comparisons. In addition, we calculated the area under the receiver operating curve (AUC) with bootstrapped 95% confidence intervals (CI) using the MATLAB MES (measures of effect size) toolbox [59]. Results are presented as median values with first and third quartile.
For the comparison of the PSD we again calculated AUC and 95% CI. We considered a difference between the two distributions significant, if the 95% CI did not contain 0.5 [59] in at least two neighboring frequencies. [60]

4. Discussion:

Although the clinical impact of intraoperative BSupp has been recognized by different anesthetic societies and initiatives, there are some ambiguities in BSupp detection that still need to be clarified. To start with, the definition of BSupp varies greatly depending on the used source of information [3, 9]. What they all have in common is the description of alternating periods of low voltage suppression and high voltage bursts. Yet no uniform and clear definition of anesthetic-induced BSupp or detection guidelines are available.

The automated BSupp detection algorithms of the monitoring systems predominantly base their index calculations on the identification of suppressions, rather than bursts and suppressions [41]. This method could be part of the reason for the monitor's underestimation of the actual occurrence of BSupp [16]. Furthermore, the complexity of the rhythm makes its definition and recognition pretty difficult. To improve the BSupp identification we need more information regarding the architecture of the BSupp rhythm during general anesthesia and also need to understand why some BSupp episodes are not correctly interpreted by automated EEG-based monitors.

4.1. Differences in the anesthetic-induced BSupp:

The architecture of different EEG rhythms during general anesthesia is very heterogenous. The EEG activity varies strongly depending on certain criteria, e.g. the age of the patient [9]. Similar phenomena can be seen in the BSupp rhythm as well. The duration of the suppression episodes, for instance, become longer with increasing depth of anesthesia, hence with an increasing inactivation of the brain [4, 61, 62]. The BSupp pattern itself again is dependent on different factors. Various studies suggest changes in the BSupp architecture depending on the patient's age. Kratzer and colleagues described a significant decrease of alpha band power, EEG amplitude and maximum EEG slope, but at the same time an increase of the PeEn with advanced age [10].

Investigations in animals have pointed out substance-dependent differences in the BSupp architecture. Akrawi et al. compared the BSupp pattern of isoflurane and intravenously applied anesthetic agents. They described substantial differences, mostly in the peak-to-peak amplitude of the bursts [11]. Another study, again, discovered significantly higher burst amplitudes in isoflurane-induced bursts, compared to propofol-induced bursts [14]. More recently, Kenny and colleagues were able to show a significant higher peak-to-peak amplitude, greater power and longer duration in sevoflurane bursts in comparison to propofol bursts in

rats [13]. Although these studies show substantial differences in animals, they may not simply be transferred to humans.

Equivalent to the animal studies, we were able to show significant differences in the BSupp pattern of propofol, sevoflurane and isoflurane in humans. Propofol bursts had the lowest absolute burst amplitude, yet strongest oscillatory component around 10 Hz (α-activity). Isoflurane bursts showed the steepest slope, while sevoflurane had the lowest PeEn and thereby the most regular bursts of the three agents. The PSD significantly differed between the substances as well, showing a higher general power in the volatile-induced bursts. This newly gained information contributes important information to the field. [36]

4.2. Evaluation of the Entropy module's BSupp detection accuracy:

The BSupp detection precision of automated anesthetic depth monitors was scrutinized by multiple researchers. For the Sedline module, Muhlhofer and colleagues [16] compared the total seconds of BSupp in the raw EEG to the total seconds of BSR>0 in the Sedline module and showed a significant underestimation of the actual BSupp duration. However, they only analyzed the EEG with a BSR>0 and thereby did not determine the general BSupp detection accuracy of the module. Similar to the algorithms of the monitors, their grading system mainly focuses on the suppression episodes.

With our comparison of the number of patients with BSR>0 and the number of patients with BSupp in the EEG, we were able to classify the BSR values as mutually detected, visual only, processed only and no BSupp. The focus of our analysis was on the patients with visual only BSupp. These patients are at risk to be overlooked and misconceived by the anesthesiologist, which may result in unnecessarily "deep" anesthesia. We were able to show that a significant number of patients were falsely classified with BSR=0 by the module, even though BSupp was present in the EEG. Furthermore, we found the duration of an elevated BSR to be strongly dependent on the BSR cut off. [55]

A presumable problem with the Entropy module is the failure of switching from the entropy algorithm to the suppression NLEO algorithm. This can result in a misinterpretation of the totally suppressed EEG as an awake EEG and result in incorrectly high SE and RE values [17]. Due to the missing interconnection between BSR and SE/RE, incorrectly high SE/RE values (indicating an awake patient) and elevated BSR (indicating excessively "deep" anesthesia) can be present at the same time [18]. Looking at the Entropy values of our visual only BSupp patients, we were able to see intraoperative high SE values as well.

4.3. Potential reasons for the module's inaccuracy:

Although the manufacturers have revealed information about the mathematical algorithms behind the index value calculation, some uncertainties still remain. To accurately identify BSupp the modules most probably need an amplitude threshold for the suppressions. However, this amplitude cut off has not been revealed for most monitors, including the Entropy module. To further understand why some BSupp episodes are not correctly identified by the monitor, we specifically analyzed the architecture of those unrecognized suppression phases. Our results strengthen the assumption of the use of a suppression amplitude cut off for the Entropy's BSupp detection. We were able to show significantly higher amplitudes in the suppressions that were classified as visual only compared to the mutually detected BSupp. These higher amplitudes could be caused by several reasons, including individual EEG characteristics of the patients that result in a general amplitude increase of the EEG activity. However, they could also be triggered by differences in age or anesthetic substance, as well as by artefacts.

4.4. Impact of our findings on the monitoring devices:

With our findings we can show a significant underestimation of the actual BSupp occurrence of the Entropy module, similar to the results of Muhlhofer and colleagues for the Sedline PSI [16]. Although these monitors function with totally different algorithms, they both do not perform as well as they should. Information regarding the details of the algorithms are kept rather confidential. Neither for the CSI, nor for the Entropy module, suppression amplitude cut offs have been disclosed, as has been done for the BIS monitor [3]. Too narrow amplitude thresholds could cause the misinterpretation of higher-amplitude suppressed EEG as awake EEG, as those could look very alike [4].

Another important consideration refers to the distinct substance-specific BSupp characteristics. An adjustment regarding the used anesthetic agent might be of great importance to properly detect BSupp, as volatile-induced bursts have significant higher amplitudes. The suppression phases might have those high amplitudes as well, which could exceed the modules suppression amplitude cut offs and again result in an incorrect grading of the anesthetic effects on the brain.

Our additional knowledge on why automated anesthetic depth monitors might inaccurately detect BSupp could be of great importance for future monitoring adaptation and development.

4.5. Impact of our findings on the anesthesiologist:

To reduce the number of patients with unnecessarily excessive dosing of anesthesia, it is important to detect BSupp as precisely as possible. The results of our two studies, in combination to the current literature, highlight the importance of the role of anesthesiologists regarding the correct detection of intraoperative BSupp. The module's calculated index values do not always represent the actual brain effects of anesthesia, but the native EEG helps to ascertain if the displayed index values could be correct. Every anesthesiologist should be able to distinguish a BSupp EEG from a sleep EEG and thereby critically question the displayed indices. Therefore, it is also important to keep potential EEG altering factors, such as age and anesthetic, in mind.

Barnard and others assessed how anesthesiologists perform at interpreting intraoperative EEG compared to processed EEG monitors. They showed that both, the monitors and the anesthesiologist, made mistakes in differentiating a conscious from an anesthetized patient. However, in clinical context they are convinced that a combined interpretation of index values and EEG trace will bring the most accurate results for a correct BSupp detection. [63]

We highly agree with Barnard's opinion and want to encourage every anesthesiologist to take a quick look at the EEG trace before further actions effecting the anesthetic administration are taken.

4.6. The definition of anesthetic-induced BSupp:

Due to the limited concordance regarding the definition of BSupp during general anesthesia in the literature we had to come up with our own transparent and clearly reproducible detection technique. The 'silent second' method was initially used to identify BSupp in the animal model [64], but has become a widely accepted and commonly used strategy to detect BSupp in humans as well [53]. In contrast to other prior investigations, we tried to be very transparent with our BSupp analysis. Throughout analysis of the "raw" EEG, it was sometimes fairly difficult to decide if certain patterns were classifiable as BSupp or not. By using such a precise technique and focusing on our definition, we might have left out some episodes that could have been classified as BSupp as well, e.g. suppressions that lasted shorter than 1 second of duration. The first step in future investigations should be to focus on defining a commonly usable definition of anesthetic-induced BSupp and a transparent and clearly reproducible detection technique.

4.7. Conclusion:

Due to the high life expectancy of patients and the improvement of surgical procedures, the number of elderly undergoing anesthesia will further increase. With increasing age the probability for pNCD, such as POD, rises [46]. At the same time, intraoperative EEG monitoring devices come to the fore to diminish the patient's risk for POD [5, 49]. Due to the automated BSupp detection inaccuracy of the different modules, an adaption of the algorithm would be needed. The anesthesiologist should consider that the BSupp rhythm does not always look the same, is dependent on various factors and it may not be sufficient to rely on index values alone.

The various factors, influencing the BSupp pattern during general anesthesia, suggest that a patient-adapted monitoring, based on the patient's age and physical status and the predominantly used anesthetic agent, may be of priority in the future.

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6. Glossary:

ASA= American Society of Anesthesiologists
AUC= area under the receiver operating curve
BIS= Bispectral Index
BSR= Burst Suppression Ratio
BS%= Burst Suppression Ratio
BSupp= Burst Suppression
CI= confidence interval
CSI= Cerebral State Index
CSM= Cerebral State Monitor
EEG= Electroencephalogram
EMG%= Electromyographic Activity
EMG= Electromyogram
MAC= minimum alveolar concentration
MAP= mean arterial pressure
NLEO= nonlinear energy operator
PACU= post-anesthesia care unit
PDMS= patient data management system
PeEn= Permutation Entropy
pNCD= postoperative neurocognitive dysfunctions
POD= postoperative delirium
POSTS= posterior occipital sharp transients of sleep
PSD= Power Spectral Density
PSI= Patient State Index
RE= Response Entropy
SE= State Entropy
SQI%= Signal Quality Indicator

7. List of tables and figures:

Substance-Specific Differences in Human Electroencephalographic Burst Suppression Patterns

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Intraoperative Burst Suppression is a complex and still not fully understood phenomenon, that is associated with poor postoperative outcome. It is believed to be primarily triggered by extensively deep anesthesia. The commonly used automated anesthetic depth monitors use EEG based algorithms to calculate index values, that reflect the patient's approximate depth of anesthesia and Burst Suppression occurrence. Unfortunately, these monitors do not work as accurate as they should. To improve the intraoperative depth on anesthesia monitoring, it is necessary to gain as much valuable information around the architecture of the Burst Suppression rhythm as possible. Different studies in animal models have shown substance-specific differences in the Burst Suppression pattern. However, no studies in humans have been done before.

As part of a pre-investigation to determine what methods can best be used for the Burst Suppression analysis, we retrospectively analyzed a previously recorded dataset. This dataset consisted of 45 patients divided into three groups, based on the used anesthetic agent. The EEG data were recorded by SP and TK a couple of years ago at the Klinkum rechts der Isar. The study protocol divided the patient in groups based on three commonly used anesthetics: propofol, sevoflurane and isoflurane. The group allocation was made by the anesthesiologist in charge based on clinical aspects.

