Supplementary materials

Table S1. The capture dates of the individual seals included in the experimental trials.

Seal ID	Date
L'Hollie	06/07/18
Marvin	06/07/18
Gruber	05/09/18
Haans	05/09/18
Jones	05/10/18

Table S2. Mass (kg), girth (cm), and length (cm) of individual seals on the dates of the experimental procedures. Not all measurements were obtained on all dates of experimentation.

Seal ID	Date	Mass (kg)	Girth (cm)	Length (cm)
Marvin	13/11/18*	73.2	n/a	n/a
Marvin	14/11/18	n/a	n/a	n/a
L'Hollie	14/11/18	55.0	n/a	n/a
Haans	08/11/18*	73.6	n/a	146
Haans	15/11/18	75.6	n/a	n/a
Gruber	08/11/18*	54.4	n/a	n/a
Jones	08/11/18*	65.6	n/a	n/a
Gruber	16/11/18	n/a	n/a	n/a
Jones	16/11/18	n/a	n/a	n/a
Marvin	20/11/18	73.4	n/a	n/a
Haans	21/11/18	n/a	n/a	n/a
L'Hollie	21/11/18	n/a	n/a	n/a
Gruber	22/11/18	n/a	n/a	n/a
Jones	22/11/18	n/a	n/a	n/a
Marvin	27/11/18	76.6	110	133
L'Hollie	27/11/18	57.8	91	121
L'Hollie	06/12/18	60.6	102	122
Gruber	06/12/18	60.0	103	134
Jones	06/12/18	68.2	106	132
Marvin	06/12/18	80.0	113	131

*No data were obtained from these dates but morphometric measurements were included in this table as they were taken close to some dates of experimentation when morphometric measurements were not obtained.

Table S3. The number of drugging trials for each individual seal that were used in analysis for the effects of ketamine and midazolam.

Seal ID	Number of drugging trials
Ketamine	
Marvin	9
L'Hollie	3
Gruber	5
Haans	3
Jones	7
Midazolam	
Marvin	1
L'Hollie	2
Gruber	6
Jones	2

Example model selection code

The model selection process for modelling the response in change in concentration of deoxygenated haemoglobin (ΔHHb) (μ mol. L^{-1}) to ketamine administration. Coding was carried out using RStudio (Version 1.2.1335). The "gamm" function of the "mgcv" package (Version 1.8-31) was used to construct GAMMs. Plotting was completed using the "ggplot" function of the "ggplot2" package (Version 3.3.2).

```
# Load required packages
require(mgcv) # required for the gamm() function
require(ggplot2) # required for plotting

setwd() # set the working directory
ket1 <- read.csv("updated_ket.csv") # retrieve relevant data table

# Select every fifth row
ket <- ket1[seq(1,nrow(ket1),5),]

# Make another HHb column (HHb: change in concentration of deoxygenated haemoglobin) with transformed positive values
min(ket$HHb) # -7.19
ket$tHHb<-ket$HHb+10

################### 1. FAMILY SELECTION  €€€€€€€€€€€€€€€€€€€€

# Gaussian log Link
ket1 = gamm(tHHb ~ s(Time, k=4) +
          s(Time.since.initial.s, k=4) +
          s(K.bolus.vol.ml, k=4) +
          s(Total.bolus.vol.ml, k=4) +
          s(Resp_zero, k=4) +
          as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))
par(mfrow=c(2,2))
gam.check(ket1$gam) # visualise diagnostic plots

# Gaussian
ket1.1 = gamm(HHb ~ s(Time, k=4) +
```

```
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML', family=gaussian)
par(mfrow=c(2,2))
gam.check(ket1.1$gam)

# Gamma
ket1.2 = gamm(tHHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML', family=Gamma)
par(mfrow=c(2,2))
gam.check(ket1.2$gam)

# Gamma log Link
ket1.3 = gamm(tHHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=Gamma(link=log))
par(mfrow=c(2,2))
gam.check(ket1.3$gam)

# Tweedie
ket1.4 = gamm(tHHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML', family=Tweedie)
par(mfrow=c(2,2))
gam.check(ket1.4$gam)

# Poisson
ket1.5 = gamm(tHHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML', family=poisson)
par(mfrow=c(2,2))
gam.check(ket1.5$gam)

# Quasipoisson
ket1.6 = gamm(tHHb ~ s(Time, k=4) +
```

```
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML', family=quasipoisson)
par(mfrow=c(2,2))
gam.check(ket1.6$gam)

# Gaussian Identity link
ket1.7 = gamm(HHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=identity))
par(mfrow=c(2,2))
gam.check(ket1.7$gam)

# Gaussian(link=log) was the chosen family based on the diagnostic plots

###################### 2. MODEL SELECTION €€€€€€€€€€€€€€€€€€€€

# Full model
ket1 = gamm(HHb ~ s(Time, k=4) +
          s(Time.since.initial.s, k=4) +
          s(K.bolus.vol.ml, k=4) +
          s(Total.bolus.vol.ml, k=4) +
          s(Resp_zero, k=4) +
          as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))
par(mfrow=c(2,2))
gam.check(ket1$gam)
par(mfrow=c(1,1))
plot(ket1$gam)
summary(ket1$gam)
summary(ket1$lme)

# Second model - remove Time Series
ket2 = gamm(HHb ~ s(Time.since.initial.s, k=4) +
          s(K.bolus.vol.ml, k=4) +
          s(Total.bolus.vol.ml, k=4) +
          s(Resp_zero, k=4) +
          as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))
