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# Transient electroencephalographic alpha power loss during maintenance of general anaesthesia

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# TITLE: Transient electroencephalographic alpha power loss during maintenance of general anaesthesia

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ABSTRACT

Background

Electroencephalographic (EEG) activity in the extended alpha frequency range (7 to 17 Hz) during maintenance of general anaesthesia is primarily driven by effect-site concentrations of the hypnotic and analgesic drugs. Intermittent alpha loss during surgery, unexplained by changes in anaesthetic or opioid levels, could represent arousal of the cortex due to increased surgical stimulation.

Methods

A generalised linear model was fitted to alpha power recorded from patients undergoing general anaesthesia from induction until waking using three explanatory variables: age-adjusted volatile anaesthetic effect-site concentration, estimated effect-site propofol, and opioid concentrations. Model residuals were decomposed into uncorrelated white noise and a fluctuating auto-correlated trend. Deviations of this local trend were classified as 'unexpected alpha dropout events'. To see if these alpha dropouts might be explained by the effect of noxious stimulation, we related their occurrence to whether a patient was undergoing surgery involving the body-cavity or not. ~~surgical data.~~

Results

Alpha power dropouts occurred in 73 of the 237 patients included in the final analysis (31 %, median amplitude of -3.5 dB, duration = 103 s). They showed a bi-modal or broadly skewed distribution, being more probable soon after initial incision (32%), dropping to around 10% at one hour, and then again increasing to >30% in operations lasting more than 3 hours. Multivariate analysis showed that alpha dropouts were significantly associated with body-cavity surgery ($p = 0.003$) and with longer operations ($p < 0.001$).

Conclusions

A loss of alpha power, unexplained by changes in anaesthetic or opioid levels, is suggestive of thalamocortical depolarization induced by body cavity noxious stimuli, and could provide a measure of nociception during surgery.

Keywords:

Alpha Rhythm; Anesthesia, General; Electroencephalography

During surgical anaesthesia the patient is rendered unresponsive and immobile while surgery is taking place, and hemodynamic measures such as heart-rate and blood-pressure are kept within a safe range. Unfortunately, achieving these clinical objectives is no guarantee that the patient's brain is not responding to the noxious stimulation of surgery in some way, even if the patient is not consciously experiencing the surgery. Ostensibly, the responsiveness of the cortex to a given noxious stimulus will depend on three factors: the current concentrations of the anaesthetic providing hypnosis, the opioid providing anti-nociception, and the intensity of the noxious stimulus itself. Given that these three factors change dynamically in the clinical situation, some kind of proxy measure of cortex responsiveness would be helpful for clinicians to navigate through surgery.

One promising measure of cortex responsiveness is the spectral power in the electroencephalogram (EEG) within the extended alpha frequency range (7 to 17 Hz). Alpha oscillations measured at a frontal location are ubiquitous during a typical intravenous or volatile-based general anaesthetic[1 2] and have been shown in numerous experiments to originate in the thalamocortical neural system, as has been extensively reviewed.[3 4 5] The presence of strong alpha waves in the anaesthetised EEG represents a state of hyperpolarization of the thalamocortical system. As a corollary, when alpha waves disappear in the absence of any change in hypnotic drug concentrations, it is likely to be caused by noxious stimulation inducing unopposed thalamocortical depolarization.

A string of studies looked specifically at using alpha power as a marker for nociception in the surgical situation and have reported both increases and decreases in response to noxious stimulation.[6 7 8] This difference in direction of alpha power change may be in part due to the mitigating influence of opioids and the extent of surgical manipulation. Deeper surgical incisions involving muscle and viscera have been associated with a loss of alpha power, whereas stimulation of the skin or mucosa can sometimes

be associated with an increase in alpha power.[7] It would be reasonable therefore to expect that any 'body-cavity surgery', would be more likely to be associated with an alpha power loss.

It remains unclear how often these alpha power loss events occur over the course of normal clinical surgery where the opioid, hypnotic, and surgical stimulus levels are changing dynamically. In a typical clinical situation, the anaesthesia is induced in a patient by giving a bolus of fentanyl and propofol, and then volatile anaesthetic is administered to maintain anaesthesia during surgery. Opioid levels are then 'topped-up' as necessary with additional boluses. Any model of alpha power during surgery would need to account for these fluctuating drug influences.

The purpose of this study therefore was to develop a method of quantifying the expected alpha power from knowledge of ongoing changing volatile anaesthetic, propofol and opioid concentrations. This in turn would allow us capture any decreases in alpha activity that were 'unexpected' (i.e. not associated with changes in drug levels), and to assess if the presence of these unexpected events is linked to whether the patient is undergoing body cavity surgery. This method also allows us to characterise any unexpected *increases* in alpha power. Here we offer a generalised linear model method of variation in alpha power during surgery developed from a large patient dataset.

Methods:

Ethical approval for this cross-sectional observational study was granted by the New Zealand Health and Disability Ethics Committee (Ref. 12/CEN/56). Recordings were completed at the Waikato District Health Board Hospital, Hamilton, New Zealand, from patients undergoing a broad range of types of surgery (predominantly general, vascular, & gynaecological). Patients (aged 18 to 90 years) had an American Society of Anaesthesiologists' (ASA) physical status between I and IV. Anaesthetic regime was left completely at the discretion of the clinical anaesthetist, and all patients gave written informed consent to participate in the study.



EEG Recording and spectral processing:

Frontal bipolar electroencephalograms ($FP_{7\ or\ 8} – FP_Z$) were recorded from 305 patients during general anaesthesia for surgery using either a Bispectral Index (BIS ®, Aspect Medical Systems. Newton, MA, USA, sampling rate: 128 $s^{-1}$) or Entropy (GE Healthcare, Helsinki, Finland, sampling rate: 100 $s^{-1}$) depth of anaesthesia monitors. EEG was de-trended and filtered using a phase-preserving high pass (0.25 Hz) and low pass (48.5 Hz) 3rd order Butterworth filter (filtfilt.m) in MATLAB (The MathWorks, *Inc.*, Natick, MA, USA). BIS recordings were re-sampled to 100 Hz for ease of comparison to Entropy recordings.