I was substantially responsible for the raw EEG evaluation. During the visual raw EEG analysis, all raters were blinded to the used anesthetic agent. I highlighted all episodes of Burst Suppression and conferred my evaluation with my co-authors SP and MK. We extracted the first 2 seconds of the very first clearly identifiable burst. The extracted bursts were plotted and compared between the three groups of anesthetics. We compared the groups based on the amplitude, the slope, the Permutation Entropy and the Power Spectral Density. We clinically discussed the results of the analysis with the help of the co-authors.

We were able to show that volatile induced bursts had significant higher amplitudes and higher burst power than propofol induced bursts. Propofol bursts had a significant higher relative power in the EEG alpha-range. The steepest burst slope was found in isoflurane bursts. All our results concur with the previous animal-based findings. Our results might be of valuable contribution to improve automated EEG based anesthetic depth monitoring and help to prevent unnecessarily deep anesthesia and its postoperative side effects.

The results were published in 2018 in the journal *Frontiers in Human Neuroscience*. I was substantially responsible for the writing of the manuscript.

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Substance-Specific Differences in Human Electroencephalographic Burst Suppression Patterns

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Different anesthetic agents induce burst suppression in the electroencephalogram (EEG) at very deep levels of general anesthesia. EEG burst suppression has been identified to be a risk factor for postoperative delirium (POD). EEG based automated detection algorithms are used to detect burst suppression patterns during general anesthesia and a burst suppression ratio (BSR) is calculated. Unfortunately, applied algorithms do not give information as precisely as suggested, often resulting in an underestimation of the patients' burst suppression level. Additional knowledge of substance-specific burst suppression patterns could be of great importance to improve the ability of EEG based monitors to detect burst suppression. In a re-analysis of EEG recordings obtained from a previous study, we analyzed EEG data of 45 patients undergoing elective surgery under general anesthesia. The patients were anesthetized with sevoflurane, isoflurane or propofol (n = 15, for each group). After skin incision, the used agent was titrated to a level when burst suppression occurred. In a visual analysis of the EEG, blinded to the used anesthetic agent, we included the first distinct burst in our analysis. To avoid bias through changing EEG dynamics throughout the burst, we only focused on the first 2 s of the burst. These episodes were analyzed using the power spectral density (PSD) and normalized PSD, the absolute burst amplitude and absolute burst slope, as well as permutation entropy (PeEn). Our results show significant substance-specific differences in the architecture of the burst. Volatile-induced bursts showed higher burst amplitudes and higher burst power. Propofol-induced bursts had significantly higher relative power in the EEG alpha-range. Further, isoflurane-induced bursts had the steepest burst slopes. We can present the first systematic comparison of substance-specific burst characteristics during anesthesia. Previous observations, mostly derived from animal studies, pointing out the substance-specific differences in bursting behavior, concur with our findings. Our findings of substance-specific EEG characteristics can provide information to help improve automated burst suppression detection in monitoring devices. More specific detection of burst suppression may be helpful to reduce excessive EEG effects of anesthesia and therefore the incidence of adverse outcomes such as POD.

Keywords: burst suppression, anesthesia, general, electroencephalography, anesthetic monitoring, anesthetics, EEG patterns, humans

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INTRODUCTION

Burst suppression is a pattern of neuronal network activity that is characteristically seen in a highly inactivated brain, observed in a range of conditions such as hypothermia (Stecker et al., 2001), coma (Young, 2000), and in deep levels of general anesthesia (Rampil, 1998; Brown et al., 2010). In the electroencephalogram (EEG) burst suppression is marked by high voltage brain activity (bursts) and relatively low voltage activity (suppression; Rampil, 1998). Derbyshire et al. (1936) described different EEG patterns including burst suppression induced by the anesthetic avertin back in 1936. Thalamic cells that discharge synchronous rhythmic spikes to an otherwise unresponsive cortex seem to present a key mechanism of burst suppression (Steriade et al., 1994). Visual, somatosensory or auditory stimuli are capable of triggering bursts (Yli-Hankala et al., 1993; Hartikainen et al., 1995b; Hudetz and Imas, 2007). Kroeger and Amzica (2007) therefore considered burst suppression as a state of cortical hypersensitivity. Their results emphasized the absence of involvement of the autonomic nervous system, as no heart rate variations were recorded in response to the provocations. No large body of literature regarding the substance-specific differences of the EEG features during drug-induced burst suppression bursts does exist. Jäntti et al. (1993) found spindles to be characteristic for propofol induced burst suppression. The isoflurane bursts were described to have sharp waves, but not quite as sharp as the bursts in enflurane anesthesia. A very similar description has been made by Lipping et al. (1995) reporting the isoflurane bursts to have smoother waveforms compared to the very sharp enflurane spikes. Hartikainen et al. (1995b) studied the effects of isoflurane during burst suppression anesthesia. They found that with deeper states of anesthesia, suppression periods increase in duration while the total duration of bursts decreases (Hartikainen et al., 1995b). Most of the work regarding substance-specific differences comes from animal models. In 1996 Akrawi et al. (Akrawi et al., 1996) were first to describe substantial electrophysiological differences, in EEG burst suppression patterns, of different anesthetic agents in rats. They compared isoflurane, thiopental, etomidate and propofol at cortical and subcortical sites during burst suppression finding significant differences in EEG characteristics. Isoflurane showed the greatest peak-to-peak voltage and area under the curve (AUC), compared to the other three agents. For all agents, subcortical leads showed greater peak-to-peak voltage and AUC (a measurement for total power within bursts), compared to cortical leads. Differences were found in all agent pairs, except propofol and etomidate, both known to be $GABA_A$ agonists. A comparison of isoflurane and I653 anesthesia (a volatile anesthetic structurally similar to enflurane) in pigs led to the conclusion that EEG patterns were similar at equipotent concentration (Rampil et al., 1988). Another animal study (Murrell et al., 2008) analyzing the burst suppression ratio (BSR) of various volatile anesthetic agents in rats, pointed out that isoflurane, sevoflurane and desflurane all cause burst suppression at concentrations necessary to provide surgical anesthesia. On the other hand, this study did not show suppression at any halothane concentration. Results from a more recent investigation in chicken show that burst suppression can occur at halothane MAC levels $\geq$2 (Mcilhone et al., 2018). Kenny et al. (2014) showed, in rats, that propofol and sevoflurane produce distinct burst suppression patterns. The duration, the peak-to-peak amplitude and the power of the sevoflurane-induced bursts were significantly greater than the propofol-induced bursts. Results from another study describe propofol burst suppression as smooth wave and isoflurane bursts as a clear on-off pattern, between bursts and suppression. The amplitudes during isoflurane bursts were significantly higher than the ones in propofol bursts (Hartikainen et al., 1995a). These results stem from experiments in rabbits and the authors highlight the general difficulty of translating findings from animal models to humans. These described differences show that substance-specific bursts have intrinsic EEG features. Nevertheless, current EEG-based monitoring systems that evaluate the hypnotic component in a patient of anesthesia by displaying an index only use very coarse algorithms for burst suppression (BS) detection.

They calculate an index—(B)SR—that indicates the occurrence and intensity of burst suppression defined as the duration of suppression periods. This information as well as the displayed EEG trace help to identify burst suppression patterns. This identification is important, because burst suppression seems to be an independent predictor for postoperative delirium (POD; Radtke et al., 2013; Fritz et al., 2016), a complication of general anesthesia frequently observed in elderly patients. The use of EEG-based monitors like the bispectral index (BIS, Medtronic, Dublin, Ireland) can help to titrate anesthetic agents to adequate levels of anesthesia and help to prevent unnecessarily deep levels with burst suppression and possible neurotoxic effects (Fedorow and Grocott, 2010). Nevertheless, adequate automatic detection of burst suppression does not seem straightforward (Palanca et al., 2009; Muhlhofer et al., 2017). A possible difference in substance-specific characteristics in the burst EEG may add to these difficulties. Such differences have been reported for animal models (Hartikainen et al., 1995b; Akrawi et al., 1996; Murrell et al., 2008; Kenny et al., 2014), and here we present findings from a patient study with controlled navigation to EEG burst suppression.

MATERIALS AND METHODS

Study Design

We analyzed data from a previous clinical study conducted to evaluate the EEG and cerebral state index (CSI) characteristics at different levels of general anesthesia. In short, the CSI is an unitless index that inversely correlates to a patient's level of consciousness. A CSI of 90–100 for instance reflects a fully awake patient, and a range between 40 and 60 is considered an adequate range to perform surgery. The publication by Jensen et al. (2006) provides a very detailed description of the underlying algorithms. Our study was carried out in accordance with the recommendations of the "Ethics Committee of Technical University of Munich, Munich, Germany" with written informed

consent from all subjects in accordance with the Declaration of Helsinki. The protocol was approved by the "Ethics Committee of the Technische Universität München, Munich, Germany", Ethical Committee N° 1239/05. After informed written consent to the study, 45 adult patients were included undergoing elective surgery under general anesthesia with an American Society of Anesthesiologists physical status I or II. Exclusion criteria were neurological or psychiatric diseases in the past, medications affecting the central nervous system, alcohol or drug abuse, and the indication of a rapid sequence induction (e.g., pregnancy, emergency).

The patients were assigned to three different study groups (sevoflurane group, isoflurane group, propofol group, n = 15 each), chosen by the anesthetist in charge. A randomization was deliberately abandoned, to reflect clinical daily routine. Sufentanil was administered as analgesic for the isoflurane and sevoflurane group and remifentanil for the propofol group. Atracurium or mivacurium were applied as neuromuscular blocking agents. Anesthesia was slowly induced with intravenous injections of propofol. After tracheal intubation, propofol, sevoflurane and isoflurane were administered according to clinical practice. After skin incision, anesthetic depth was increased until burst suppression pattern appeared in the EEG. Burst suppression was identified by the first episode of suppression with a length of at least 3 s. Thereafter, a return to baseline (general anesthesia adequate for surgical procedure) was performed by decreasing anesthetic depth.

EEG Recording

The used EEG traces were recorded at a sample rate of f_s = 100 Hz using the cerebral state monitor (CSM) Link software (Danmeter, Odense, Denmark). Electrode positions were according to the manufacturer recommendation with one electrode placed on the central forehead, another on the left mastoid, and the third electrode on the left side of the forehead. The recommended electrode placements is described in the manual for the CSI[1]. Recorded EEG, the CSI, as well as the processed BSR were stored in a .csv file.

Burst Suppression Selection

The selection of the first burst after a suppression episode was based on visual inspection. To the researcher, the anesthetic agent used in the single recordings was blinded during the selection of bursts. The first distinct burst identified in the EEG was cut out for further analysis. BSR and CSI (generated by the CSM) provided guidance in finding the first burst. A burst was defined as a sharp increase in amplitude and frequency following a period of suppression longer than 1 s, i.e., a "silent second" (Pilge et al., 2014) Initially the silent second presented a visual criterion to identify BS in an animal model (Korkmaz and Wahlström, 1997). If the very first burst was showing artifacts, the first clear burst without interference was selected. The selection was approved by an independent investigator. **Figure 1** displays representative bursts for each anesthetic agent and **Supplementary Figure S1** presents exemplary bursts inclusive the "silent second."

FIGURE 1 | Representative bursts for isoflurane (left, purple), sevoflurane (middle, orange) and propofol (right, blue).

Burst Analysis

For the analysis we limited ourselves to the first 2 s of the burst. We decided on this approach to focus on substance-specific effects on EEG characteristics and not to bias our investigations by different burst lengths, endings of a burst that cannot be clearly identified and changing burst dynamics with ongoing burst duration.