par(mfrow=c(2,2))
gam.check(ket2$gam)
par(mfrow=c(1,1))
plot(ket2$gam)
summary(ket2$gam)
summary(ket2$lme)
```

```
# Third model - remove Time since initial drugging
ket3 = gamm(HHb ~ s(Time, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))
par(mfrow=c(2,2))
gam.check(ket3$gam)
par(mfrow=c(1,1))
plot(ket3$gam)
summary(ket3$gam)
summary(ket3$lme)

# Fourth Model - Remove ketamine bolus volume
ket4 = gamm(HHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))
par(mfrow=c(2,2))
gam.check(ket4$gam)
par(mfrow=c(1,1))
plot(ket4$gam)
summary(ket4$gam)
summary(ket4$lme)

# Fifth Model - Remove total drug bolus volume
ket5 = gamm(HHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))
par(mfrow=c(2,2))
gam.check(ket5$gam)
par(mfrow=c(1,1))
plot(ket5$gam)
summary(ket5$gam)
summary(ket5$lme)

# Sixth model - Remove respiratory band
ket6 = gamm(HHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))
par(mfrow=c(2,2))
```

```
gam.check(ket6$gam)
par(mfrow=c(1,1))
plot(ket6$gam)
summary(ket6$gam)
summary(ket6$lme)

# Seventh model - remove left & right factor variable
ket7 = gamm(HHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            s(Resp_zero, k=4), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))
par(mfrow=c(2,2))
gam.check(ket7$gam)
par(mfrow=c(1,1))
plot(ket7$gam)
summary(ket7$gam)
summary(ket7$lme)

# Record the AIC and DF for each model

#################### 3. MODEL PREDICTION  €€€€€€€€€€€€€€€€€€€€

# The model without the respiratory band had the lowest AIC
ket1 = gamm(tHHb ~ s(Time, k=4) +
            s(Time.since.initial.s, k=4) +
            s(K.bolus.vol.ml, k=4) +
            s(Total.bolus.vol.ml, k=4) +
            as.factor(Side), data=ket, random=list(Animal=~1), method='REML',
family=gaussian(link=log))

# Check the median value for each covariate
summary(ket$Time.since.initial.s) #1730
summary(ket$K.bolus.vol.ml) #1.90
summary(ket$Total.bolus.vol.ml) #6.200

# Create prediction data frame
Time <- seq(-60,179.9,0.1)
Time.since.initial.s <-seq(1730,1730,1)
K.bolus.vol.ml <-seq(1.9,1.9,1)
Total.bolus.vol.ml <-seq(6.2,6.2,1)
Side <- c("L","R")

newdata <- expand.grid(Time=Time, Time.since.initial.s=Time.since.initial.s,
K.bolus.vol.ml=K.bolus.vol.ml, Total.bolus.vol.ml=Total.bolus.vol.ml,Side=Side)

newdata$y <- as.numeric(predict.gam(ket1$gam,newdata,type="response",
                                    se.fit=TRUE)[[1]])
newdata$SE <- as.numeric(predict.gam(ket1$gam,newdata,type="response",
                                     se.fit=TRUE)[[2]])
```

```
newdata$y <- newdata$y-10 # Subtract 10 to transform data back

# Baseline shift: Move model predictions to 0mmolL-1 at 0s to show relative changes from time of
administration
newdata1 <- newdata[which(newdata$Side=="R" & newdata$Time==0),]
newdata2 <- newdata[which(newdata$Side=="L" & newdata$Time==0),]
Conc1 <- as.numeric(newdata1$y)
Conc2 <- as.numeric(newdata2$y)
offset <- min(c(Conc1,Conc2))+(abs(Conc2-Conc1)/2)
newdata$y <- newdata$y-offset # Move plot down so the middle point of the two hemispheres at 0s is
at 0 mmolL-1

newdata$lCI <- newdata$y-(1.96*newdata$SE) # convert standard error to 95% confidence intervals
newdata$uCI <- newdata$y+(1.96*newdata$SE)

names(newdata) # rename newdata column headings
colnames(newdata) <- c("Time","Time.since.initial.s","K.bolus.vol.ml","Total.bolus.vol.ml", "Side",
"Conc","SE","lCI","uCI")

# Plot prediction dataset
Plot <-ggplot(newdata, aes(Time, Conc,group=Side)) +
 theme(panel.grid.major = element_blank(), panel.grid.minor = element_blank(),
       panel.background = element_blank(), axis.line = element_line(colour = "black"),axis.text =
element_text(size=15),
       legend.title = element_text(size = 15),
       legend.text = element_text(size = 12),
       legend.key.size = unit(0.5, "cm"),
       legend.key.width = unit(0.5,"cm"),
       plot.title = element_text(size = 20,hjust=0.5)) +
 ylab( expression(paste(Delta ,"concentration " ( mu ~ "mol."~L^-1)))) +
 xlab(bquote('Seconds'))  +
 ggtitle("HHb response to IV ketamine") +
 scale_x_continuous(breaks=c(-60,0,60,120,180))+
 scale_fill_manual(values = c("blue","green"), labels=c( "Left", "Right")) +
 scale_color_manual(values = c("blue","green"), labels=c( "Left", "Right"))+
 theme(axis.title = element_text(family = "Trebuchet MS", color="black", face="bold", size=12))+
 geom_ribbon(aes(ymin=Conc-SE, ymax=Conc+SE, x=Time,fill=Side), alpha=0.4,color=NA)+
 geom_line(aes(Time,Conc,colour=Side), size=0.5)+
 geom_hline(yintercept=0)+
 geom_vline(xintercept = 0)

Plot # see plot
```