Relevant routine monitoring data (such as end-tidal volatile gas anaesthetic (VGA) concentrations, heart-rate, and systolic blood pressure) were recorded from the S/5 Anaesthesia Monitor (GE Healthcare, Helsinki, Finland) using the S/5 Collect program from the same company. The timing and dosage of all propofol and opioid boluses (fentanyl and morphine) were noted so that we could estimate effect-site concentrations of these drugs using standard pharmacodynamical models. In brief,

effect-site propofol was estimated using the two-compartment model and parameters of Wiczling et al, [9] and opioid concentrations using the two- compartment models of Shafer & Varvel [10] for fentanyl, and Mazoit et al [11] for morphine, where a 2 mg morphine dose seen as approximately equal to the efficacy of 100 µg fentanyl. End-tidal VGA concentrations were converted to MAC values for ease of comparison between gas types, and age-adjusted. [12] Effect-site VGA concentration ($C_e$MAC) was determined using an end-tidal to brain effect-site lag model with a $K_{eo}$ half-time of 144 seconds as determined by McKay and colleagues~~.~~[13]. Patients were also categorised as having body cavity surgery (e.g., major thoracic, abdominal or gynaecological surgery) or not according to whether the surgery involved entering of the peritoneum or pleura. Clinical observations led us to suspect that this kind of surgery would have a higher noxious surgical stimulus.

Power spectral densities were obtained from the EEG using a multi-taper method available in the Chronux toolbox (www.chronux.org) [14]. Spectra were calculated from 4 second moving windows, (1 second offset) at a resolution of 0.25~~5~~ Hz, applying 3 tapers. Alpha power was measured as the maximal absolute power (in decibels relative to 1µV) within the 7 to 17 Hz frequency range.

Modelling expected alpha power and characterizing alpha dropouts:

$C_e$MAC, propofol, fentanyl, and peak alpha power measurements were down-sampled to one observation every 5 seconds to minimize autocorrelation. Alpha power values greater than the mean peak alpha power +/- 3 standard deviations were replaced with the patient's peak mean alpha power value in order to minimize the influence of artefactual extreme alpha power values due to impedance checks. A generalised linear model was then applied to the outcome variable, peak alpha power, using the three explanatory variables of effect-site VGA (CeMAC), propofol, and opioid concentrations; beginning at the start of induction until the time when the patient could respond to a verbal command,

which defined the end of the emergence period. At each time-point the differences between the modelled alpha power and the measured alpha power (i.e. model residuals), were smoothed using a Whittaker filter [15] with the smoothing parameter ε set to 5000. The Whittaker decomposition dissociates out the component of the residuals that was uncorrelated white-noise from the auto-correlated local trend. We classified deviations of this trend as 'unexpected alpha dropout' events (see below and Figure 1) which were defined as time-periods when the smoothed alpha power decreased by more than 1.5 standard deviations (of the white noise) from the modelled value. We also applied the same 1.5 standard deviation threshold to detect unexpected alpha power increases.

The progression of analysis is shown in figure 1. This method is comparable to using a tracking signal as developed by Trigg, [16] and further developed by Cembrowski et al. [17] The choice of threshold was decided pragmatically by visually checking the detected dropouts against the spectrograms. We found that a threshold of 2 standard deviations seemed to miss many unexpected alpha dropouts visually present in spectrogram, but that 1 standard deviation was catching a large amount of noise (unpublished data). The final threshold of 1.5 standard deviations seems to us a reasonable and yet conservative measure.

The number, duration, and timing relative to the start of surgery of these alpha dropouts occurring between first incision and completion of the final stitch of surgery were recorded. All alpha dropouts were visually checked, and excluded if due to noise or burst-suppression.

To see if alpha dropouts were associated with immediate changes in haemodynamic factors (specifically mean arterial blood pressure (MAP) or heart-rate (HR)) we compared the mean MAP or HR value over 2 minutes prior to each dropout with the mean value during the dropout.

[Insert figure 1 around here]

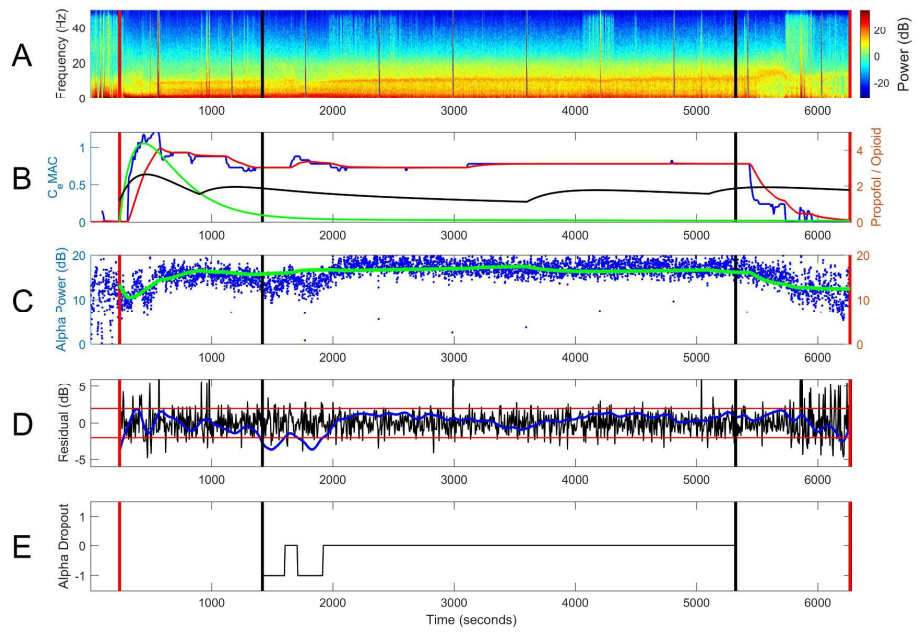


Figure 1: Method of assessing alpha power dropouts from the EEG of an anaesthetised patient. Section A: Spectrogram of the EEG. Vertical red lines on all sections (A to E) indicate time of induction with a bolus of propofol (at around 300 seconds), and of return of responsiveness to command (near 6500 seconds). Black vertical lines show time of first surgical incision and completion of the final stitch respectively, defining the duration of surgery. Section B: End-tidal (red) and effect site VGA concentrations ($C_e$MAC). Also shown are effect-site propofol (green, mg $ml^{-1}$) and opioid concentrations (black, in equivalent Fentanyl concentrations, ng $ml^{-1}$). Section C: Measured peak alpha power (blue, from the 7 to 17 Hz range), and the expected alpha power from linear regression (green line). Section D: The residual (difference between measured and expected alpha power) decomposed into two components; the uncorrelated white noise fluctuating around a

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zero-mean (black), and the auto-correlated local trend (blue). Horizontal red lines are shown at 1.5 standard deviations of the white noise residual component. Section E: When the local trend in section D exceeds the limits of noise so defined it is characterised as an unexpected alpha dropout (-1 on this scale).