Power Spectral Density

We calculated the power spectral density (PSD) of the burst episode using the MATLAB *pwelch* function with default settings and the NFFT set to 128, resulting in a frequency resolution of 0.78 Hz. We obtained the normalized PSD (nPSD) by dividing the power at each frequency by the sum of power between 6.25 Hz and 30.47 Hz. We chose this normalization interval because of the CSM cutoff frequency of the high pass at 6 Hz. The 30.47 Hz limit is arbitrary, but based on published findings that suggest EEG frequencies below 30 Hz mainly reflect cortical activity and higher frequencies may be increasingly contaminated by EMG (Greif et al., 2002; Bonhomme and Hans, 2007). The decimal places are because of the frequency bins constructed by the *pwelch* function. We dismissed the first 100 ms of burst onset to make sure we did not include any suppression.

Amplitude and Slope Analysis

In order to evaluate the absolute amplitudes during the first 2 s of the first burst, we evaluated the 99th percentile of the absolute amplitudes. We chose the percentile approach to add some robustness to our analyses. A similar percentile approach was used to analyze REM sleep episodes (Silvani et al., 2017). In order to evaluate the slope, i.e., the amplitude change over time, we calculated the first derivative of the EEG and defined the 99th percentile absolute value of the derivative as absolute slope.

Permutation Entropy

We further calculated the permutation entropy (PeEn; Bandt and Pompe, 2002), an ordinal time-domain parameter. PeEn has been used to evaluate different levels of general anesthesia and showed superior results when compared to other (spectral) approaches (Jordan et al., 2008; Olofsen et al., 2008) Essentially, entropic measures like PeEn present a signal analytical approach to evaluate EEG features in the time domain. Recent research revealed that PeEn seems to function as

[1]https://www.danmeter.dk/en/files/CSM-Monitor-MKII---Manual-561105003--US-only-.pdf

TABLE 1 | Demographic data of the three patient groups; Kruskal-Wallis and Freeman-Halton test for multiple comparison of age, size, weight, gender and ASA status.

Group	Propofol	Sevoflurane	Isoflurane	Kruskal-Wallis
Age (years)	57 [45 67]	43 [38.5 63.5]	40 [33 46.5]	$p = 0.1008$
Size (cm)	168 [161 178.5]	173 [167 179]	180 [173 185.5]	$p = 0.1059$
Weight (kg)	71 [68 77]	75 [69.5 79.5]	90 [81 100]	$p = 0.0021$*
BMI	25.4 [23.2 31.2]	25.8 [23.8 36.6]	28.4 [25.8 34.1]	$p = 0.1474$
				Freeman-Halton
Sex (m/f)	7/8	9/6	11/4	$p = 0.3296$
ASA (I/II)	10/5	8/7	10/5	$p = 0.6839$

*The data are presented as median with 1st and 3rd quartile in square brackets. *The Dunn's test revealed a significantly ($p < 0.05$) higher weight in the isoflurane group.*

a proxy for EEG oscillation characteristics (Berger et al., 2017). PeEn evaluates the probability distribution of ordinal rank patterns of length m. Considering our short EEG segments, we defined the embedding dimension $m = 3$ and the time lag $\tau = 1$, parameter settings that were commonly used for EEG analysis (Jordan et al., 2008; Olofsen et al., 2008).

Statistical Analysis

Demographics

We analyzed the demographic data with MATLAB using the Kruskal-Wallis test with a *post hoc* Dunn's test for multiple comparisons for age, weight and height. For evaluation of differences in sex and ASA status we used the Freeman-Halton extension of the Fisher exact test using an online source[2].

EEG Analysis

In order to evaluate possible substance-specific effects on EEG burst features, we used a series of statistical approaches. Therefore, we used the first 2 s of EEG of the first burst of each patient.

For the descriptive statistics, we decided to present the median and median absolute deviation or the median and the single experiments. For the evaluation of differences in the spectral power features we calculated the AUC of the receiver-operating characteristic and 10k-fold bootstrapped 95% confidence intervals (CIs) using the MATLAB-based MES toolbox (Hentschke and Stüttgen, 2011). We chose this approach because of its nonparametric nature. In general, it is related to a Wilcoxon statistic (Jordan et al., 2010). Following studies using a similar approach with a different test we report only results as significant when neighboring frequencies showed significant differences (Akeju et al., 2014). We considered a difference between two distributions significant, if the 95% CI did not contain 0.5. We further decided to indicate AUC > 0.7 that depict a fair and relevant effect (Vivo and Franco, 2008). For analysis of differences in amplitude, slope, and PeEn we used the Kruskal-Wallis test with a *post hoc* Dunn's test being the appropriate multiple comparison test (Elliott and Hynan, 2011). We used the *dunn* function for MATLAB (Cardillo, 2006). Additionally, we also calculated the AUC as a measure of effect size.

[2]http://vassarstats.net/fisher2x3.html

RESULTS

Demographics

We did not observe a significant difference in the distribution of age, size, sex, and ASA status among the groups. The patients undergoing isoflurane anesthesia had a significant higher body weight ($p < 0.05$; Dunn's test) than the patients in the sevoflurane and propofol group, but the body mass index (BMI) was not significantly different among the groups. **Table 1** contains the detailed information regarding the demographics. Further, 13 out of 15 patients received benzodiazepines for oral premedication according to standard clinical practice shortly before they were transported to the operation theatre: they primarily received 3.75–7.5 mg midazolam or in rare cases 10–20 mg clorazepate.

Power Spectral Density of the Bursts

We found significant differences in the PSD and nPSD among substance-specific bursts. Isoflurane-induced bursts had higher power in the almost complete frequency range when compared to propofol-induced bursts. Compared to sevoflurane, isoflurane-induced bursts had higher power in the higher frequencies of ∼14 Hz and more. Sevoflurane-induced bursts had potentially higher power in the lower frequencies from 6 Hz to ∼10 Hz. In the analysis of nPSD, isoflurane-induced bursts maintained their higher power in frequencies corresponding to the EEG beta-range (i.e., ∼12–25 Hz) when compared to sevoflurane. Propofol-induced bursts had higher normalized power in the ∼12 Hz range than isoflurane- and sevoflurane-induced bursts. Sevoflurane-induced bursts had a lower frequency compared to propofol. **Figure 2** presents the PSD plots and **Figure 3** the nPSD plots together with corresponding AUC values with 95% CIs.

Burst Analysis

Absolute Amplitude

We found different absolute burst amplitudes (99th percentile) in a substance specific manner (Kruskal-Wallis: $p = 0.0119$, Chi-squared = 8.87) with lower amplitudes for propofol (isoflurane vs. propofol: $p < 0.05$ Dunn's *post hoc*, AUC (95% CI): 0.81 (0.62 0.96); sevoflurane vs. propofol $p > 0.05$, AUC (95% CI): 0.72 (0.51 0.90)). Hence, AUC indicated a medium to strong effect on burst amplitude when comparing the volatiles to propofol (**Figure 4A**). **Table 2** contains the median values together with the 1st and 3rd quartile of the absolute amplitude.

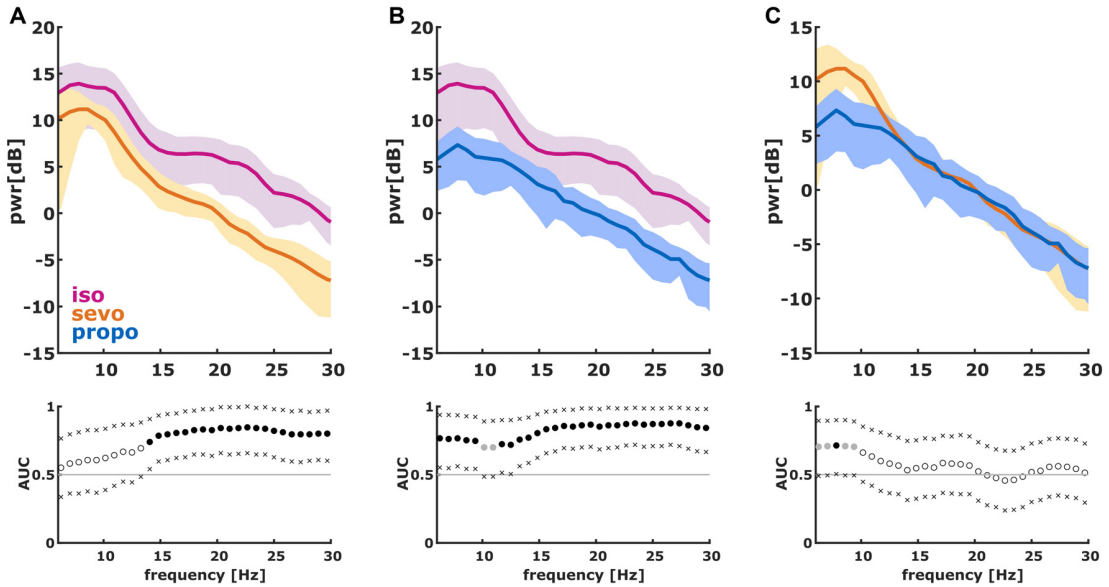

FIGURE 2 | Power spectral density (PSD) in the 6–30 Hz range of the first 2 s of the first burst. (We dismissed the first 100 ms of burst onset to make sure we did not include any suppression). The solid lines present the median and the shaded areas the median absolute deviation for the comparisons of **(A)** isoflurane and sevoflurane, **(B)** isoflurane and propofol, and **(C)** sevoflurane and propofol. In the area under the curve (AUC) plots, a filled circle in black indicates significance and a gray circle indicates a non-significant AUC > 0.7. The non-filled circles indicate AUC < 0.7 with 95% confidence intervals (CIs) inclusive 0.5, i.e., there is no effect. The x indicate the upper and lower limits of the 95% Ci.