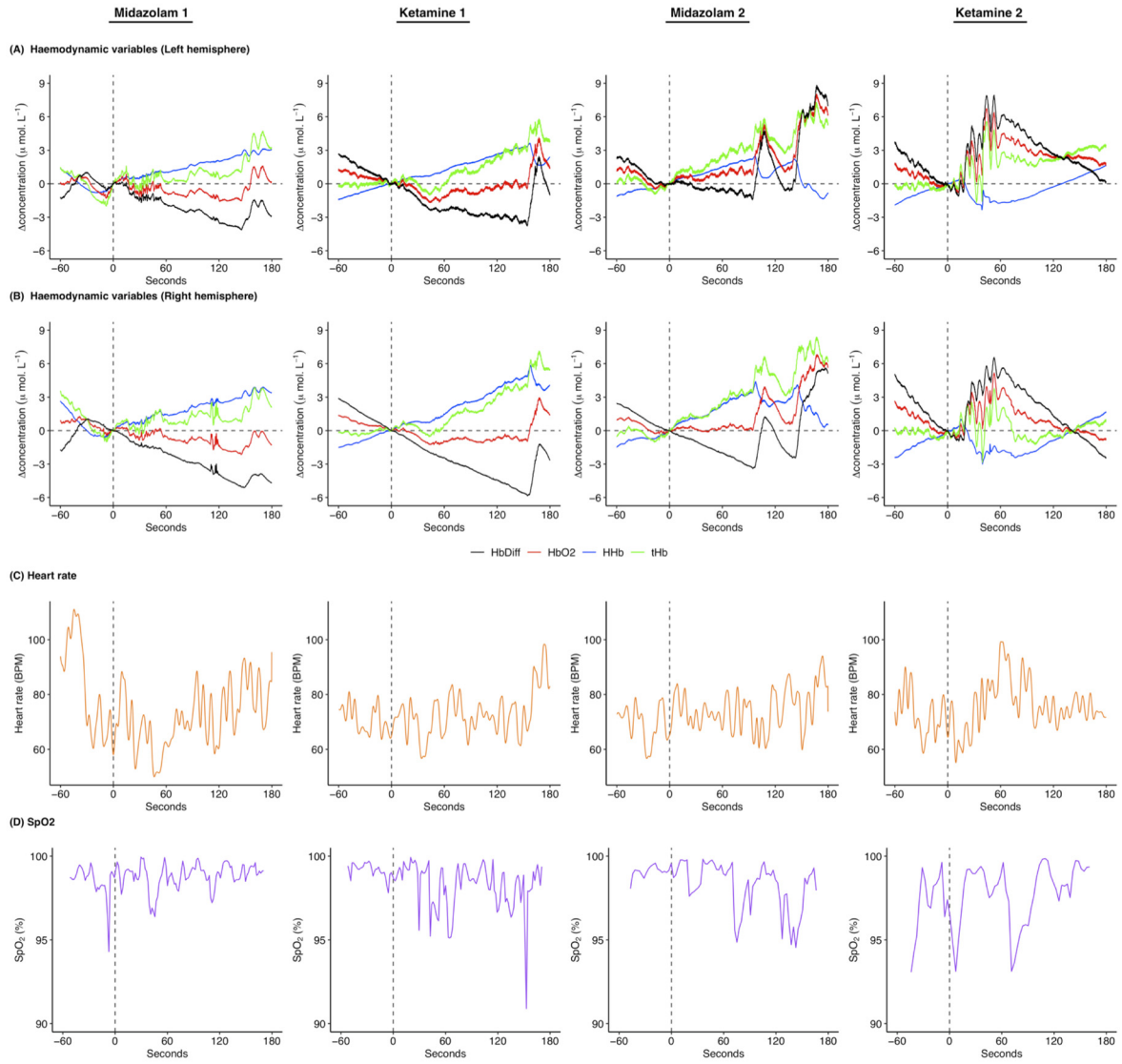

Figure S1. Example of cerebral haemodynamics and global systemic changes for a series of ketamine and midazolam druggings administered in succession. Within each drugging trial, the respective drug was administered at time 0s and data are presented for 60s before and 180s after drug administration. Cerebral haemodynamics include [ΔHHb] (μ mol L^{-1}), [ΔO_2Hb] (μ mol L^{-1}), relative cerebral blood volume changes [ΔtHb] (μ mol L^{-1}), and relative haemoglobin oxygenation changes [ΔHb_{diff}] (μ mol L^{-1}) in the (A) left and (B) right hemispheres of the brain. Systemic changes include (C) heart rate (BPM) and (D) SpO_2 (%). All concentrations are expressed as relative changes from a baseline (0 μ mol L^{-1}) at time of drug administration. The drugging trials were taken from Gruber on 06 December 2018 and were preceded by an initial intramuscular dose of midazolam, one intravenous dose of midazolam, and three intravenous ketamine doses. Midazolam 1 was administered 49s after the preceding ketamine dose. Ketamine 1 was administered 561s after Midazolam 1. Midazolam 2 was administered 60s after Ketamine 1 and Ketamine 2 was administered 580s after Midazolam 2.

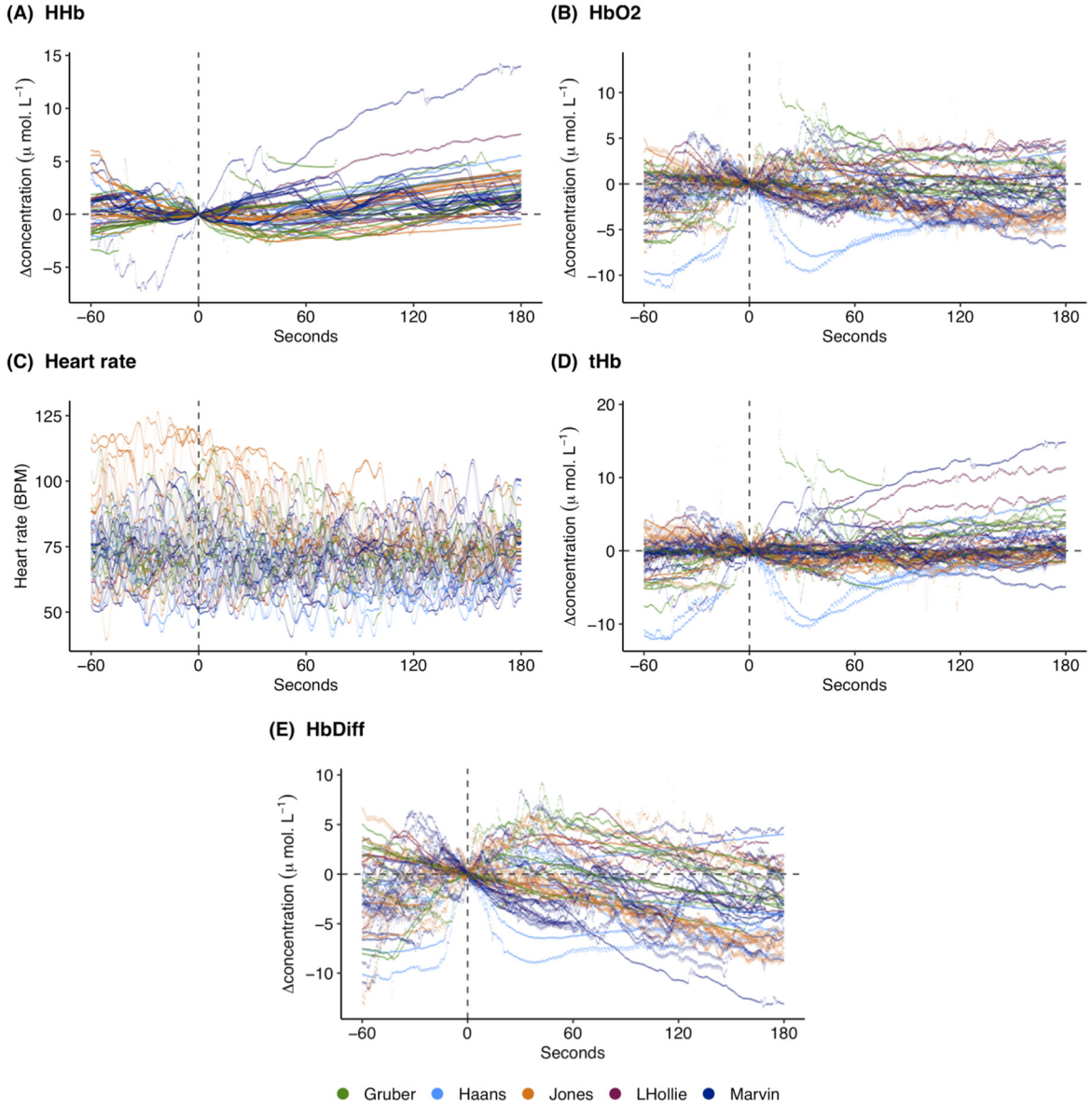

Figure S2. Cerebral haemodynamics of (A) [ΔHHb] (μ mol L^{-1}) and (B) [ΔO$_2$Hb] (μ mol L^{-1}), (C) heart rate (BPM), (D) relative cerebral blood volume changes [ΔtHb] (μ mol L^{-1}), and (E) relative haemoglobin oxygenation changes [ΔHb$_{diff}$] (μ mol L^{-1}) for 60s before and 180s after ketamine administration at time 0s for *n*=27 trials across five grey seals. All concentrations are expressed as relative changes from a baseline (0 μ mol L^{-1}) at time of drug administration. Haemodynamic changes and heart rate represent the full datasets and are shown as a combination of one channel in the left hemisphere and one channel in the right hemisphere for each trial (*n*=54 trials across five seals). Individual seals are distinguished by colour. [ΔHHb], change in concentration of deoxygenated haemoglobin; [ΔO$_2$Hb], change in concentration of oxygenated haemoglobin; [ΔtHb], change in concentration of total haemoglobin; [ΔHb$_{diff}$], difference in concentration of oxygenated and deoxygenated haemoglobin.