Statistical Analysis:

All data are presented as medians (interquartile range, IQR). Our primary outcome measure was the presence or absence of unexpected alpha dropout events in the EEG. Using the Mann-Whitney-U test for continuous measurements, and the Chi-square test for comparison of categorical data, univariate analysis to test for statistical association was done with the following variables: age, length of surgery, mean CeMAC during surgery, mean alpha power during surgery, proportion of patients having body cavity surgery, proportion of patients having a remifentanil infusion, and proportion of patients having an epidural or nerve block (see Table 1). Mean MAP or HR change over the dropout was assessed using a t-test.

An initial full multivariate logistical regression model allowing interactions was created including all variables in Table 1. Mean alpha power decreased with age and was therefore excluded to minimize multicollinearity. Using stepwise elimination, predictor variables with p-values above 0.20 in the initial multivariate model were excluded from the final multivariate logistic regression model. Adequacy of the model fit was tested using the Hosmer-Lemeshow test. From this final model an equation predicting the probability of a patient having an unexpected alpha dropout was created.

Results:

Of the 305 patients enrolled in the study, 68 were excluded from the final analysis due to the following reasons: having a total intravenous anaesthesia with propofol (14), or having problems with late, missing, or excessively noisy EEG data, or missing monitoring data (54). Of the 237 patients included in the final analysis, nine patients with burst suppression were re-categorised as erroneous non-alpha dropout events. In 73 patients (31 %) an alpha dropout was noted according to our measure. Of the 73 patients who had alpha dropouts, 37 (51%) had only one dropout, a further 19 (26 %) had two dropouts, and the remaining 17 patients (23 %) had between 3 and 8 dropouts (with only 2 patients having more than 6 dropouts).~~Seventeen of 73 patients had more than two alpha dropout events.~~ Median peak amplitude of alpha dropouts,(i.e. the magnitude of the drop in alpha power from that expected by the generalised linear model) -was -3.5 dB (IQR 1.6 dB), and the median duration of dropouts was 103 seconds (IQR 130 s). Population cumulative distributions for these variables are shown in Figure 2 (sections A and B). The median time from onset of surgery (first surgical incision) until alpha dropout was 94 minutes (IQR 125 mins). ~~The distribution of times until alpha dropout were bimodal (see figure 2, section C) with a larger probability of dropouts occurring either immediately after surgery onset (within 10 minutes), or with increasing probability as the operation became more prolonged.~~ The distribution of times until alpha dropout were bimodal or a broad skewed distribution, as it showed peaks soon after incision and also later in the surgery. To adjust for the obvious confounder of duration of surgery increasing event occurrence we used the number of operations still happening at the time of the event as the denominator when calculating the probability of event at a particular time (figure 2, section D). The probability of an alpha dropout occurring immediately after the initial surgical incision was 0.32. As seen in figure 2C, 23 out of the total 158 alpha dropouts (15 %) occurred within 10 minutes of the initial surgical incision.

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[Insert figure 2 around here]

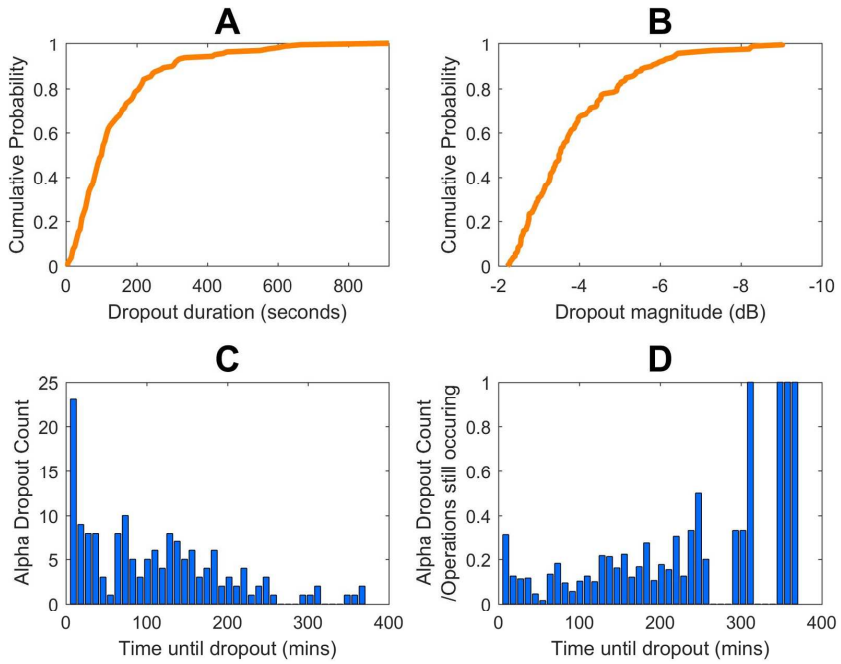


Figure 2: Probability of alpha dropouts. Section A shows the cumulative probability distribution of alpha dropout amplitude, and dropout magnitude (Section B). Section C displays counts of dropout onset times (i.e. time from start of surgery until onset of alpha dropout), whereas section D displays counts of dropout onset times divided by the number of operations still occurring at that onset time.

Univariate Associations:

As seen in Table 1, 73 patients (31%) had one or more alpha dropouts. Increasing operation length, body cavity surgery, and presence of an epidural or nerve block were all significantly associated with

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increased alpha dropout probability ($p < 0.05$). In contrast age, mean $C_eMAC$, mean alpha power, and presence or absence of a remifentanil infusion, were not. The mean opioid concentration during surgery was not significantly associated with alpha dropouts occurring ($p = 0.08$).