Absolute Slope

The slope analysis revealed a steeper burst slope for isoflurane compared to sevoflurane and propofol (Kruskal-Wallis: $p = 0.0102$, Chi-squared = 9.18). Again, the AUC indicated substance-specific medium to strong effects on the burst slope (isoflurane vs. sevoflurane: $p > 0.05$, AUC (95% CI): 0.72 (0.51 0.91); isoflurane vs. propofol: $p < 0.05$, AUC (95% CI): 0.82 (0.64 0.97)). **Table 2** contains the median values together

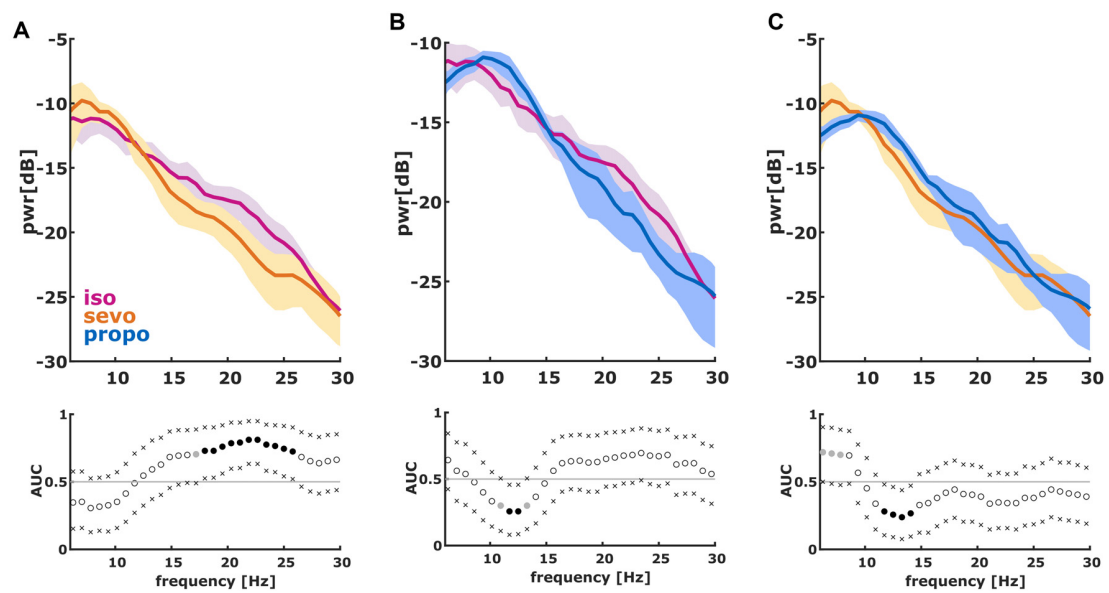

FIGURE 3 | Normalized PSD (nPSD) in the 6–30 Hz range of the first 2 s of the first burst. (We dismissed the first 100 ms of burst onset to make sure we did not include any suppression). The solid lines present the median and the shaded areas the median absolute deviation for the comparisons of **(A)** isoflurane and sevoflurane, **(B)** isoflurane and propofol and **(C)** sevoflurane and propofol. In the AUC plots, a filled circle in black indicates significance and a gray circle indicates a non-significant AUC > 0.7. The non-filled circles indicate AUC < 0.7 with 95% CIs inclusive 0.5, i.e., there is no effect. The x indicate the upper and lower limits of the 95% Ci.

TABLE 2 | Median values inclusive 1st and 3rd quartile for the absolute amplitude, the absolute slope, as well as the permutation entropy (PeEn) of the substance-specific bursting activity.

	Absolute amplitude (μV)	Absolute slope (μV/10 ms)	PeEn (m = 3, tau = 1)
Isoflurane	42.5 [24 66]	34.5 [20 42]	2.29 [2.23 2.31]
Sevoflurane	32.5 [19 46]	18.5 [15 25]	2.20 [2.10 2.23]
Propofol	22 [16 15.5]	18 [15 20.5]	2.22 [2.18 2.31]

with the 1st and 3rd quartile of the absolute slope and **Figure 4B** the single patients' results.

Permutation Entropy

Isoflurane-induced bursts showed higher PeEn than sevoflurane-induced bursts. There were no differences in PeEn between isoflurane-and propofol-induced bursts as well as between sevoflurane- and propofol-induced bursts (**Figure 4C**; Kruskal-Wallis: $p = 0.0153$, Chi-squared = 8.63; isoflurane vs. sevoflurane: $p < 0.05$, AUC (95% CI): 0.83 (0.67 0.96)). **Table 2** contains the median values together with the 1st and 3rd quartile of the PeEn analysis.

DISCUSSION

General anesthesia is defined as a drug-induced, reversible state of unconsciousness including amnesia, immobility and analgesia (Brown et al., 2010). As the level of anesthesia deepens, the EEG shows an increase in low-frequency, high-amplitude activity. Finally, at even higher doses of different volatile or intravenous anesthetics burst suppression can occur in the EEG (Brown et al., 2010). As described in the "Introduction" section, the knowledge regarding substance-specific differences in EEG features of BS bursts is rather sparse (Jäntti et al., 1993; Lipping et al., 1995), whereas there is some information from animal models (Rampil et al., 1988; Hartikainen et al., 1995a; Akrawi et al., 1996; Kenny et al., 2014). With our results we can add more information regarding substance-specific differences in humans and help to link some findings from animal models. We focused on the first 2 s of the first burst observed. This procedure ensures that we evaluated the burst right after the EEG (i.e., the state of the brain) switched for non-BS to BS patterns. This helps to overcome the fact that BS features change with concentration (Hartikainen et al., 1995b).

We also found, as has been described in animals (Akrawi et al., 1996; Kenny et al., 2014), that propofol bursts had the lowest amplitudes when compared to volatile anesthetics. Further, isoflurane-induced bursts in our study had the steepest slopes, while sevoflurane-induced bursts had the lowest PeEn indicative of a very regular signal. Another finding was the strong oscillatory component around 10 Hz in the propofol-induced bursts as determined by the nPSD analysis agreeing with the described spindles (Jäntti et al., 1993). In our analyses, the bursts induced by volatiles did not show this oscillatory component.

Possible Mechanistic Description for the Differences in Burst Characteristics

Cortical burst suppression bursts seem to be mediated by an excitatory thalamic input to hyperexcitable cortical neurons (Kroeger and Amzica, 2007), i.e., the unresponsive cortex is captured by strong and synchronized thalamic activity (Steriade et al., 1994; Brown et al., 2010). They may also be triggered by glutamate-mediated excitatory transmission (Lukatch et al., 2005). Therefore, a substance-specific modulation of anatomic

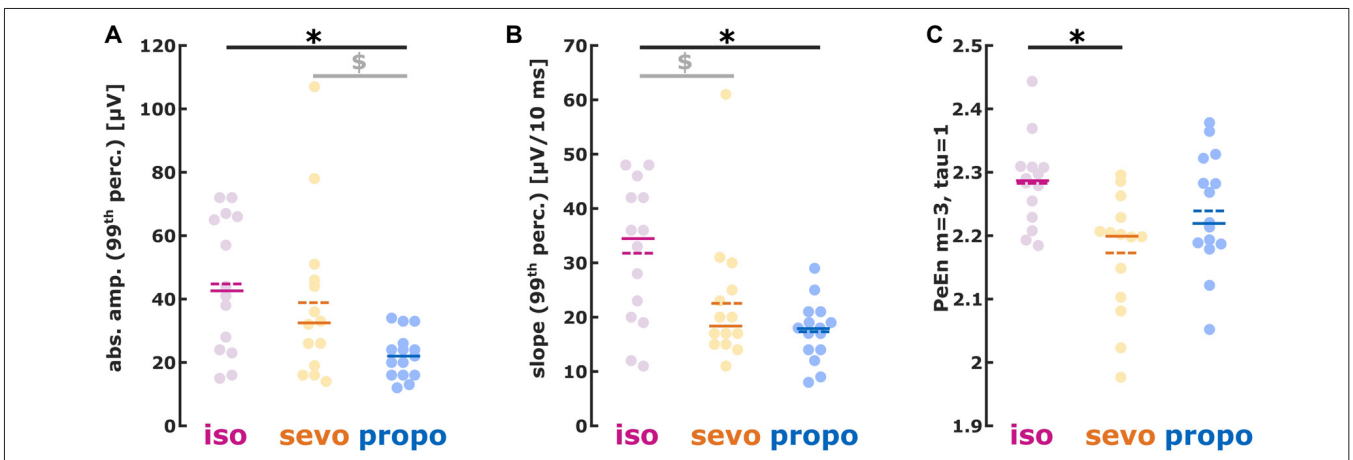

FIGURE 4 | (A) Absolute amplitude, **(B)** first derivative (slope) and **(C)** permutation entropy (PeEn) of burst activity. **(A)** isoflurane- and sevoflurane-induced had higher amplitudes than propofol-induced bursts; **(B)** isoflurane-induced showed a steeper slope than sevoflurane- and propofol-induced bursts. **(C)** Sevoflurane-induced bursts had lower PeEn than isoflurane-induced bursts. *$p < 0.05$ after *post hoc* correction; $AUC > 0.7$ i.e., relevant effect with the 95% CI not containing 0.5, i.e., the effect being different from chance.

or molecular key structures within the thalamocortical network may account for the observed differences in bursts. Since the different anesthetics modulate substance-specific molecular targets that differ to some extent (Franks, 2008), the generated burst patterns can be different as well. Propofol seems to decrease thalamocortical excitatory neurotransmission by increased GABAergic inhibition of cortical pyramidal neurons in combination with an enhancement of the inhibitory input from the reticular thalamic nucleus to thalamocortical relay neurons (Koyanagi et al., 2014). However, results from *in vitro* experiments showed that propofol, in contrast to sevoflurane, does not decrease the intensity of cortical depolarization after thalamic stimulation (Kratzer et al., 2017). In the EEG, propofol leads to pronounced slow-wave and alpha-band activity during general anesthesia (Akeju et al., 2014). In our analyses, we could also observe a more pronounced alpha-oscillation in the propofol-induced bursts when compared to the volatiles. The volatile anesthetics, like isoflurane and sevoflurane, exert more unspecific effects on multiple neuronal targets. They enhance GABA- and glycinergic inhibition, impair excitatory neurotransmission and affect a variety of voltage-gated ion channels (Rudolph and Antkowiak, 2004). These different mode of actions between volatiles and propofol seem to account for differences in the EEG under general anesthesia (Akeju et al., 2014) and, as shown here under burst suppression. Another interesting result is the difference in burst EEG between isoflurane and sevoflurane, despite similar mechanisms of action. Burst duration and amplitude are sensitive to NMDA receptor antagonists, gap junction blockers, and extracellular calcium (Kroeger and Amzica, 2007). Isoflurane seems to inhibit NMDA receptors with a higher potency than sevoflurane (Solt et al., 2006). Hence, our observed differences in isoflurane- and sevoflurane induced bursts may arise from differential impacts on NMDA receptors, but it is too early to draw definitive conclusions.

Impact of Our Study

Our results suggest that the described substance-specific differences occur in human EEG bursts in similar fashion. Isoflurane and sevoflurane bursts were of higher amplitude than propofol bursts. Isoflurane bursts had the steepest slopes, i.e., the strongest changes in amplitude within a short time. Sevoflurane in contrast seemed to trigger the most regular bursts as depicted by low PeEn. All of these findings are reflected in the PSD that indicate a higher general power in the bursts during volatile anesthesia. In contrast to sevoflurane, isoflurane-induced bursts showed more activity in the higher frequencies, a behavior also reflected in the lower PeEn of sevoflurane-induced bursts.

Implications for Monitoring

With our study we could identify substance-specific differences in EEG burst patterns. These findings could help to optimize EEG-based "depth of anesthesia" monitoring at these very deep levels of general anesthesia. The BSR of the BIS detects suppression using an amplitude threshold of 0.5 μV (Rampil, 1998). For low index values indicating very deep anesthesia, the BSR is defining the BIS (Bruhn et al., 2000). A very similar, threshold-based detection-algorithm is part of the CSI (Jensen et al., 2006). The Entropy Module (GE Healthcare, Chicago, IL, USA), another EEG-based monitoring system that evaluates the hypnotic component of anesthesia (Viertiö-Oja et al., 2004), uses a nonlinear energy operator that is calculated from two different (slow/fast) EEG frequency bands (Särkelä et al., 2002). For the SEDLine patient state index (Masimo, Irvine, CA, USA), also a EEG-based system to evaluate the patients' level of (un-)consciousness (Drover and Ortega, 2006), that burst detection algorithm is proprietary. We are confident that substance-specific burst detection, based on differences described in this article, may help to optimize monitoring. Scientific investigations also dealt with the automated detection of EEG burst suppression. Some of these approaches also use defined EEG thresholds (Chemali et al., 2013) or local signal variance (Brandon Westover et al., 2013; An et al., 2015), or higher order spectral analysis (Schack et al., 2001). Hence, substance-specific differences in EEG burst characteristics may also influence the performance of these classifiers. A number of limitations of automated machine-generated burst suppression detection were described in a study by Muhlhofer et al. (2017). The authors report that the automated burst suppression detection of the SEDLine significantly underestimated the real occurrence of burst suppression as identified through visual expert assessment. Furthermore, the neurologists' consensus rating was significantly associated with the incidence of POD, while the relationship between the calculated SEDLine BSR and the incidence of POD was not significant. Our findings regarding substance-specific EEG burst features may help to develop better strategies to reliably catch these episodes in the recorded signal.