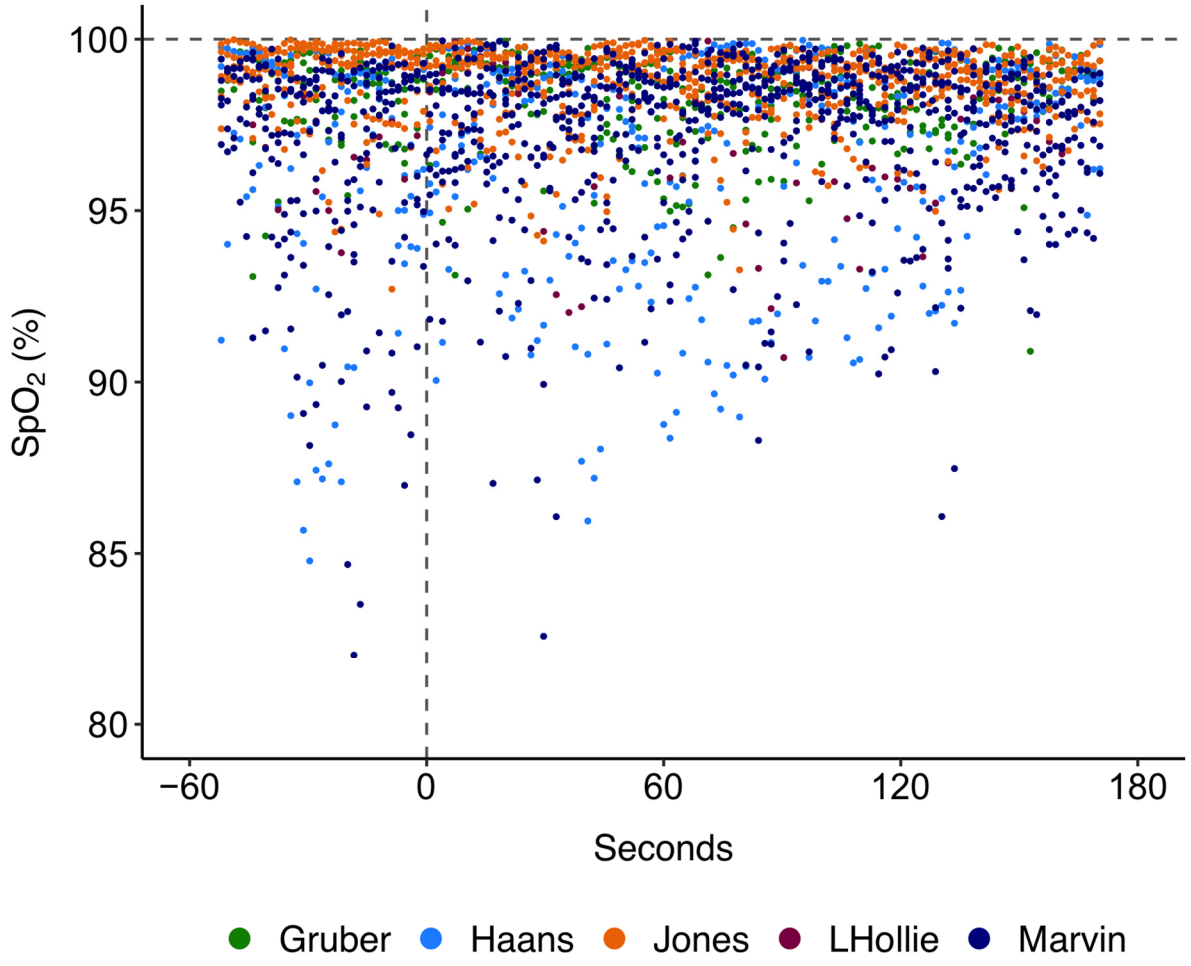

Figure S3. The SpO_2 (%) for 60s before and 180s after ketamine administration at time 0s for *n*=23 trials across five grey seals. Individual seals are distinguished by colour. SpO_2, arterial oxygen saturation.

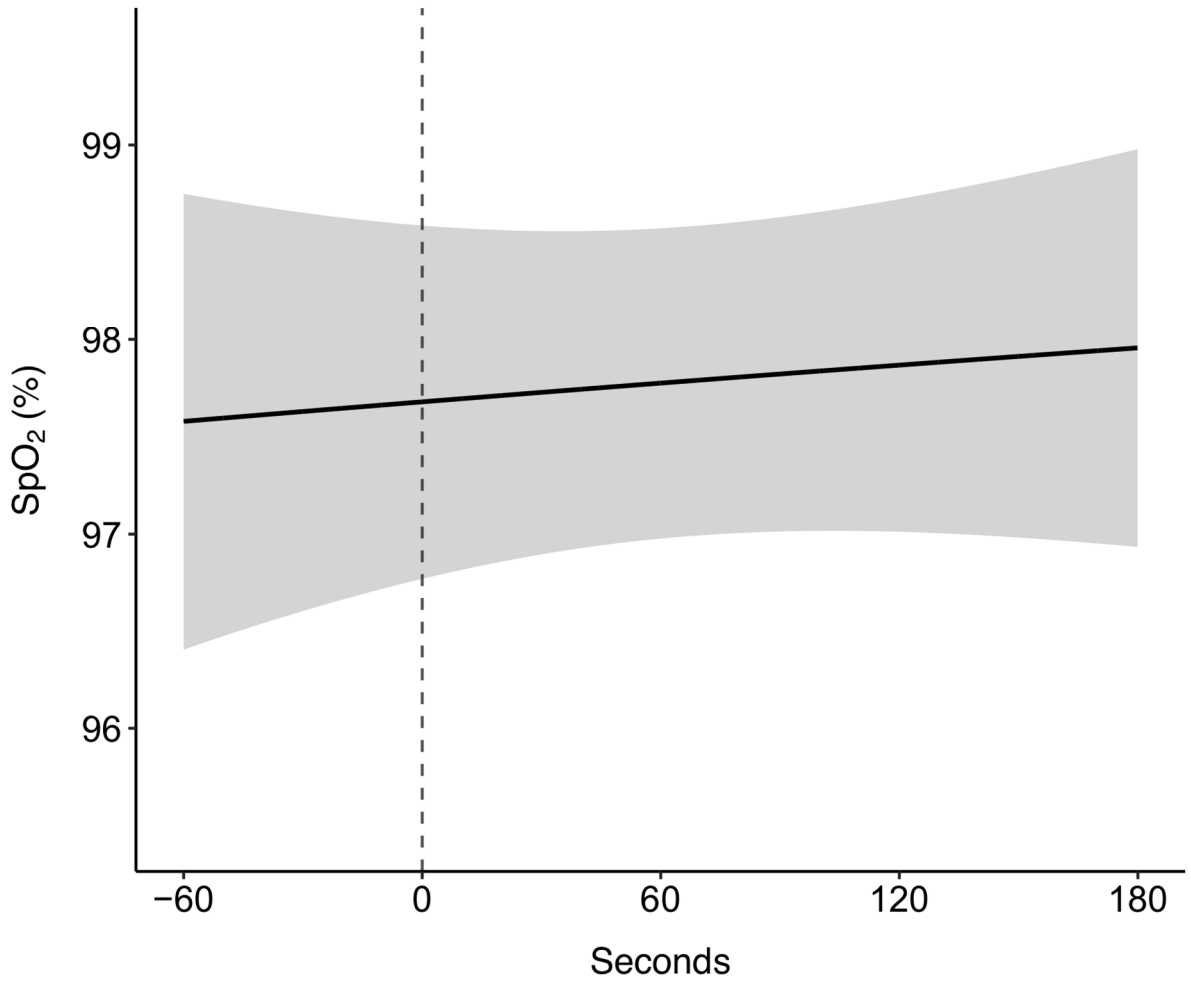

Figure S4. GAMM model prediction outcomes for SpO_2 (%) 60s before and 180s after ketamine administration at time 0s for *n*=23 trials across five grey seals. Changes in SpO_2 are systemic, meaning the presented model prediction outcomes for SpO_2 are the same for the left and right hemispheres. The shaded regions represent the 95% confidence intervals. GAMM, generalised additive mixed model; SpO_2, arterial oxygen saturation.