[Insert Table 1 around here]

Table 1: Univariate associations with the presence of alpha dropout events (using either a Mann-Whitney-U or a Chi-square test) with interquartile ranges or percentages in parentheses:

| **Predictor Variable** | **Patients *without* alpha dropouts (n = 164)** | **Patients *with* alpha dropouts (n = 73)** | **P-value** |
|---|---|---|---|
| **Median age (IQR)** | 64 (27) | 64 (25) | 0.40 |
| **Median length of Surgery (mins, IQR)** | 56 (82) | 125 (120) | < 0.001 |
| **Mean VGA during surgery ($C_eMAC$, IQR)** | 0.85 (0.74) | 0.89 (0.76) | 0.52 |
| **Mean opioid during surgery (ng/ml, IQR)** | 0.76 (0.74) | 0.94 (0.76) | 0.08 |
| **Mean alpha power during surgery (dB, IQR)** | 10.3 (5.9) | 10.2 (5.9) | 0.95 |
| **Patients having body cavity surgery (%)** | 44/164 (27 %) | 40/73 (55 %) | < 0.001 |
| **Patients having concurrent Remifentanil infusion (%)** | 13/164 (8 %) | 4/73 (5 %) | 0.50 |
| **Patients having concurrent Epidural or Nerve Block (%)** | 14/164 (9 %) | 16/73 (22 %) | 0.004 |



Multivariate Results:

The same variables were significantly associated with the presence of alpha dropouts as for the univariate analysis, with the exception of mean opioid during surgery now gaining a significant

association ($p < 0.01$). The final logistic regression model included the factors operation length, mean opioid concentration during surgery, and surgery type. Coefficients for each variable and associated p-values, as well as odds ratios with 95% confidence intervals, are shown in Table 2.

[Insert Table 2 around here]

Table 2: Variable coefficients with standard errors and p-values for the final model. Also shown are the odds ratios (with 95% Confidence Intervals (CI)) for each variable.

| **Variable** | **Coefficient** | **Standard error of coefficient** | **Odds Ratio (95% CI)** | **P – value** |
|---|---|---|---|---|
| **Intercept** | - 3.319 | 0.505 | 0.036 (0.014, 0.097) | < 0.001 |
| **Length of Operation** | 0.014 | 0.003 | 1.014 (1.009, 1.019) (per minute) | < 0.001 |
| **Opioid Concentration** | 0.927 | 0.331 | 2.526 (1.321, 4.832) | 0.005 |
| **Surgery Type** | 1.663 | 0.565 | 5.275 (1.743, 15.961) | 0.003 |
| **Opioid * Surgery Type** | - 0.891 | 0.457 | 0.410 (0.168, 1.005) | 0.051 |

From the final statistical model, the equation predicting the probability of a patient having an unexpected alpha dropout event is:

$$\text{Probability (Alpha dropout event occurring)} = \frac{1}{1 + e^{-(-3.319 + 0.014 \times Surglen + 0.927 \times Opioid + 1.663 \times SurgType - 0.891 \times Opioid \times SurgType)}}$$

where 'Surglen' is the Length of Surgery in minutes, 'Opioid' is the mean opioid concentration during surgery expressed in ng $ml^{-1}$, and 'SurgType' is the type of surgery (coded 1 if involving body cavity surgery, coded 0 if not).

For example, if a patient is undergoing surgery involving the body cavity, and has a mean blood opioid concentration of 2 ng $ml^{-1}$ during surgery, an increase in operation length from 1 to 3 hours will increase their probability of having an alpha dropout from 0.32 to 0.70. The interaction between opioid concentration, length of surgery, and type of surgery is visually displayed in figure 3. In this figure the left plot shows that for a given length of surgery (x-axis) increasing mean opioid concentrations (y-axis) are associated with an increasing probability of alpha dropout (warmer colours). In contrast, when surgery involves the body-cavity (right plot), for a given length of surgery increasing opioid concentrations do not increase the probability of an alpha dropout occurring. During body-cavity surgery, the interaction term acts to cancel the effect of opioids, as the interaction and opioids terms in the equation above are of similar magnitude but opposite sign.

[Insert figure 3 around here]

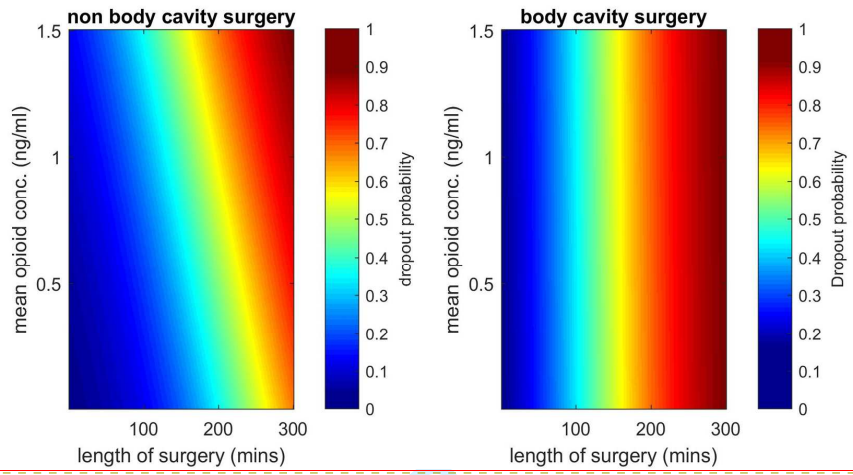


Figure 3: Probability of an alpha dropout occurring (colour scale) for increasing surgery lengths (in minutes) and mean opioid concentrations (ng $ml^{-1}$ fentanyl equivalent) for non-body-cavity (left) and body-cavity surgery (right).

~~[Insert Table 2 around here]~~

The final model was well calibrated (p = 0.51 in the Hosmer-Lemeshow test,[18] using centiles), and had reasonable discrimination; using a probability threshold of 0.5, 76 % of patients were classified correctly according to the final model. Receiver operating curves showed a clear deviation from the diagonal, and had an area under the curve of 0.78 (Figure 4A).

[Insert figure 4 around here]

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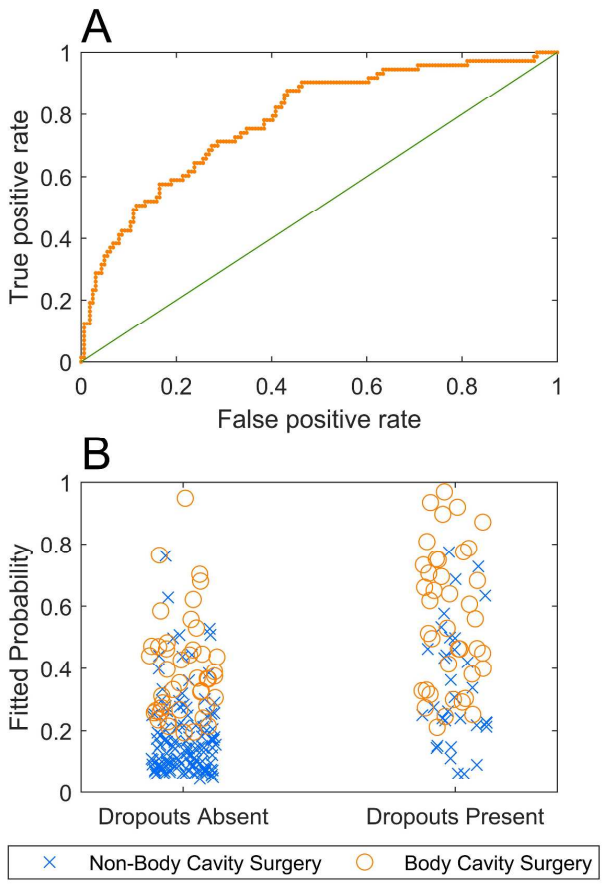


Figure 4: Logistic regression model results. Section A: Receiver operating characteristic curves. Section B: Fitted probabilities of a patient having an alpha dropout event (y-axis) according to whether patients did actually have an alpha dropout or not (x-axis), and according to whether they were undergoing body cavity surgery (blue X = non body cavity surgery, red O = body cavity surgery).