Limitations

Of course, there are some limitations to our investigation. First of all, our EEG recordings do not contain the very low delta frequencies because of the intrinsic filter settings of the CSM device. Hence, we could not evaluate differences in these low frequencies. But other groups used similar frequency ranges for their burst suppression classification (Chemali et al., 2013). Because we used only single channel EEG recordings, we cannot describe any substance-specific differences in e.g., interhemispheric EEG synchrony. The frontal recording sites do not allow any speculations regarding differences in EEG burst patterns at other recording sites. These issues should all be part of future investigations. We also only focused on the initial 2 s of a burst and hence we do not draw any conclusions regarding burst length and changes in burst features with burst time. An EEG based monitor should be able to indicate the onset of burst suppression as soon as possible. This is important because both—incidence and increasing duration of EEG suppression—increase the risk of POD. Another issue we would like to mention and that possibly should be investigated in the future, is the difference of opioids used between the volatile anesthetic groups and the propofol group. Opioids in general may have some influence on burst suppression (Kortelainen et al.,

2008). Further, benzodiazepines may have an effect on EEG activity: they increase beta (spindle) activity and reduce lower (alpha) frequency activity (Schulte am Esch and Kochs, 1990). Very high intravenous doses of benzodiazepines, e.g., as used for drug-induced coma in refractory status epilepticus, can lead to burst suppression EEG (Kang et al., 2015). In our study, we predominately used low oral doses of short-acting benzodiazepines. An additive sedative effect may be assumed but may have affected study patients in a comparable manner.

CONCLUSION

Our findings describe substance-specific characteristics of EEG burst onset during burst suppression under general anesthesia. This new information can help to improve the reliable and fast routine detection of burst suppression and hence help to prevent unnecessarily deep levels of anesthesia.

AUTHOR CONTRIBUTIONS

MK designed and conducted analysis, wrote the manuscript. AF analyzed data and wrote the manuscript. TK and SP designed the study, conducted the study and helped to write the manuscript. SK helped to write the manuscript and provided critical feedback. GS helped to design the study, helped to write the manuscript and provided critical feedback.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2018.00368/full#supplementary-material

FIGURE S1 | The first burst after an initial silent second for three patients from each substance category each. The ivory boxes display the silent second and the 2 s of burst electroencephalogram (EEG) used for analysis. This 2 s approach was chosen because for monitoring purposes the burst onset is of significant interest. Further, with ongoing burst duration, the EEG features of the bursts change. Further, the bursts are of different length, within and between groups, but the offset detection is not straightforward.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Always Assess the Raw Electroencephalogram: Why Automated Burst Suppression Detection May Not Detect All Episodes

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The intraoperative monitoring of Burst Suppression has become increasingly important during the last years. Although the benefits of automated EEG based monitors are controversially discussed, they are used to help the anesthesiologist evaluate the patient's anesthetic depth. Unfortunately, they seem to not detect Burst Suppression as accurately as promoted by their manufacturers. An analysis of the Sedline PSI monitor showed a substantially underestimation of the BSR>0 duration of the module compared to the actual visually evaluated Burst Suppression duration. Nevertheless, evaluations on the Entropy module's Burst Suppression detection performance have not been done before. Furthermore, analysis on what Burst Suppression characteristics lead to undetected episodes by the monitor were missing.

The EEG data for this retrospective analysis was collected during an interventional study conducted at the Klinikum rechts der Isar from January 2019 until December 2020. All patients were recorded using an Entropy monitor as well as a 10-channel raw EEG. With this patient setup we were able to compare the module's BSR values to the actual Burst Suppression presence in the raw EEG and obtain insights on the architecture of the unrecognized Burst Suppression phases.

First of all, we evaluated the Burst Suppression detection performance of the Entropy module. We compared the patients based on the concordance of BSR value and presence of Burst Suppression in the raw EEG and divided them into four groups: *mutually detected, visual only, processed only and no BSupp*. We were able to see that the BSR did not recognize Burst Suppression in 13 out of 90 patients. In order to define the concordance within the duration, we compared the total seconds of elevated BSR and the total seconds of visual Burst Suppression in the *mutually detected* group. We were able to see that the concordance is strongly dependent on the BSR value used as a cut off. To establish what EEG features result in a misinterpretation by the Entropy module, we compare the architecture of the suppression of the *mutually detected* and *visual only BSupp*. We evaluated the suppressions based on amplitude range, Permutation Entropy and Power Spectral Density and found a significantly higher suppression amplitude in the group of *visual only BSupp*. This higher amplitude could be one of the main reasons for the module's misinterpretation. Finally, we analyzed the intraoperative RE and SE values of the *visual only* patients and were also able to show that a significant number of patients showed intraoperative elevated RE and SE value, indicating an awake patient. I was mainly responsible for the Burst Suppression selection in the raw EEG traces, as well as the suppression analysis. The results highlight the importance of assessing the raw EEG trace and not solely rely on processed EEG index values.

The results of the analysis were published in *Anesthesia & Analgesia*. I was the main person in charge for the writing of the manuscript. All results were discussed with my co-authors.

Always assess the raw EEG: Why automated burst suppression detection may not detect all episodes

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Gerhard Schneider: This author helped with the study design and writing the manuscript, provided critical feedback and gave the final approval of the manuscript to be published.

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ABSTRACT

Background:

EEG-based monitors of anesthesia are used to assess the patients' level of sedation and hypnosis as well as to detect burst suppression during surgeries. One of these monitors, the Entropy™ Module, uses an algorithm to calculate the burst suppression ratio (BSR), that reflects the percentage of suppressed EEG. Automated burst suppression detection monitors may not reliably detect this EEG pattern. Hence, we evaluated the detection accuracy of BSR and investigated the EEG features leading to errors in the identification of burst suppression.

Methods:

With our study, we were able to compare the performance of the BSR to the visual burst suppression detection in the raw EEG and obtain insights on the architecture of the unrecognized burst suppression phases.

Results:

We showed that the BSR did not detect burst suppression in 13 out of 90 (14%) patients. Furthermore, the time comparison between the visually identified burst suppression duration and elevated BSR values, strongly depended on the BSR value being used as a cut off. A possible factor for unrecognized burst suppression by the BSR, may be a significantly higher suppression amplitude ($p=0.002$). 6 out of the 13 patients with undetected burst suppression by BSR showed intraoperative state entropy values >80, indicating a risk of awareness while being in burst suppression.

Conclusion:

Our results complement previous results regarding the underestimation of burst suppression by other automated detection modules and highlight the importance, to not solely rely on the processed index, but to assess the native EEG during anesthesia.

Key Points:

Question: Why are some burst suppression episodes incorrectly interpreted by the Entropy module?

Findings: Undetected burst suppression episodes have a significant higher suppression amplitude.

Meaning: The anesthesiologist should assess the raw EEG in order to identify burst suppression correctly.

Glossary of terms:

EEG	Electroencephalogram
BSupp	Burst Suppression
pNCD	Postoperative neurocognitive dysfunctions
BSR	Burst Suppression Ratio
SE	State Entropy
RE	Response Entropy
NLEO	Nonlinear energy operator
PeEn	Permutation entropy
PSD	Power spectral density
AUC	Area under the receiver operating curve
CI	Confidence interval

INTRODUCTION

Electroencephalographic (EEG) burst suppression (BSupp) indicates excessively deep levels of anaesthesia[1-3] and may be associated with postoperative neurocognitive dysfunctions (pNCD), longer hospital stays and increased morbidity and mortality[4, 5], although this topic is matter of controversial discussions[6, 7].

EEG-based monitors such as the Bispectral Index (BIS, Medtronic, Dublin Ireland), the SedLine Patient State Index (PSI, Masimo, Irvine, Ca, USA), and the Entropy Module (GE Healthcare, Helsinki, Finland) are commonly used to monitor the patient's level of anesthesia. The monitors calculate an index, the (burst) suppression ratio (BSR), that reflects the occurrence and duration of BSupp, and helps the anesthetist to titrate the needed anesthetic dosage and assess the level of anesthesia. Unfortunately, these monitors may not be as precise as promoted by the manufacturers[8-11]. The index accuracy may also vary between different monitors[12]. For the SedLine, Muhlhofer and colleagues found that the BSR significantly underestimated the total duration of suppression compared to the visual evaluation of the rawEEG[9]. The underestimation of BSupp, which in the worst case could lead to indices suggesting an awake patient[10], could result in an overdose of anesthetics and thereby possibly badly affect the patient's postoperative outcome[13]. An evaluation of the accuracy of the Entropy Module's BSR has not been performed yet. Further, a description of EEG features leading to a misinterpretation by the BSR is also missing.

Compounding the problem is the fact that although anesthetic-induced BSupp has been a subject of research for years, there still is no unique and general definition for this phenomenon in EEG guidelines. A possible factor could be its heterogeneity; it can vary in its duration[14] as well as in its burst architecture[15, 16]. This makes it difficult for researchers to interpret the EEG unambiguously, and even more difficult for the monitors to process it correctly.

With our dataset, we provide a comparison of the native EEG with index values (BSR, SE, RE) of the Entropy Module, to not only determine their accuracy, but also take a closer look into the architecture of unrecognized BSupp phases. Additional knowledge on the module's detecting weak spots, could help in adjusting the algorithms to identify BSupp more precisely and possibly help decrease the risk of undesired postoperative side effects.

METHODS

Study protocol

The dataset for our retrospective investigation, was recorded in a randomized monocentric interventional study[17] conducted at the Klinikum rechts der Isar from January 2019 to December 2020. The study was approved by the ethics committee of the medical faculty at the Technical University of Munich (Chairperson Prof. Dr. Georg Schmidt) on August 13th 2018. Written informed consent was given by all participants. Inclusion criteria were age >60 years, surgery with an estimated duration longer than 60 minutes and intervention under general anesthesia (volatile and intravenous).

110 patients were included in the study and randomly divided into two groups, an intervention and a control group. In both groups the patients' setup consisted of the standard clinical intraoperative monitoring (including arterial blood pressure, oxygen saturation, heart rate, expiratory CO2 and other respiratory parameters), a GE Healthcare Entropy module, and a 10-channel EEG. The exact details of the interventional study have been published elsewhere[17].

Due to technical problems, only 90 out of the 110 screened patients were included in the analysis (**Figure 1**).

Data storage and EEG recordings

The EEG electrode strip of the Entropy Module was placed on the forehead as suggested by the manufacturer[18]. The module's index values were stored as trends in .csv format in our patient data management system. All intraoperative patient data, such as vital or respiratory parameters, surgery timepoints and drug application were also stored here. Resolution of the trend data was 10s.

In addition, we recorded a 10-channel EEG using the Medtronic NIM Eclipse System. The electrodes were placed according to the 10-20 system. EEG data were stored in .eeg format and converted to .mat files.

This manuscript adheres to the applicable CONSORT guidelines.