Table S4. GAMM equations for [ΔHHb] (μ mol L^{-1}), [ΔO_2Hb] (μ mol L^{-1}), heart rate (BPM), and SpO_2 (proportion of [ΔO_2Hb] to [tHb]) for 60s before and 180s after ketamine administration at time 0s for *n* number of trials across five grey seals. The Akaike Information Criterion (AIC) is presented for full model equations and ΔAIC (Full model AIC – Chosen model AIC) is additionally presented for models in which some covariates of the full model were not retained. Degrees of freedom (DF), adjusted R^2, the number of drugging trials (*n*), and the number of observations are presented for all models. For model outputs see Tables S5-S8. GAMM, generalised additive mixed model; [ΔHHb], change in concentration of deoxygenated haemoglobin; [ΔO_2Hb], change in concentration of oxygenated haemoglobin; SpO_2, arterial oxygen saturation.

<table>
<tr><td rowspan="3">1</td><td colspan="6">gamm([ΔHHb] ~ s(Time (-60 to 180s), k=4) + s(Time since initial drugging (s), k=4) + s(Ketamine bolus volume (ml), k=4) + s(Total bolus volume (ml), k=4) + as.factor(Side), random=list(Animal ID=~1), method='REML', family=gaussian (link=log), data=ketamine)</td></tr>
<tr><td>AIC</td><td>ΔAIC</td><td>DF</td><td>R^2</td><td>Number of trials (n)</td><td>Number of observations</td></tr>
<tr><td>-24335</td><td>1.090</td><td>24940</td><td>0.047</td><td>27</td><td>24950</td></tr>
<tr><td rowspan="3">2</td><td colspan="6">gamm([ΔO_2Hb] ~ s(Time (-60 to 180s), k=4) + s(Time since initial drugging (s), k=4) + s(Ketamine bolus volume (ml), k=4) + s(Total bolus volume (ml), k=4) + s(Respiratory band, k=4) + as.factor(Side), random=list(Animal ID=~1), method='REML', family=gaussian (link=identity), data=ketamine)</td></tr>
<tr><td colspan="2">AIC</td><td>DF</td><td>R^2</td><td>Number of trials (n)</td><td>Number of observations</td></tr>
<tr><td colspan="2">109319</td><td>24939</td><td>0.135</td><td>27</td><td>24950</td></tr>
<tr><td rowspan="3">3</td><td colspan="6">gamm(Heart rate ~ s(Time (-60 to 180s), k=4) + s(Time since initial drugging (s), k=4) + s(Ketamine bolus volume (ml), k=4) + s(Total bolus volume (ml), k=4) + s(Respiratory band, k=4), random=list(Animal ID=~1), method='REML', family=gaussian (link=log), data=ketamine)</td></tr>
<tr><td colspan="2">AIC</td><td>DF</td><td>R^2</td><td>Number of trials (n)</td><td>Number of observations</td></tr>
<tr><td colspan="2">-20640</td><td>24940</td><td>0.053</td><td>27</td><td>24950</td></tr>
<tr><td rowspan="3">4</td><td colspan="6">gamm(SpO_2 (proportion) ~ s(Time (-60 to 180s), k=4) + s(Ketamine bolus volume (ml), k=4) + s(Total bolus volume (ml), k=4), random=list(AnimalID=~1), method='REML', family=binomial, data=ketamine)</td></tr>
<tr><td>AIC</td><td>ΔAIC</td><td>DF</td><td>R^2</td><td>Number of trials (n)</td><td>Number of observations</td></tr>
<tr><td>29772</td><td>155.0</td><td>5202</td><td>0.016</td><td>23</td><td>5210</td></tr>
</table>

Table S5. The estimates and standard error for coefficients of a GAMM of the response in [ΔHHb] (μ mol L^{-1}) to ketamine administration (*n*=27) across five grey seals (Equation (1), Table S4). Edf is presented for smooth terms of the model. [ΔHHb], change in concentration of deoxygenated haemoglobin; GAMM, generalised additive mixed model.

Coefficient	Estimate	Standard Error	edf
Left hemisphere factor variable (Intercept)	2.401	0.043	n/a
Right hemisphere factor variable	-0.011	0.002	n/a
Time (s)	-0.006	0.004	2.995
Time since initial drugging (s)	-0.014	0.005	2.996
Ketamine bolus volume (ml)	0.104	0.006	2.967
Total bolus volume (ml)	-0.089	0.007	2.980

Table S6. The estimates and standard error for coefficients of a GAMM of the response in [ΔO_2Hb] (μ mol L^{-1}) to ketamine administration (*n*=27) across five grey seals (Equation (2), Table S4). Edf is presented for smooth terms of the model. [ΔO_2Hb], change in concentration of oxygenated haemoglobin; GAMM, generalised additive mixed model.

Coefficient	Estimate	Standard Error	edf
Left hemisphere factor variable (Intercept)	-0.704	0.527	n/a
Right hemisphere factor variable	-0.176	0.027	n/a
Time (s)	1.060	0.064	2.994
Time since initial drugging (s)	-1.341	0.070	2.995
Ketamine bolus volume (ml)	-1.060	0.087	2.827
Total bolus volume (ml)	-0.231	0.093	2.995
Respiratory band	-0.486	0.052	2.988

Table S7. The estimates and standard error for coefficients of a GAMM of the response in heart rate (BPM) to ketamine administration (*n*=27) across five grey seals (Equation (3), Table S4). Edf is presented for smooth terms of the model. GAMM, generalised additive mixed model.

Coefficient	Estimate	Standard Error	edf
Intercept	4.295	0.043	n/a
Time (s)	0.026	0.005	2.980
Time since initial drugging (s)	-0.039	0.005	2.990
Ketamine bolus volume (ml)	0.112	0.005	2.369
Total bolus volume (ml)	-0.036	0.007	2.984
Respiratory band	-0.033	0.003	2.991

Table S8. The estimates and standard error for coefficients of a GAMM of the response in SpO_2 (proportion of [ΔO_2Hb] to [tHb]) to ketamine administration (*n*=23) across five grey seals (Equation (4), Table S4). Edf is presented for smooth terms of the model. GAMM, generalised additive mixed model; SpO_2, arterial oxygen saturation.

Coefficient	Estimate	Standard Error	edf
Intercept	3.767	0.180	n/a
Time (s)	0.046	0.093	1.000
Ketamine bolus volume (ml)	-0.141	0.138	1.000
Total bolus volume (ml)	0.085	0.173	1.000