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Unexpected alpha power increases

The methods we developed to detect alpha dropouts also allowed us to analyse unexpected alpha power increases. Forty-eight patients (19 %) had unexpected positive alpha events, and half of these patients (24) had also had an alpha dropout, while half had not. In terms of descriptive statistics, unexpected alpha increases lasted a median of 85 seconds (IQR 95 seconds), had a median amplitude of 3.1 dB (IQR 1.0 dB), and occurred a median time of 40 minutes (IQR 72 minutes) after surgery onset (first incision). Statistically, the presence of an unexpected alpha power increase was significantly associated with increasing length of operation ($p < 0.001$, also using the Mann Whitney U test), but not with age, mean volatile anaesthetic or opioid concentration over the operation, nor with mean alpha power (all $p > 0.05$). Interestingly, the proportion of patients who had concurrent remifentanil infusions was significantly *larger* for those who had alpha increases (10/48, so 21%) compared to those who did not (7/189, 4%, $p < 0.05$). Additionally, the proportion of patients who were undergoing surgery involving the peritoneum was also significantly larger for those who had alpha increases (26/48, 54%) compared to those who did not (58/189, 31%).

When we placed all the aforementioned variables into a logistic regression stepwise model, only the variables operation length and if the surgery involved manipulation of the peritoneum came out as significant predictors ($p < 0.001$ and $p = 0.049$ respectively) of whether a patient would have an unexpected alpha increase event during their surgery. In summary, unexpected alpha increases are of similar duration and magnitude as alpha dropouts, but less common, tend to occur earlier in the operation than alpha dropouts, and are associated with longer operations and body cavity surgery.

Blood pressure was not less during a dropout compared to the two minutes prior to the dropouts ($p = 0.188$), but a significant decrease in HR during the dropout as compared to immediately prior ($p <$

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0.01) was seen. The magnitude of this HR decrease was a small two beats per minute (confidence interval: 1.1 to 3.0 bpm).

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Discussion:

Our results are the first report and characterisation of the transient alpha power loss phenomena, and provide a novel method of detecting them. We show that EEG alpha power instabilities (which also include unexpected alpha power increases) are more likely to occur during longer operations and operations involving body-cavity surgery. The increased occurrence of alpha dropouts during such typically more painful surgery provides some support for the hypothesis that ~~that cortical responsiveness, as measured by pharmacologically unexplained transient loss of alpha power, is indicative of thalamocortical depolarization due to~~ unsuppressed noxious stimuli could be causing a depolarisation of the thalamocortical system leading to alpha loss, but the increased occurrence of alpha power *increases* during body-cavity surgery tempers this support somewhat. We think it possible that such alpha power increases might be a phenomenon akin to the abrupt increases in delta power (0.5 - 4 Hz) in response to intra-abdominal irrigation (which involves peritoneal distension) in the context of low analgesia,[21] but we did not assess delta power in this study. Further studies will be needed to clarify the biological causes of these phenomena. The unexpected alpha power increases were not as readily apparent as the alpha dropouts in the spectrogram.

During body cavity surgery alpha dropouts were more frequent. The peritoneum is a biologically active membrane innervated primarily by the vagus nerve, which carries neural information directly to the central nervous system, bypassing the spinal cord. [19] Vagal stimulation can be used clinically to reduce excessive neural synchrony in patients with epilepsy.[20] This is in accord with our findings which show that the nociception elicited by peritoneal manipulation during surgery reduces EEG alpha power; this power reduction is a manifestation of neural desynchronization.

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Alpha dropouts are more likely to occur during longer operations. Because the probability of an alpha dropout occurring increased with increasing operation length – even when the number of operations still occurring at a given time was taken into account – this effect cannot represent an increased chance of a random event being detected due to increased time available. Rather, we speculate that longer operations are associated with increased surgical severity and a progressive increase in inflammation, which somehow leads to changes in alpha power stability, presumably through gene expression alterations.

In our results, in patients undergoing surgery not involving the body cavity higher opioid concentrations were associated with an *increased* ~~in the~~ probability of an alpha dropout occurring. This finding is perhaps unexpected from a clinical perspective. We interpret this as a higher opioid dose ~~is~~ being administered for ~~more serious~~ operations where higher levels of noxious stimulation are to be expected, but that this increased dose is not sufficient to block nociceptive barrage~~, particularly via the vagal pathway~~, and subsequently manifests in alpha dropouts. Alternatively it is possible that we are seeing some manifestation of acute tolerance to opioids, or opioid induced hyperalgesia. In patients undergoing body-cavity surgery, that this effect of opioids is removed fits well with our suspicion that dropouts are vagally mediated; these kinds of operations involve the peritoneum and lead to vagally mediated noxious stimulation, and alpha dropouts occur irrespective of opioid dose.

~~In this study we did not look at changes in delta power (0.5 – 4 Hz). Intraabdominal irrigation (which involves peritoneal distension) has been observed to increase delta power in the context of low analgesia,[21] though this effect may have been enhanced by the presence of nitrous oxide. Delta activity, at least during propofol based anaesthesia, travels over the cortex,[22] and is not spatially coherent[23] and thus not necessarily a measure of thalamocortical synchrony.~~

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The statistically significant but small decrease in heart-rate during alpha dropouts when compared to immediately prior we interpret as alpha dropouts tending to occur when heart-rate was decreasing.

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*Limitations*

The use of a general linear model assumes the dose-response relationship of alpha-power to $C_e$MAC to be linear. This seems to have worked well over the typical range of intraoperative drug concentrations, and has allowed us to tease out the effect of noxious stimuli; but further refining the fitting using a non-monotonic link function such as a sigmoid, or even bi-sigmoidal curve fitting procedure, might better capture this phenomenon.