Visual burst suppression selection

We used MATLAB (R2020b; The Mathworks, Natick, Massachusetts, USA) for our analysis. Possible BSupp in the raw EEG was selected by offline visual analysis of the frontal EEG channel by three of the authors (AF, SP, MK). The information if the BSR also detected BSupp was not shown to the raters. We used the frontal EEG, because the monitors also record from the forehead.

So far, no explicit definition of anesthesia-induced BSupp in the native EEG exists. Hence, we identified BSupp, if a visually recognized suppression of >1s, the silent second[19], was followed by a burst of strong oscillatory activity. The visual verification was conducted in two steps. One of the authors (AF) screened every EEG recording and selected episodes of possible BSupp. These episodes were automatically extracted and reviewed by two other authors (SP, MK) who agreed, together with AF, on the final selection. The periodic alternation of suppressions and bursts, that we agreed on to be identified as BSupp, were extracted for further investigations. The end of the first visually clear suppression was the starting point and the end of the last definite burst the endpoint of a BSupp phase. We excluded BSupp episodes with artefacts.

Technical background of the GE Healthcare Entropy module

The Entropy Module displays three parameters; burst suppression ratio (BSR), response (RE) and state entropy (SE)[20, 21]. The exact algorithms of the index calculation are unknown. We know that SE and RE are calculated using the Shannon entropy[22] applied to the EEG power spectrum. With increasing “depth” of anesthesia, the spectral dominance shifts into lower frequencies and the entropy decreases. The RE reacts faster to arousals, because it includes a frequency range of 0.8-47 Hz and strongly reacts to EMG components. The SE is a more stable parameter which is computed over the EEG-dominant frequency range of 0.8-32 Hz and primarily reflects the cortical activity[20], although of course EEG and EMG strongly overlap[23].The highest values of 100 in RE and 91 in SE indicate a fully awake and conscious patient, while 0 indicates a fully suppressed EEG.

When the patient’s cortical activity goes into BSupp, the Entropy Module switches into a suppression algorithm based on a nonlinear energy operator (NLEO)[20, 21] that leads to a BSR>0. The BSR value represents the relative amount, i.e. the percentage, of

suppression within 60s of EEG. Amplitude cut offs to identify suppression phases have been revealed for other monitors[24], but not for the Entropy module.

Burst suppression analysis

We compared the number of patients with a visually identified BSupp in the raw EEG to the number of patients with BSR>0. We classified patients with visually identified BSupp and BSR>0 as *mutually detected BSupp* and without BSR>0 as *visual only BSupp*. If patients had no BSupp and BSR remained at 0, they were classified *no BSupp* and patients without BSupp, but BSR>0 were *processed only BSupp*.

Comparison of the processed and visually identified BSupp duration

The BSR calculates the relative time in suppression in the last minute of the EEG trace, hence BSR=1 equals 0.6 seconds of suppressed EEG. Such short suppressions are very difficult to visually identify in the EEG and also do not match the silent second strategy we used. In order to evaluate differences in the BSupp duration, we compared the visually identified BSupp duration to the duration of BSR being above certain thresholds between BSR>0 and BSR>20.

Evaluation of differences in the suppression architecture

To detect possible differences in the suppressed EEG, we selected suppression periods from the start, the end and the center of each BSupp episode in all *mutual detected BSupp* and *visual only BSupp* patients. For each selected episode we calculated the (i) amplitude range, (ii) the permutation entropy (PeEn), and (iii) the power spectral density (PSD). The amplitude range is the difference between the maximal and minimal EEG amplitude within the selected suppression. The PeEn may be considered as a measure of signal complexity[25] and was calculated with the embedding dimension m=3 and the shift tau=1. These settings allow for direct comparison between the PeEn and the spectral information[26]. For PSD calculation, we used the pwelch function with standard settings and a frequency resolution of 0.98 Hz. We also calculated the normalized PSD, i.e. dividing the PSD by the cumulative power from 0.89 to 31.25 Hz. We decided to present the findings from the spectral and entropic analysis, because the suppressed EEG may contain anesthesia relevant information, as shown for cortical down states in organotypic slice cultures [27], and the

spectrogram of the patient EEG has been suggested to be used to identify certain EEG patterns such as (burst) suppression[28].

Intraoperative RE and SE values of *visual only BSupp* patients

To evaluate if the unrecognized BSupp episodes in the *visual only BSupp* group led to SE values >80, i.e. indicating an awake patient, we took a closer look at the SE values. We evaluated the SE values starting 30s after the first anesthetic application until the beginning of the emergence of anesthesia, i.e. the last application of anesthetics. We only considered SE>80 episodes of at least 30s duration, to disregard spurious events.

Statistical analysis

Because of the retrospective nature of our study, no sample size estimation was conducted. For the comparison of our data, we used non-parametric approaches, i.e. the Mann-Whitney U test. P-values were considered significant if $p<0.05$. The p-values were supported by the area under the receiver operating curve (AUC) with bootstrapped 95% confidence intervals (CI), calculated with the MES toolbox[29]. We did not correct for multiple comparisons, but present the precise p-values for interpretation. For comparison of the PSD, we also calculated AUC and 95% CI and we considered differences to be significant, if the 95% CI did not contain 0.5 in at least two neighboring frequencies[30]. All these tests were conducted in MATLAB. We did a Chi-square test to check for differences in the applied anesthetic regimens between the *mutually detected BSupp* and *visual only BSupp* patients using the online test at www.socscistatistics.com.

RESULTS

Patients characteristics

There was no significant difference in age between the *mutually detected BSupp* (72 [68; 79] years) and *visual only BSupp* (70 [66; 74] years; p=0.14; AUC=0.63 [0.47; 0.78]) group. The distribution of maintenance anesthetic was also not significantly different (Chi-Square=2.06; p=0.15; **Supplemental Table S1**). Perioperative characteristics of all patients and the distribution of surgical disciplines are presented in **Supplemental Table S1 and S2**.

Differences in visual and processed burst suppression detection

We found that 56 patients (62%) were *mutually detected BSupp* and 20 patients (22%) *no BSupp*, while 13 patients (14%) were classified *visual only BSupp* and 1 patient (1%) *processed only BSupp* (**Figure 2A**). **Figure 2B** displays BSupp intervals of all 13 *visual only BSupp* and of age-matched *mutually detected BSupp* patients. **Figure 2C** shows detailed examples of a *mutually detected BSupp* and a *visual only BSupp* case.

Comparison of the processed and the visually identified BSupp duration

The agreement regarding the BSupp duration strongly depended on the BSR cutoff value (**Figure 3**). With the cutoff set to BSR>0, the duration of a positive BSR as displayed by the Entropy Module was significantly longer compared to the visually identified BSupp episodes (Median ratio visual BSupp/BSR=0.93; p=0.181; AUC=0.39 [0.28; 0.49]). However, from BSR>4 onwards the visually defined duration was significantly longer. **Supplemental Table S3** displays the Median ratios and AUC with 95% CI for each BSR value.

Differences in the suppression EEG characteristics

The amplitude range (**Figure 4A)** was significantly higher in the *visual only BSupp* (17.7 [12.8; 24.5] µV) compared to the *mutually detected BSupp* BSR group (11.2 [10.2; 14.0] µV; p=0.002; AUC=0.21 [0.07; 0.39])**.** PeEn was not significantly different (p=0.380; AUC=0.58 [0.38; 0.77]; **Figure 4B**). The absolute PSD of the *visual only BSupp* (**Figure 4C**) shows a significantly higher power in almost the entire frequency range, whereas the relative PSD (**Figure 4D**) did show significant differences.

Intraoperative SE values of visual only BSupp patients

Out of the 13 *visual only BSupp* patients, 6 showed intraoperative SE values >80 over at least 30s. In 4 cases these episodes were longer than 60s.

Figure 5 represents a case from the *visual only BSupp* group with elevated RE and SE values during anesthetic induction.

DISCUSSION

Burst suppression is a non-physiological EEG rhythm mostly present during excessively deep levels of anesthesia[2, 24], coma[31], or deep hypothermia[32]. It may be associated with pNCD, such as postoperative delirium[5, 33], despite its multifactorial genesis[34].

So far, there is no standardized definition for anesthetic-induced BSupp, nor a unitary method to detect it in the EEG. Rampil[24] described BSupp to be alternating periods of normal to high voltage activity changing to low voltage activity or even isoelectricity, of at least 0.5s duration with amplitudes below +/-5µV. A more current specification of terminology by Hirsch at al.[35] proposed a <10µV absolute amplitude range for suppression periods. Daube and others[36] described BSupp as intermittent bursts of paroxysmal sharp and slow activity separated by episodes of relative quiescent EEG activity, without defining minimum duration or amplitude cutoffs for the suppression. Due to this limited concordant information and the difficulty to project it on BSupp during anesthesia, we had to come up with our own unified and clearly reproducible characterization, based on the silent second[19] strategy.

Between the clearly identifiable BSupp and non-BSupp rhythms, there is a grey area of patterns not being unambiguously classifiable. Cartailler and colleagues[37] described these discontinuous alpha suppressions to be a predictor for isoelectrical suppression, thus BSupp. We found alpha suppressions with suppression duration <1s and without clear bursts in a large number of our patients. In order to stick to our detection technique, and to pursue a rather conservative approach, we intentionally did not include these in our analysis. Hence, we neither understand the consequences of their presence, nor do we know how the monitor classifies them.

Following up on previous studies questioning the precision of automated anesthetic depth monitors[8, 9], we can describe the accuracy of the Entropy Module to detect BSupp. Muhlhofer and co-workers[9] compared BSupp durations in the Sedline module. For their visual BSupp detection they divided the EEG into 30s epochs and scored each epoch individually using the Kugler EEG grading method[38]. They analyzed EEG traces with BSR>0 and therefore did not determine the Sedline's general BSupp detection accuracy. Therefore, they focused on EEG suppression and not on the entire BSupp pattern[9]. Although this method resembles the monitoring approach, it does not totally match the prevailing BSupp definition. With our analyses, we were able to show

that 13/90 (14%) patients had visually detected BSupp that did not lead to BSR>0. Furthermore, the duration comparison was strongly dependent on the BSR value used as a cutoff.

The BSR seems to strongly depend on the suppression amplitudes. EEG suppression amplitudes were significantly higher for visually identified BSupp not detected by the monitor. The absolute PSD showed significantly higher power in almost the entire frequency range of the *visual only BSupp*, highlighting the differences in the suppression amplitude. Since BSR most likely depends on suppression amplitude cutoffs to detect BSupp, those higher amplitudes could be one of the main reasons for the module's inaccuracy. Although suppression episodes can have amplitudes that are higher than the cutoff, artefacts could also lead to high amplitudes during suppression. PeEn and normalized PSD were not significantly different between groups, indicating that the suppression EEG architecture may be rather similar in both groups. If BSupp is not detected, the monitoring systems will treat the EEG as non-suppression EEG and hence apply the respective algorithms. Because the suppressed EEG is of high frequency and low amplitude, i.e. EEG features that also occur during wakefulness[2], the monitors may misinterpret the suppressed EEG as awake EEG and incorrectly display high SE and RE values as shown by us and by Hart and colleagues[10] as well. These falsely elevated SE and RE could be misinterpreted by the anesthesiologist as an inadequately low level of anesthesia and result in an additional application of drugs, even though the anesthesia is already excessively “deep”. The presented case also highlights the importance of evaluating the native EEG trace, where the suppression episode can be visually identified. A quick look and the recognition of BSupp can prevent a further misinterpretation of inadequate anesthetic depth. As suggested by Barnard and others[39] we are convinced that a combined interpretation of index values and visual EEG analysis, will result in the most accurate interpretation of the intraoperative EEG.