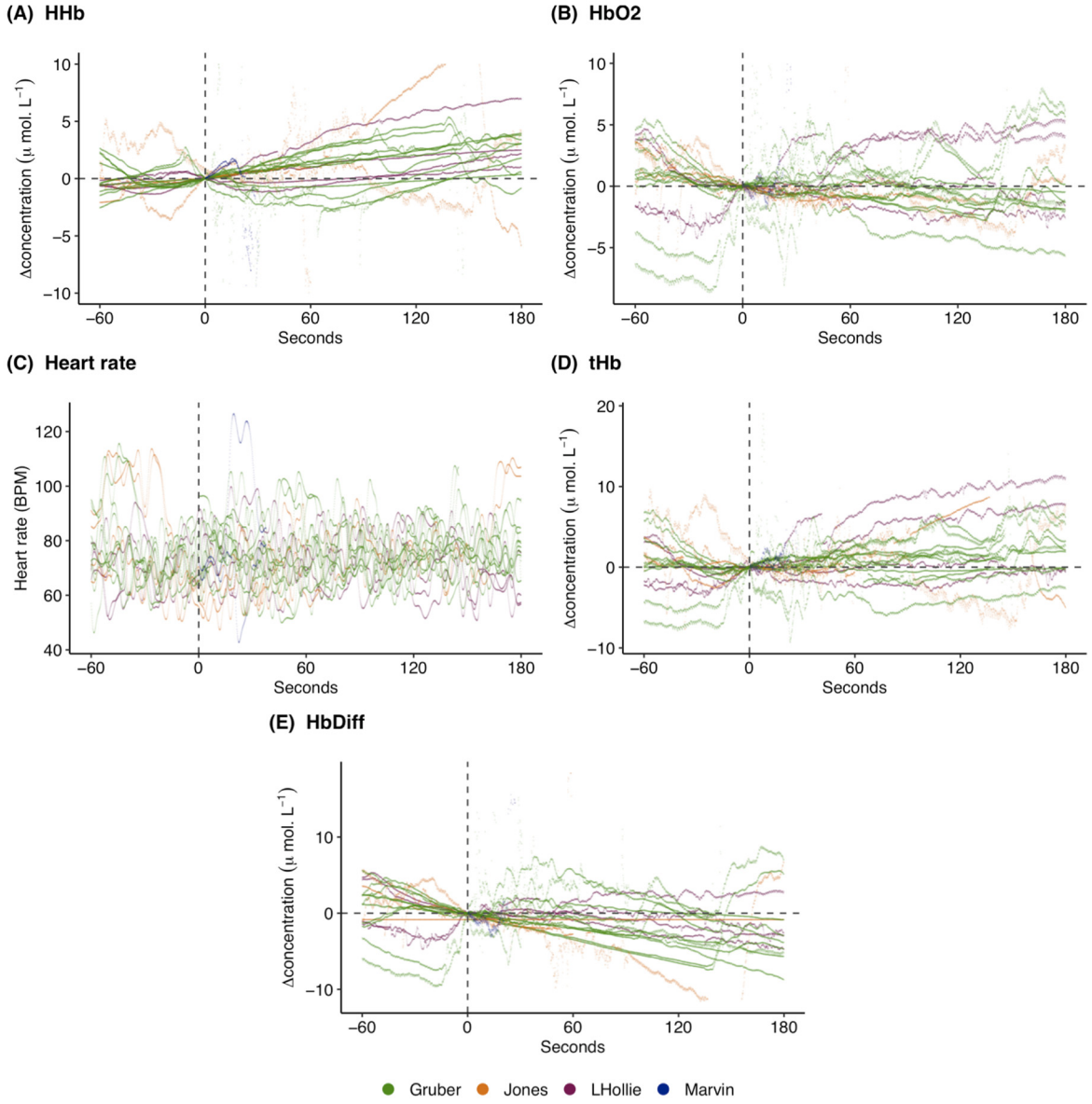

Figure S5. Cerebral haemodynamics of (A) [ΔHHb] (μ mol L^{-1}) and (B) [ΔO_2Hb] (μ mol L^{-1}), (C) heart rate (BPM), (D) relative cerebral blood volume changes [ΔtHb] (μ mol L^{-1}), and (E) relative haemoglobin oxygenation changes [ΔHb_{diff}] (μ mol L^{-1}) for 60s before and 180s after midazolam administration at time 0s for *n*=11 trials across four grey seals. All concentrations are expressed as relative changes from a baseline (0 μ mol L^{-1}) at time of drug administration. Haemodynamic changes and heart rate represent the full datasets and are shown as a combination of one channel in the left hemisphere and one channel in the right hemisphere for each trial (*n*=22 trials across four seals). Individual seals are distinguished by colour. [ΔHHb], change in concentration of deoxygenated haemoglobin; [ΔO_2Hb], change in concentration of oxygenated haemoglobin; [ΔtHb], change in concentration of total haemoglobin; [ΔHb_{diff}], difference in concentration of oxygenated and deoxygenated haemoglobin.

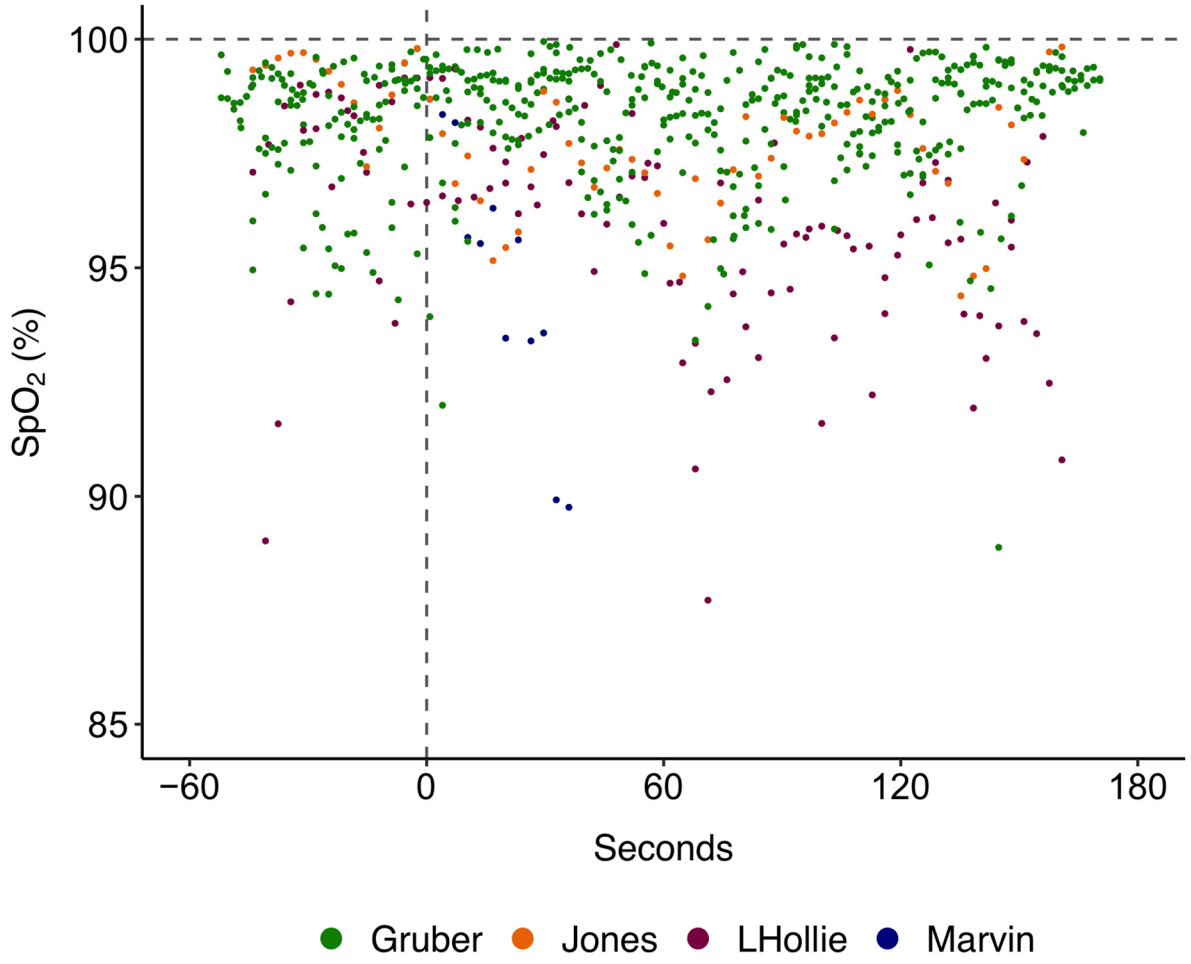

Figure S6. The SpO_2 (%) for 60s before and 180s after midazolam administration at time 0s for *n*=9 trials across four seals. Individual seals are distinguished by colour. SpO_2, arterial oxygen saturation.