Most depth of anaesthesia monitors do not explicitly quantify alpha power; the BIS uses comparisons between the entire frequency range and fast or slow frequencies, [24] and the Entropy module evaluates the shape of the entire spectrum. [25] While the subtle changes in alpha power can be difficult to detect in the raw signal, these changes are easily seen in the spectrogram. [26] As ongoing anaesthetic and opioid delivery is under direct control of the physician anaesthetist, any pharmacologically unexpected alpha dropouts could be quickly detected. This study also has clinical implications regarding opioid dosing; while it is not known if thalamocortical depolarization to noxious stimuli has negative post-operative clinical implications, if the goal is to maintain thalamocortical~~ex~~ stability, our results suggest, in line with Hagihira and colleagues [27] that opioid dosing rather than hypnotic dosing should be targeted.

To conclude, this report is the first characterisation of the alpha dropout phenomenon, i.e., a pharmacologically unexplained transient loss of alpha power during surgery, and provides a novel method of detecting them. Alpha dropouts occur more often during surgery involving the peritoneum,

as do unexpected increases in alpha power, suggesting that unsuppressed noxious stimulation can manifest as thalamocortical instability.

~~We conclude that pharmacologically unexplained transient losses of alpha power during surgery, which are originate from thalamocortical depolarizations, can provide a helpful measure of unsuppressed nociception during surgery.~~

**Authors' Contributions:**

D.H.: Patient recruitment, data collection, data analysis, and writing the manuscript.

A.G.: Patient recruitment, data collection, writing manuscript

M.K.: Data analysis and writing the manuscript

L.V.: Study conception and writing the manuscript

P.G.: Study conception, writing manuscript

J.S.: Study conception and design, data analysis, writing manuscript.

**Declaration of interests:**

All authors have no conflicts of interest to declare.

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References:


1. Gugino L, Chabot R, Prichep L, John E, Formanek V, Aglio L. Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. *Br J Anaesth* 2001; **87**: 421–428

2. Akeju O, Westover MB, Pavone KJ, et al. Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. *J Am Soc Anesthesiol* 2014; **121**: 990–998

3. Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. *Sci-N Y THEN Wash-* 1993; **262**: 679–679

4. McCormick DA, Bal T. Sleep and arousal: thalamocortical mechanisms. *Annu Rev Neurosci* 1997; **20**: 185–215

5. Sleigh JW, Scheib CM, Sanders RD. General anaesthesia and electroencephalographic spindles. *Trends Anaesth Crit Care* 2011; **1**: 263–9

6. Kochs E, Bischoff P, Pichlmeier U, am Esch JS. Surgical stimulation induces changes in brain electrical activity during isoflurane/nitrous oxide anesthesia. A topographic electroencephalographic analysis. *Anesthesiology* 1994; **80**: 1026–1034

7. Wilder-Smith O, Hagon O, Tassonyi E. EEG arousal during laryngoscopy and intubation: comparison of thiopentone or propofol supplemented with nitrous oxide. *Br J Anaesth* 1995; **75**: 441–446

8. MacKay EC, Sleigh JW, Voss LJ, Barnard JP. Episodic waveforms in the electroencephalogram during general anaesthesia: A study of patterns of response to noxious stimuli. *Anaesth Intensive Care* 2010; **38**: 102

9. Wiczling P, Bienert A, Sobczyński P, et al. Pharmacokinetics and pharmacodynamics of propofol in patients undergoing abdominal aortic surgery. *Pharmacol Rep* 2012; **64**: 113–122

10. Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology* 1991; **74**: 53–63

11. Mazoit JX, Butscher K, Samii K. Morphine in Postoperative Patients: Pharmacokinetics and Pharmacodynamics of Metabolites: *Anesth Analg* 2007; **105**: 70–8

12. Nickalls RWD, Mapelson, WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. *Br J Anaesth* 2003; **91**: 170–4

13. McKay IDH, Voss LJ, Sleigh JW, Barnard JP, Johannsen EK. Pharmacokinetic-Pharmacodynamic Modeling the Hypnotic Effect of Sevoflurane Using the Spectral Entropy of the Electroencephalogram: *Anesth Analg* 2006; **102**: 91–7

14. Bokil H, Andrews P, Kulkarni JE, Mehta S, Mitra PP. Chronux: A platform for analyzing neural signals. *J Neurosci Methods* 2010; **192**: 146–51

15. Whittaker ET. On a new method of graduation. *Proc Edinb Math Soc* 1922; **41**: 63–75

16. Trigg DW. Monitoring a Forecasting System. *OR* 1964; **15**: 271

17. Cembrowski GS, Westgard JO, Eggert AA, Toren EC. Trend detection in control data: optimization and interpretation of Trigg's technique for trend analysis. *Clin Chem* 1975; **21**: 1396–1405

18. Hosmer DW, Lemeshow S. Applied logistic regression. John Wiley & Sons; 2004.

19. Kahokehr A, Sammour T, Srinivasa S, Hill AG. Metabolic response to abdominal surgery: The 2-wound model. *Surgery* 2011; **149**: 301–4

20. Bodin C, Aubert S, Daquin G, et al. Responders to vagus nerve stimulation (VNS) in refractory epilepsy have reduced interictal cortical synchronicity on scalp EEG. *Epilepsy Res* 2015; **113**: 98–103

21. Morimoto Y, Matsumoto A, Koizumi Y, Gohara T, Sakabe T, Hagihira S. Changes in the Bispectral Index During Intraabdominal Irrigation in Patients Anesthetized with Nitrous Oxide and Sevoflurane: *Anesth Analg* 2005; **100**: 1370–4

22. Murphy M, Bruno M-A, Riedner BA, et al. Propofol anesthesia and sleep: a high-density EEG study. *Sleep* 2011; **34**: 283–291

23. Cimenser A, Purdon PL, Pierce ET, et al. Tracking brain states under general anesthesia by using global coherence analysis. *Proc Natl Acad Sci* 2011; **108**: 8832–7

24. Rampil IJ. A primer for EEG signal processing in anesthesia. *J Am Soc Anesthesiol* 1998; **89**: 980–1002

25. Viertiö-Oja H, Maja V, Särkelä M, et al. Description of the Entropy™ algorithm as applied in the Datex-Ohmeda S/5™ Entropy Module. *Acta Anaesthesiol Scand* 2004; **48**: 154–161

26. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for AnesthesiologistsPart I: Background and Basic Signatures. *J Am Soc Anesthesiol* 2015; **123**: 937–960