Limitations

Of course, our study has some limitations. First of all, the number of *visual only BSupp* is rather small; yet still big enough to give an insight on possible reasons for the module’s drawbacks. Due to the inclusion age >60years and the mostly similar anesthetic procedure, we were not able to determine age- or substance-specific differences, which could also be a partial cause for the module’s inaccuracy[15, 16].

Furthermore, we only analyzed frontal EEG channels, which are the most relevant ones for intraoperative monitoring, and cannot make any assumptions on the suppression characteristics on other recording sites. These issues should be considered during future investigations.

Right now, a precise definition of anesthetic-induced BSupp is missing. Past investigations have kept it rather difficult to understand how they defined BSupp, leading to a general absence of a clear and uniform method to detect it in the raw EEG. We tried to be as transparent as possible with our detection technique and present plots of BSupp. While focusing on our clear definition, we might have left out some debatable episodes. Therefore, the first thing to do in future investigations should be to focus on creating a uniform and unambiguous definition of anesthetic-induced BSupp as well as a clearly reproducible detection technique.

Conclusion

With our study we were able to show that certain EEG characteristics during BSupp can lead to inaccuracies and misinterpretations by the Entropy Module. This information may help the user to correctly react to situations where the BSR detection does not work. A more accurate automated BSupp detection along with additional knowledge on contributing factors, could help prevent unnecessarily deep levels of anesthesia and may decrease the occurrence of pNCD.

Based on our findings, we highly want to encourage anesthesiologists to use the monitoring systems. Nevertheless, they should not only rely on the processed indices, but also take a close look at the EEG trace of the module. Even a basic understanding of EEG patterns can already help in correctly interpreting the patient's anesthetic level. To reliably detect EEG patterns occurring under general anesthesia, such as BSupp, proper training in the interpretation of the raw EEG and its spectral representation is crucial.

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Legends to figures:

Figure 1: Flowchart evaluation procedure. Out of the 110 originally screened patients, 90 were included in our analysis.

Figure 2:

A. Treemap highlighting the classifications of the visual and processed approaches: *mutually detected BSupp*: visual identification and BSR confirm BSupp; *no BSupp*: no BSupp in either detection method; *visual only BSupp*: visually identified BSupp and BSR=0; *processed only BSupp:* BSR>0 and no visual BSupp identification.

B. Burst suppression episodes that were detected by visual inspection and the processed EEG approach (blue, *mutually detected BSupp*) and episodes that were identified by visual inspection only (orange, *visual only BSupp*). The blue traces were extracted from the EEG of age-matched patients.

C. Detailed example of burst suppression that was not recognized (orange, *visual only BSupp*) by the Entropy module and burst suppression that was recognized (blue, *mutually detected BSupp*). The shaded grey area represents an amplitude range of +/- 10 µV. The suppression episodes of the *visual only BSupp* example show underlying oscillations with amplitude values outside the box, whereas the suppression amplitudes of the *mutually detected BSupp* remained inside the box.

Figure 3: Box and scatter plots visualizing the ratio between the duration of automatically or visually detected BSupp. For a low burst suppression ratio (BSR) threshold BSR>0, the automated approach identified significantly longer durations, whereas for thresholds of BSR>4, the visual approach identified significantly longer durations. * indicates significance ($p<0.05$)

Figure 4:

A. Amplitude range of *mutually detected BSupp* (blue) and *visual only BSupp* (orange) suppression episodes: The maximum range was significantly lower ($p=0.002$; AUC=0.21 [0.07; 0.39]) in the suppression episodes detected by the monitor and by visual inspection (11.2 [10.2; 14.0] µV) than the episodes detected by visual inspection only (17.7 [12.8; 24.5] µV). * indicates significance ($p<0.05$)

B. Permutation entropy of the *mutually detected BSupp* (blue) and *visual only BSupp* (orange) suppression episodes: There was no significant difference in the PeEn ($p=0.380$; AUC=0.58 [0.38; 0.77]).

C. Absolute power spectral density of the *mutually detected BSupp* suppression episodes (blue) and *visual only BSupp* (orange): The episodes that were detected by visual inspection only had higher power in the ≤22 Hz as well as the ≥27 Hz frequencies.

D. Relative power spectral density of the *mutually detected BSupp* suppression episodes (blue) and *visual only BSupp* (orange): The relative PSD did not show significant differences.

In subplots A and B the boxplots represent the median values with the first and third quartile. In C and D the solid lines present the median and the shaded areas the median absolute deviation. The black filled dots represent significance, i.e. the 95% confidence interval of the AUC does not contain 0.5. The x indicates the limits of the 95% confidence intervals.

Figure 5: Exemplary case of a *visual only BSupp* case with SE/RE values indicating an awake patient: The raw EEG displays the transition of an awake patient into BSupp. With the first anesthetic application the Entropy values start to drop to a minimum of RE=59 and SE=51. Shortly after reaching the minimal values, the RE and SE rise again to a maximum of RE=100 and SE=90 and remain at high levels >80. Meanwhile the raw EEG switches into BSupp. Throughout the process, the BSR constantly stays at BSR=0.

Figure 1:

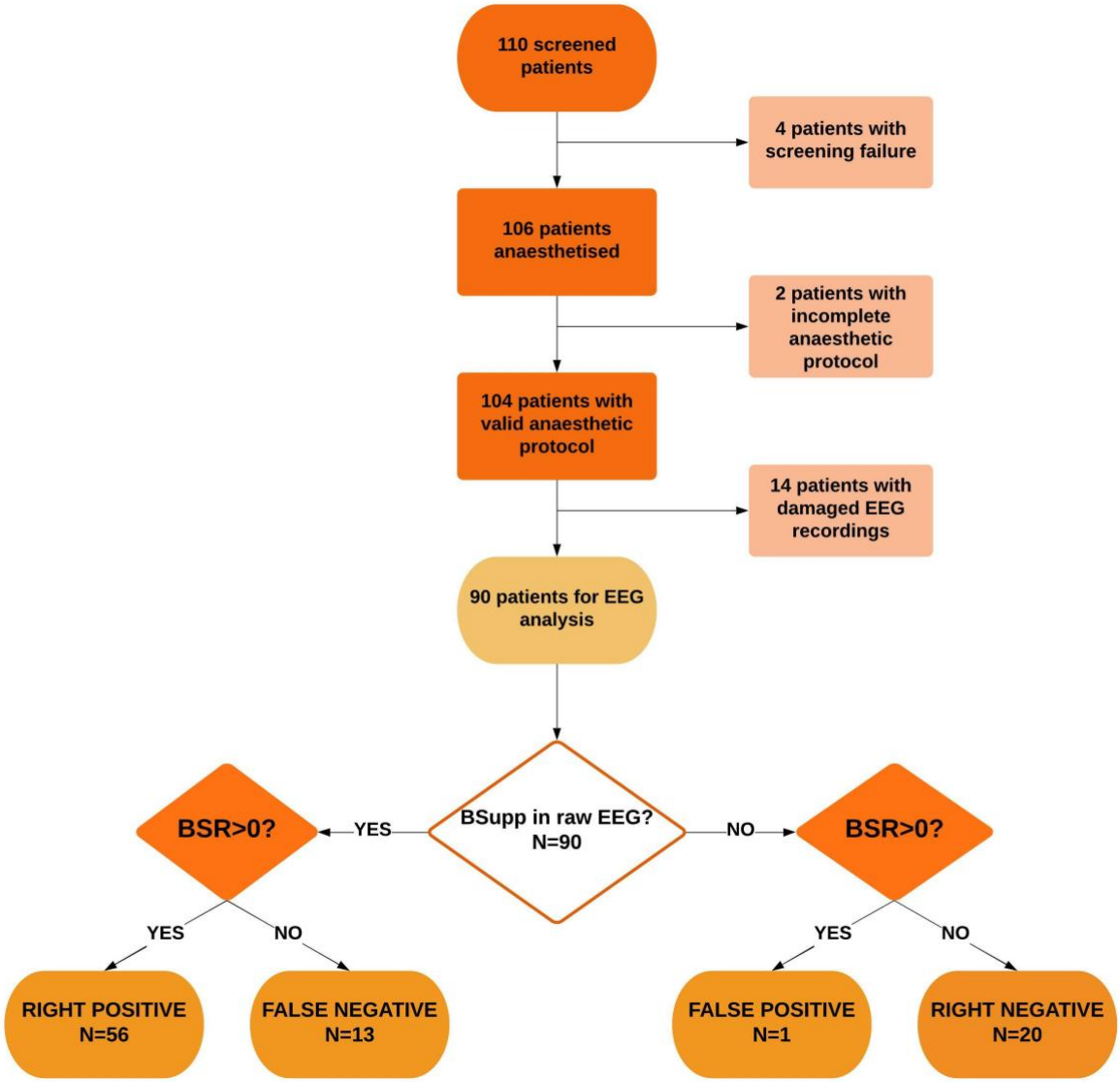

110 screened patients
4 patients with screening failure
106 patients anaesthetised
2 patients with incomplete anaesthetic protocol
104 patients with valid anaesthetic protocol
14 patients with damaged EEG recordings
90 patients for EEG analysis
BSupp in raw EEG? N=90
YES
NO
BSR>0?
BSR>0?
YES
NO
YES
NO
RIGHT POSITIVE N=56
FALSE NEGATIVE N=13
FALSE POSITIVE N=1
RIGHT NEGATIVE N=20

Figure 2:

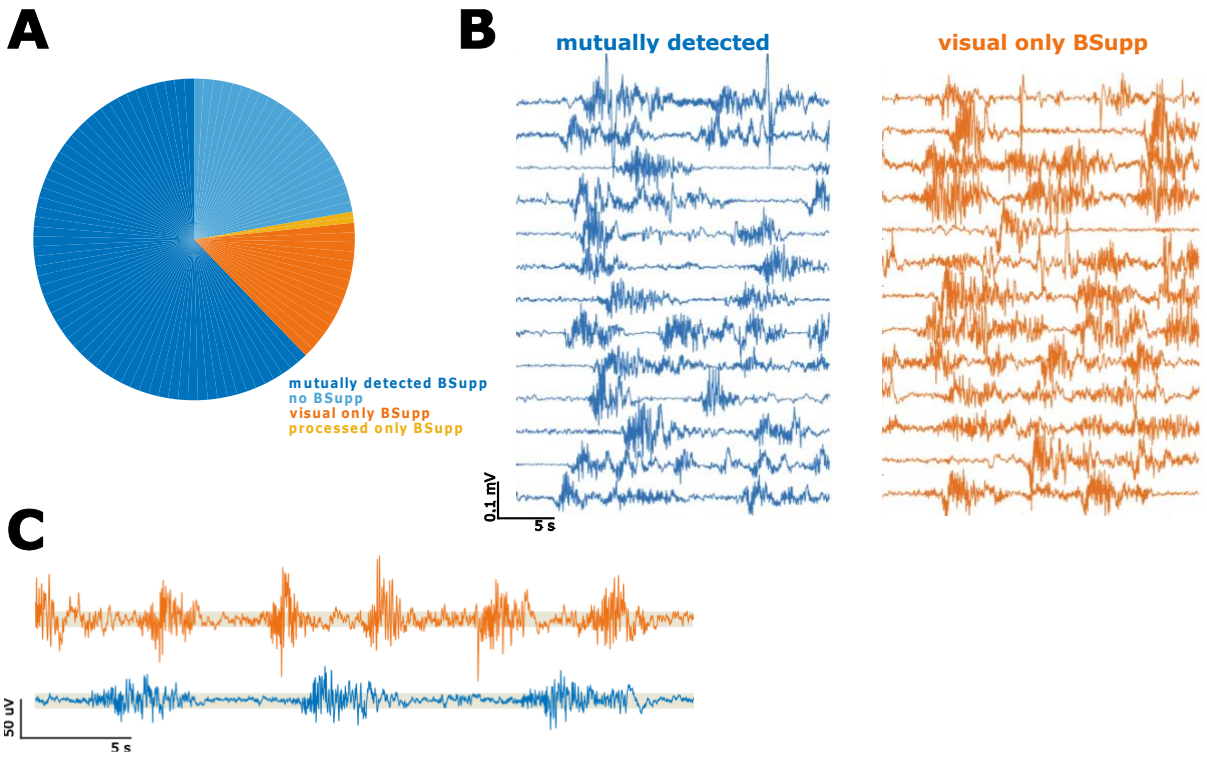


Figure 3:

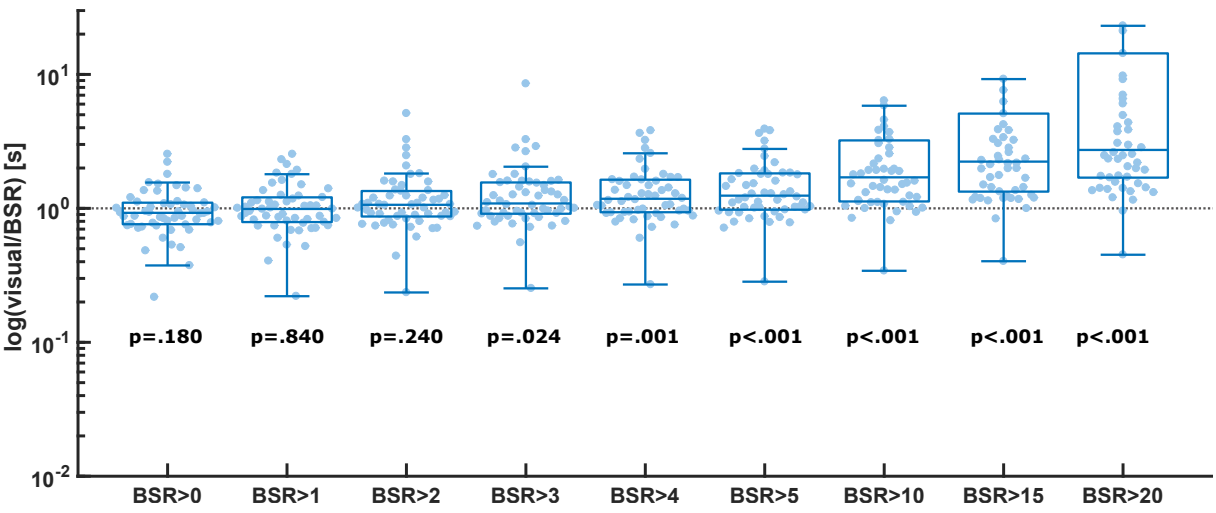


Figure 4:

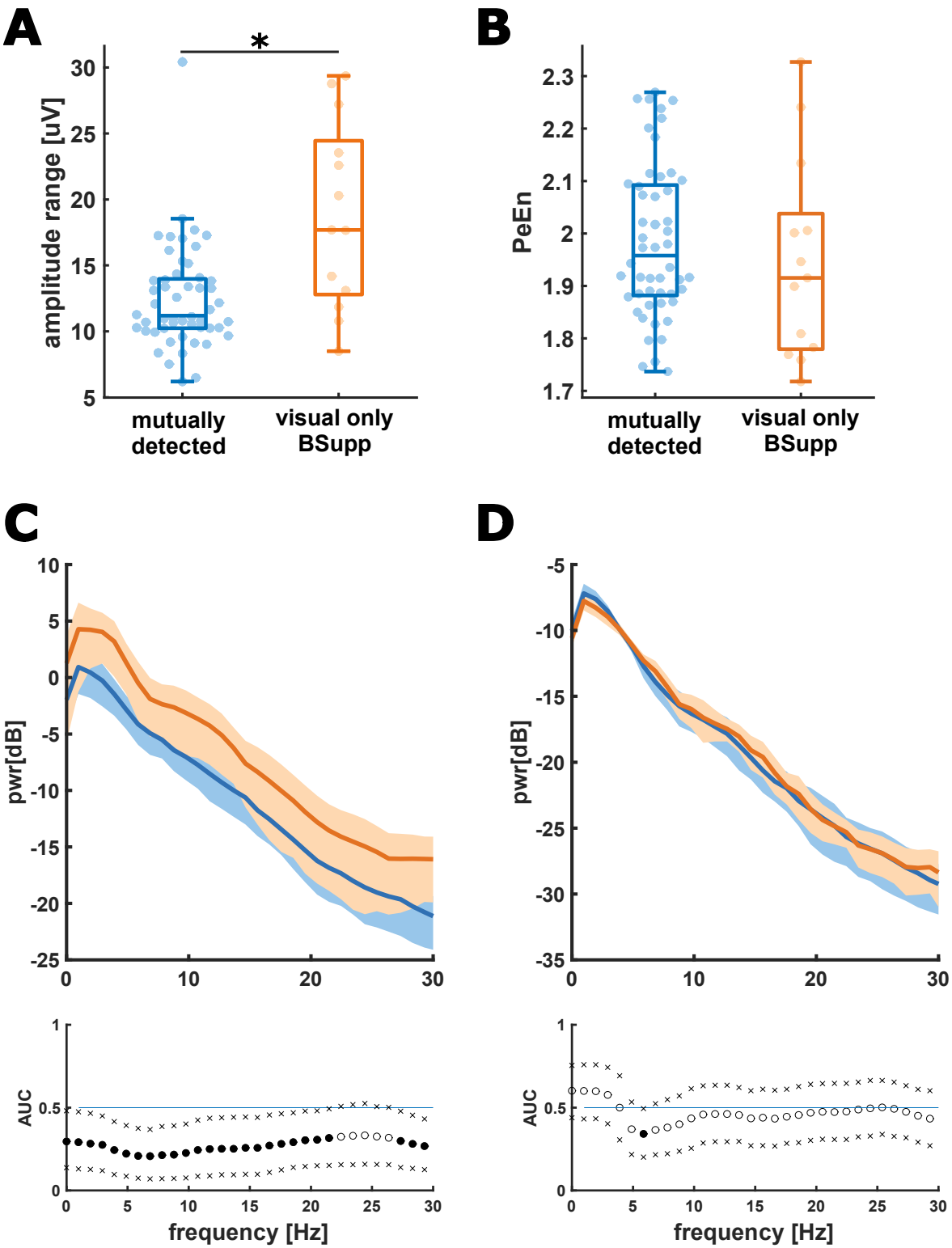
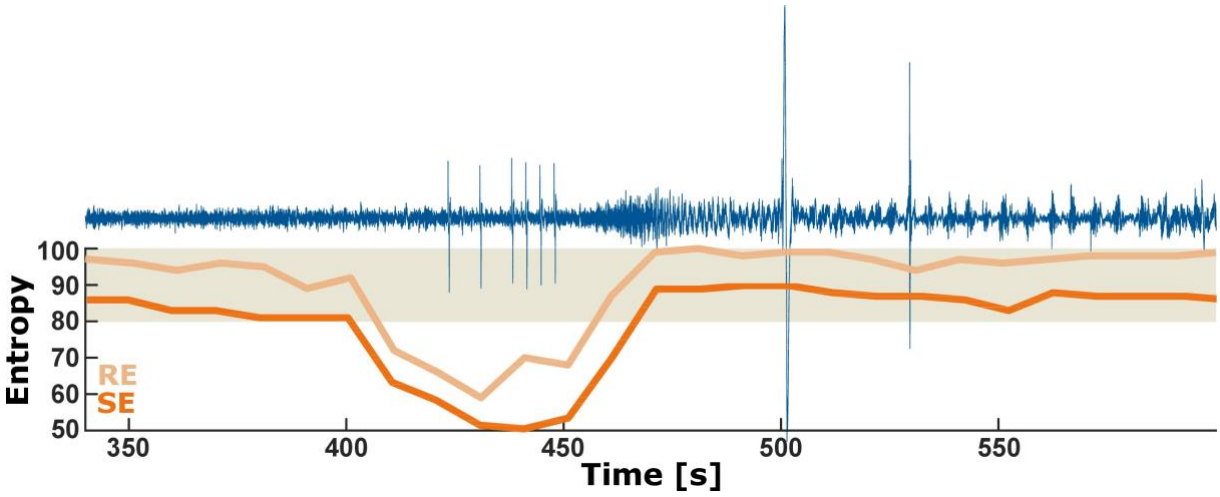

A
*
amplitude range [uV]
30
25
20
15
10
5
mutually detected
visual only BSupp
B
PeEn
2.3
2.2
2.1
2
1.9
1.8
1.7
mutually detected
visual only BSupp
C
pwr[dB]
10
5
0
-5
-10
-15
-20
-25
0
10
20
30
AUC
1
0.5
0
0
5
10
15
20
25
30
frequency [Hz]
D
pwr[dB]
-5
-10
-15
-20
-25
-30
-35
0
10
20
30
AUC
1
0.5
0
0
5
10
15
20
25
30
frequency [Hz]

Figure 5:



Supplemental Data for *Always assess the raw EEG: Why automated burst suppression detection may not detect all episodes*

Perioperative Patients Characteristics (n=90)	
Sex	
female	34 (38%)
male	56 (62%)
Age (in years)	71 [67; 78]
BMI (in cm/kg²)	26.2 [24.2; 28.5]
ASA classification	
1	5 (5%)
2	42 (47%)
3	42 (47%)
4	1 (1%)
Anaesthetic duration (in minutes)	170.5 [139; 231.8]
Maintenance anaesthetic	
Sevoflurane	81 (90%)
Desflurane	1 (1%)
TIVA (Propofol)	8 (8%)
additional epidural catheter	16 (18%)

Supplemental Table S1: Perioperative characteristics of the included patients. The data are presented in absolute numbers with percentage in brackets or media values with 1st and 3rd quartile in square brackets.

Surgical disciplines (n=90)	
orthopaedics	37 (41%)
urology	28 (31%)
visceral surgery	13 (14%)
traumatology	7 (8%)
neurosurgery	2 (2%)
sports orthopaedics	1 (1%)
gynaecology	1 (1%)
vascular surgery	1 (1%)

Supplemental Table S2: Distribution of surgical disciplines

	AUC [AUC 95% CI]	Median ratio	p-values
BSR>0	0.39 [0.28; 0.49]	0.93	0.181
BSR>1	0.48 [0.37; 0.59]	0.99	0.840
BSR>2	0.56 [0.45; 0.66]	1.06	0.240
BSR>3	0.57 [0.47; 0.68]	1.09	0.024
BSR>4	0.62 [0.52; 0.73]	1.18	0.001
BSR>5	0.73 [0.64; 0.83]	1.24	<0.001
BSR>10	0.89 [0.82; 0.95]	1.70	<0.001
BSR>15	0.93 [0.88; 0.99]	2.23	<0.001
BSR>20	0.95 [0.91; >0.99]	2.73	<0.001

Supplemental Table S3: AUC, AUC 95% confidence intervals Median Ratio and p-values for BSR>0 to BSR>20. The Median ratio is the quotient of the seconds of visually sighted BSupp and the seconds of elevated BSR.