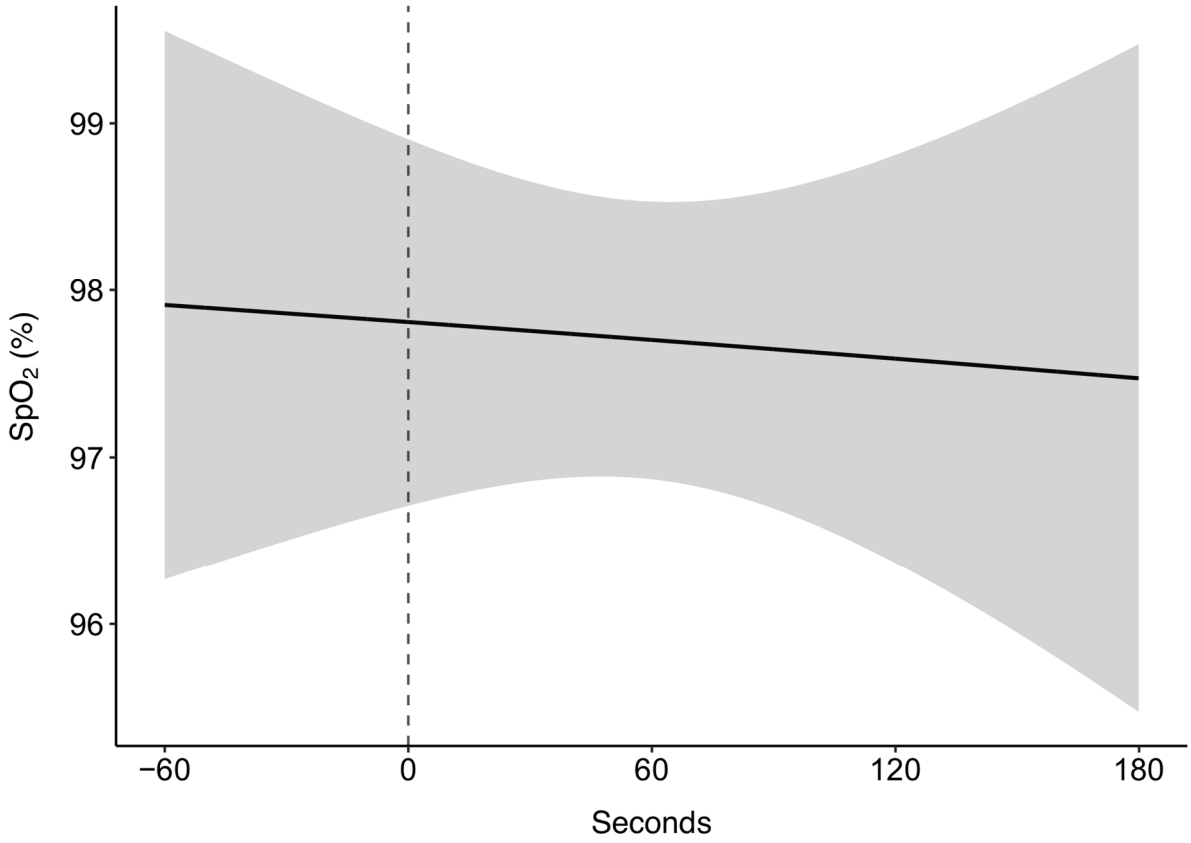

Figure S7. GAMM model prediction outcomes for SpO_2 (%) 60s before and 180s after midazolam administration at time 0s for *n*=9 trials across four grey seals. Changes in SpO_2 are systemic, meaning the presented model prediction outcomes for SpO_2 are the same for the left and right hemispheres. The shaded regions represent the 95% confidence intervals. GAMM, generalised additive mixed model; SpO_2, arterial oxygen saturation.

Table S9. GAMM equations for [HHb] (μ mol L^{-1}), [ΔO_2Hb] (μ mol L^{-1}), heart rate (BPM), and SpO_2 (proportion of [ΔO_2Hb] to [tHb]) for 60s before and 180s after midazolam administration at time 0s for *n* number of trials across four grey seals. The Akaike Information Criterion (AIC) is presented for full model equations and ΔAIC (Full model AIC – Chosen model AIC) is additionally presented for models in which some covariates of the full model were not retained. Degrees of freedom (DF), R^2, the number of drugging trials (*n*), and the number of observations are presented for all models. For model outputs see Tables S10-S13. GAMM, generalised additive mixed model; [HHb], change in concentration of deoxygenated haemoglobin; [ΔO_2Hb], change in concentration of oxygenated haemoglobin; SpO_2, arterial oxygen saturation.

1	gamm([ΔHHb] ~ s(Time (-60 to 180s), k=4) + s(Total bolus volume (ml), k=4) + s(Respiratory band, k=4) + as.factor(Midazolam bolus volume (ml)) + as.factor(Side), random=list(Animal ID=~1), method='REML', family=gaussian (link=log), data=midazolam)					
	AIC	**ΔAIC**	**DF**	**R^2**	**Number of trials (*n*)**	**Number of observations**
	-8382	1.489	8476	0.259	11	8488
2	gamm([ΔO_2Hb] ~ s(Time (-60 to 180s), k=4) + s(Total bolus volume (ml), k=4) + s(Respiratory band, k=4) + as.factor(Midazolam bolus volume (ml)) + as.factor(Side), random=list(Animal ID=~1), method='REML', family=gaussian, data=midazolam)					
	AIC	**ΔAIC**	**DF**	**R^2**	**Number of trials (*n*)**	**Number of observations**
	36680	0.490	8759	0.166	11	8771
3	gamm(Heart rate ~ s(Time (-60 to 180s), k=4) + s(Time since initial drugging (s), k=4) + s(Total bolus volume (ml), k=4) + s(Respiratory band, k=4) + as.factor(Midazolam bolus volume (ml), k=4), random=list(Animal ID=~1), method='REML', family=gaussian (link=log), data=midazolam)					
	AIC		**DF**	**R^2**	**Number of trials (*n*)**	**Number of observations**
	-9275		8879	-2.060	11	8891
4	gamm(SpO_2 (proportion) ~ s(Time (-60 to 180s), k=4) + s(Time since initial drugging (s), k=4) + s(Total bolus volume (ml), k=4), random=list(Animal=~1), method='REML', family=binomial, data=midazolam)					
	AIC	**ΔAIC**	**DF**	**R^2**	**Number of trials (*n*)**	**Number of observations**
	7810	52.78	1353	0.15	9	1360

Table S10. The estimates and standard error for coefficients of a GAMM of the response in [ΔHHb] (μ mol L^{-1}) to midazolam administration (*n*=11) across four grey seals (Equation (1), Table S9). Edf is presented for smooth terms of the model. [ΔHHb], change in concentration of deoxygenated haemoglobin; GAMM, generalised additive mixed model.

Coefficient	Estimate	Standard Error	edf
5ml midazolam bolus volume/Left hemisphere factor variables (Intercept)	2.657	0.110	n/a
6ml midazolam bolus volume factor variable	-0.372	0.032	n/a
7ml midazolam bolus volume factor variable	-0.382	0.030	n/a
8ml midazolam bolus volume factor variable	-0.487	0.036	n/a
9ml midazolam bolus volume factor variable	-0.929	0.126	n/a
Right hemisphere factor variable	-0.008	0.003	n/a
Time (s)	0.005	0.007	2.981
Total bolus volume (ml)	0.798	0.092	2.971
Respiratory band	0.002	0.005	2.424

Table S11. The estimates and standard error for coefficients of a GAMM of the response in [ΔO$_2$Hb] (μ mol L^{-1}) to midazolam administration (*n*=11) across four grey seals (Equation (2), Table S9). Edf is presented for smooth terms of the model. [ΔO$_2$Hb], change in concentration of oxygenated haemoglobin; GAMM, generalised additive mixed model.