27. Hagihira S, Takashina M, Mori T, Ueyama H, Mashimo T. Electroencephalographic bicoherence is sensitive to noxious stimuli during isoflurane or sevoflurane anesthesia. *J Am Soc Anesthesiol* 2004; **100**: 818–825

Tables:

Table 1: Univariate associations with the presence of alpha dropout events (using either a Mann-Whitney-U or a Chi-square test) with interquartile ranges or percentages in parentheses:

| **Predictor Variable** | **Patients *without* alpha dropouts (n = 164)** | **Patients *with* alpha dropouts (n = 73)** | **P-value** |
|---|---|---|---|
| **Median age (IQR)** | 64 (27) | 64 (25) | 0.40 |
| **Median length of Surgery (mins, IQR)** | 56 (82) | 125 (120) | < 0.001 |
| **Mean VGA during surgery ($C_e$MAC, IQR)** | 0.85 (0.74) | 0.89 (0.76) | 0.52 |
| **Mean opioid during surgery (ng $ml^{-1}$, IQR)** | 0.76 (0.74) | 0.94 (0.76) | 0.08 |
| **Mean alpha power during surgery (dB, IQR)** | 10.3 (5.9) | 10.2 (5.9) | 0.95 |
| **Patients having body cavity surgery (%)** | 44/164 (27 %) | 40/73 (55 %) | < 0.001 |
| **Patients having concurrent Remifentanil infusion** | 13/164 (8 %) | 4/73 (5 %) | 0.50 |

| (%) | | | |
|---|---|---|---|
| **Patients having concurrent Epidural or Nerve Block (%)** | 14/164 (9 %) | 16/73 (22 %) | 0.004 |

Table 2: Variable coefficients with standard errors and p-values for the final model. Also shown are the odds ratios (with 95% Confidence Intervals (CI)) for each variable.

| Variable | Coefficient | Standard error of coefficient | Odds Ratio (95% CI) | P – value |
|---|---|---|---|---|
| **Intercept** | - 3.319 | 0.505 | 0.036 (0.014, 0.097) | < 0.001 |
| **Length of Operation** | 0.014 | 0.003 | 1.014 (1.009, 1.019) (per minute) | < 0.001 |
| **Opioid Concentration** | 0.927 | 0.331 | 2.526 (1.321, 4.832) | 0.005 |
| **Surgery Type** | 1.663 | 0.565 | 5.275 (1.743, 15.961) | 0.003 |
| **Opioid * Surgery Type** | - 0.891 | 0.457 | 0.410 (0.168, 1.005) | 0.051 |

Figure Legends

Figure 1: Method of assessing alpha power dropouts from the EEG of an anaesthetised patient. Section A: Spectrogram of the EEG. Vertical red lines on all sections (A to E) indicate time of induction with a bolus of propofol (at around 300 seconds), and of return of responsiveness to command (near 6500 seconds). Black vertical lines show time of first surgical incision and completion of the final stitch respectively, defining the duration of surgery. Section B: End-tidal (red) and effect site VGA concentrations ($C_e$MAC). Also shown are effect-site propofol (green, mg $ml^{-1}$) and opioid concentrations (black, in equivalent Fentanyl concentrations, ng $ml^{-1}$). Section C: Measured peak alpha power (blue, from the 7 to 17 Hz range), and the expected alpha power from linear regression (green line). Section D: The residual (difference between measured and expected alpha power) decomposed into two components; the uncorrelated white noise fluctuating around a zero-mean (black), and the auto-correlated local trend (blue). Horizontal red lines are shown at 1.5 standard deviations of the white noise residual component. Section E: When the local trend in section D exceeds the limits of noise so defined it is characterised as an unexpected alpha dropout (-1 on this scale).

Figure 2: Probability of alpha dropouts. Section A shows the cumulative probability distribution of alpha dropout amplitude, and dropout magnitude (Section B). Section C displays counts of dropout onset times (i.e. time from start of surgery until onset of alpha dropout), whereas section D displays counts of dropout onset times divided by the number of operations still occurring at that onset time.

Figure 3: Probability of an alpha dropout occurring (colour scale) for increasing surgery lengths (in minutes) and mean opioid concentrations (ng $ml^{-1}$ fentanyl equivalent) for non-body-cavity (left) and body-cavity surgery (right).

Figure 4: Logistic regression model results. Section A: Receiver operating characteristic curves. Section B: Fitted probabilities of a patient having an alpha dropout event (y-axis) according to whether patients did actually have an alpha dropout or not (x-axis), and according to whether they were undergoing body cavity surgery (blue X = non body cavity surgery, red O = body cavity surgery).