Coefficient	Estimate	Standard Error	edf
5ml midazolam bolus volume/Left hemisphere factor variables (Intercept)	0.452	1.733	n/a
6ml midazolam bolus volume factor variable	-5.512	0.390	n/a
7ml midazolam bolus volume factor variable	-1.214	0.402	n/a
8ml midazolam bolus volume factor variable	3.733	0.469	n/a
9ml midazolam bolus volume factor variable	1.586	1.523	n/a
Right hemisphere factor variable	0.261	0.042	n/a
Time (s)	-0.018	0.083	2.657
Total bolus volume (ml)	5.240	1.128	2.975
Respiratory band	-0.379	0.067	2.976

Table S12. The estimates and standard error for coefficients of a GAMM of the response in heart rate (BPM) to midazolam administration (*n*=11) across four grey seals (Equation (3), Table S9). Edf is presented for smooth terms of the model. GAMM, generalised additive mixed model.

Coefficient	Estimate	Standard Error	edf
5ml midazolam bolus volume (Intercept)	2.281	0.283	n/a
6ml midazolam bolus volume factor variable	1.586	0.111	n/a
7ml midazolam bolus volume factor variable	2.943	0.247	n/a
8ml midazolam bolus volume factor variable	4.251	0.364	n/a
9ml midazolam bolus volume factor variable	5.438	0.417	n/a
Time (s)	-0.047	0.007	2.963
Time since initial drugging (s)	0.461	0.042	1.000
Total bolus volume (ml)	-1.913	0.122	1.984
Respiratory band	-0.023	0.005	2.972

Table S13. The estimates and standard error for coefficients of a GAMM of the response in SpO_2 (proportion of [ΔO_2Hb] to [tHb]) to midazolam administration (*n*=9) across four grey seals (Equation (4), Table S9). Edf is presented for smooth terms of the model. GAMM, generalised additive mixed model; SpO_2, arterial oxygen saturation.

Coefficient	Estimate	Standard Error	edf
Intercept	3.836	0.192	n/a
Time (s)	-0.050	0.188	1.000
Time since initial drugging (s)	-0.388	0.231	1.000
Total bolus volume (ml)	0.263	0.255	1.000

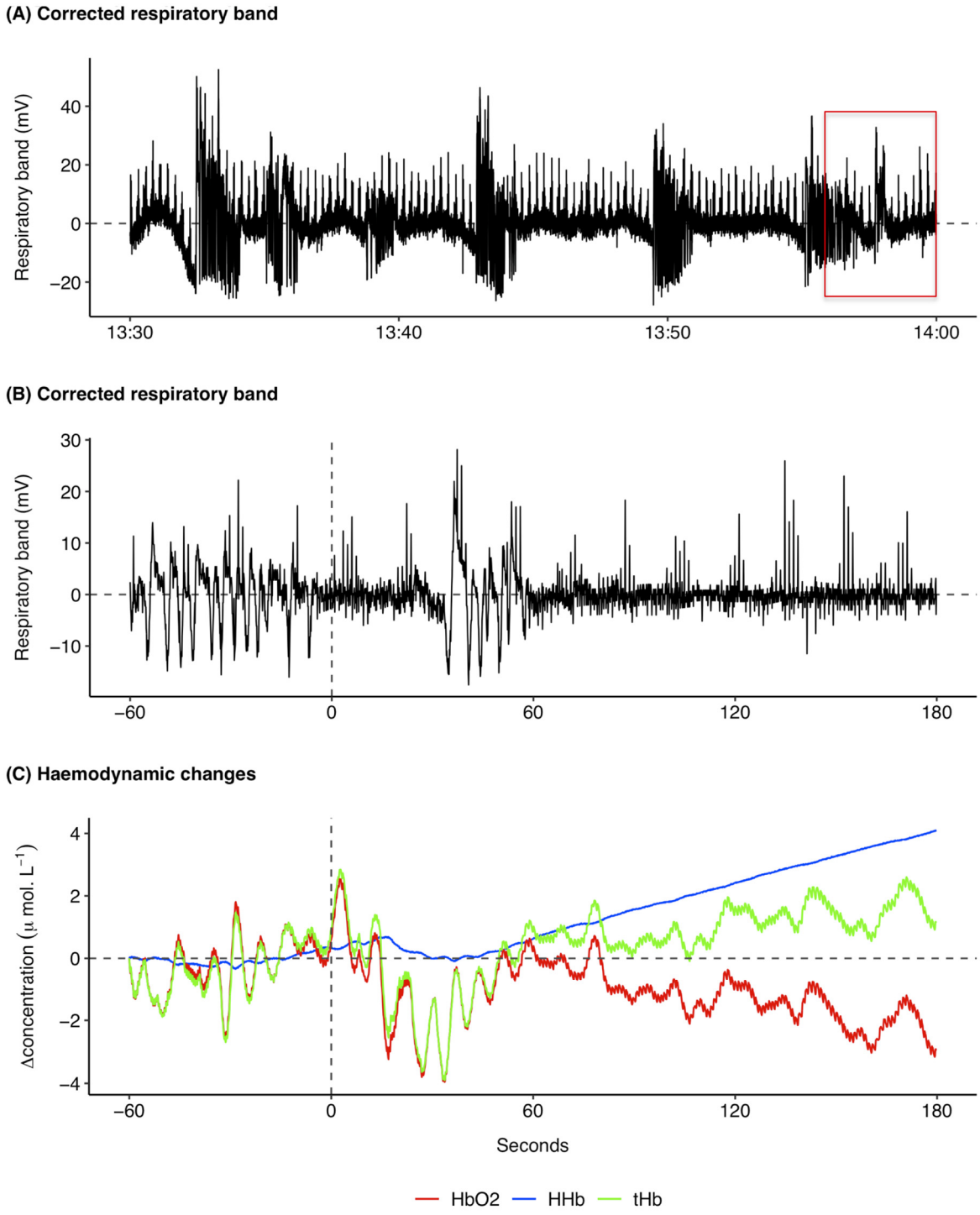

Figure S8. (A) The corrected respiratory band measurements (mV) for an experimental trial with multiple intravenous administrations of ketamine and midazolam and (B) the corrected respiratory band measurements (mV) and (C) haemodynamic measurements (μ mol L^{-1}) of a single ketamine drugging trial. These data were taken from Jones on 06 December 2018. The respiratory band data for the experimental trial (A) show several bouts of hyperventilation followed by prolonged periods of apnoea. The red outline indicates a specific ketamine drugging trial for which (B) the corrected respiratory band measurements (mV) and (C) haemodynamic measurements (μ mol L^{-1}) are presented. Ketamine administration occurred at 0s within the analysis window. The drugging trial contained two periods of hyperventilation between -60 and 60s, followed by apnoea for the remaining analysed time frame. [ΔHHb], change in concentration of deoxygenated haemoglobin; [ΔO_2Hb], change in concentration of oxygenated haemoglobin; [ΔtHb], change in concentration of total haemoglobin.