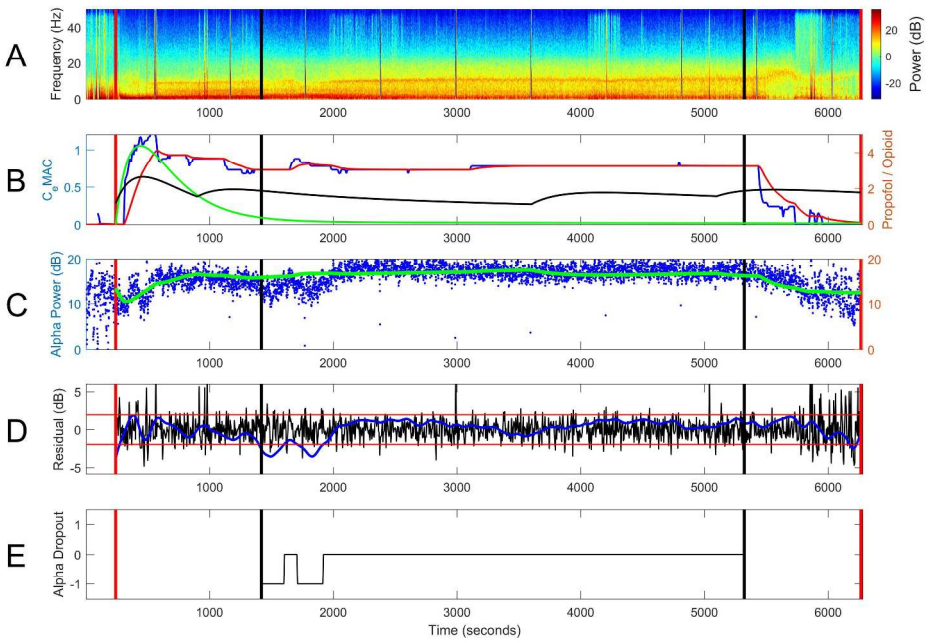


Figure 1

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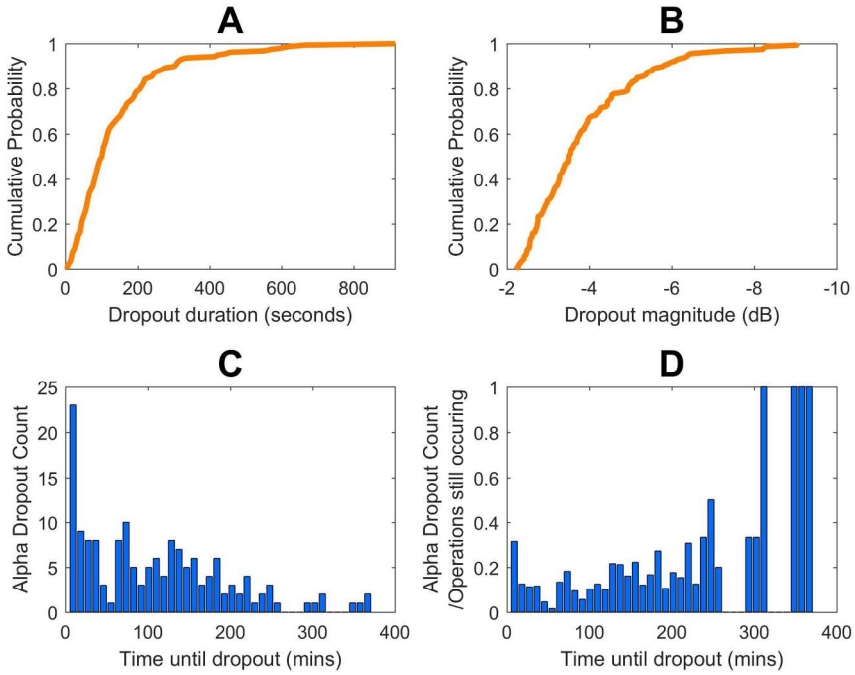


Figure 2

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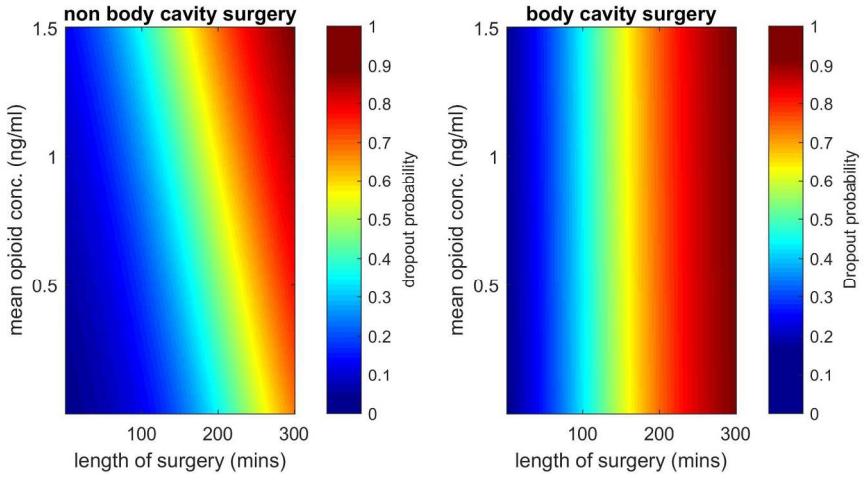


Figure 3

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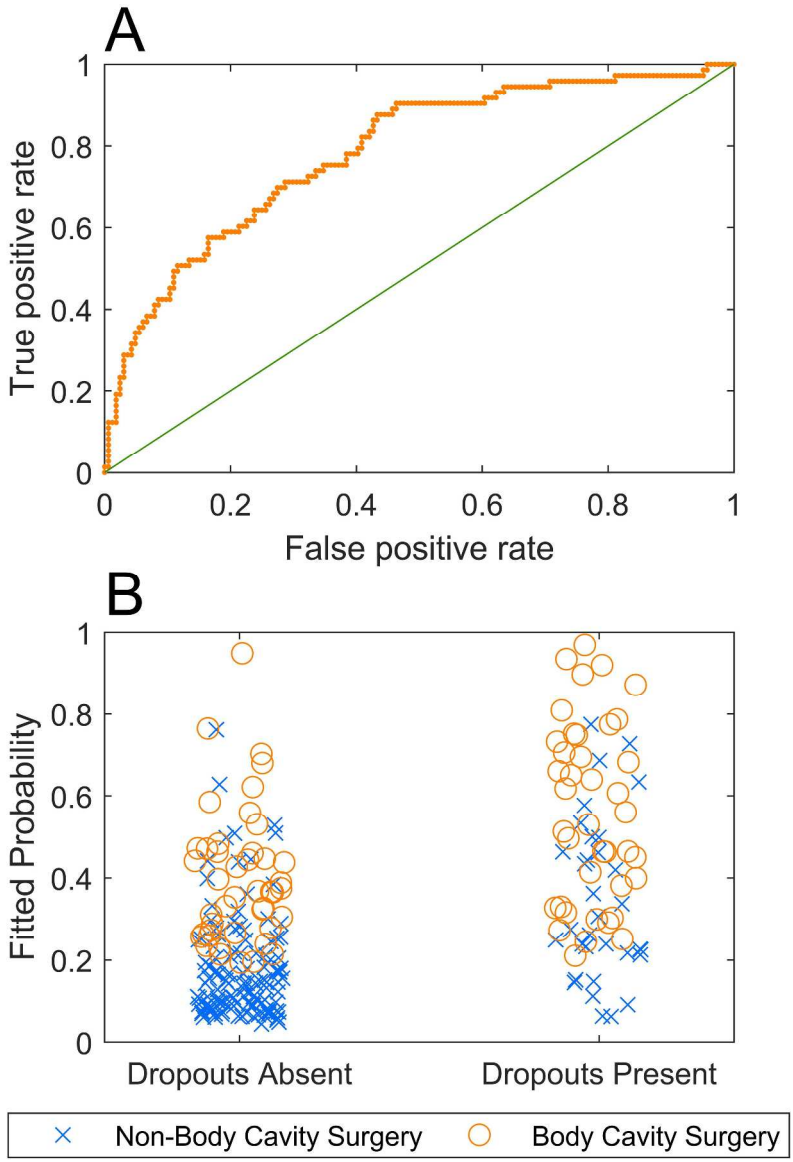


Figure 4

1187x1750mm (72 x 72 DPI)