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Supplementary Information for
An EEG Biomarker of Fentanyl Drug Effects

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1 Derivation of an Expression to Estimate Instantaneous Minute Ventilation

Minute ventilation (Ψ) is defined as the maximum change in lung volume during a given respiratory cycle ΔV_{max} multiplied by the respiratory frequency ω:

$$\Psi = \Delta V_{max} \cdot \omega. \tag{1}$$

Here we derive expressions to estimate a time-varying index related to minute ventilation. To do so, we will obtain instantaneous, time-varying estimates of ΔV_{max} and ω in terms of the chest and abdominal RIP measurements $y_c(t)$ and $y_a(t)$, respectively.

1.1 An Approximate Expression for Changes in Lung Volume as a function of Chest or Abdomen Circumference

We represent lung volume as a cylinder with time dependent radius (r) and height (d):

$$V(t) = \pi r(t)^2 d(t). \tag{2}$$

Both the radius and height can be further characterized as the sum of a constant component and an oscillatory component represented by cosines,

$$r(t) = r_0 + \tilde{r}(t) \text{ where } \tilde{r}(t) = r_m \cos \omega t \ , \ \frac{r_m}{r_0} \ll 1 \tag{3}$$

$$d(t) = d_0 + \tilde{d}(t) \text{ where } \tilde{d}(t) = d_m \cos \omega t \ , \ \frac{d_m}{d_0} \ll 1 \tag{4}$$

where r_0, r_m, d_0, and d_m are real-valued.
We note that the maximal and minimal values of $r(t)$ and $d(t)$ are:

$$\max(r(t))) = r_0 + r_m, \ \min(r(t)) = r_0 - r_m \tag{5}$$

$$\max(d(t)) = d_0 + d_m, \ \min(d(t)) = d_0 - d_m. \tag{6}$$

1.2 Estimating V_{max}

To derive an expression for ΔV_{max} in terms of r_0, r_m, d_0, and d_m, we have

$$\begin{aligned} V(t) &= \pi r(t)^2 d(t) && (7)\\ &= \pi (r_0 + \tilde{r})^2 \cdot (d_0 + \tilde{d}) && (8)\\ &= \pi (r_0^2 + 2 r_0 \tilde{r} + \tilde{r}^2) \cdot (d_0 + \tilde{d}) && (9)\\ &= \pi (r_0^2 d_0 + 2 r_0 d_0 \tilde{r} + \tilde{r}^2 d_0 + r_0^2 \tilde{d} + 2 r_0 \tilde{r} \tilde{d} + \tilde{r}^2 \tilde{d}). && (10) \end{aligned}$$

Since $r_m / r_0 \ll 1$ and $d_m / d_0 \ll 1$, we may discard the terms containing $\tilde{r}^2$ or $\tilde{r}\tilde{d}$:

$$V(t) \approx \pi (r_0^2 d_0 + 2 r_0 d_0 \tilde{r} + r_0^2 \tilde{d}). \tag{11}$$

Then ΔV_{max} is given by:

$$\begin{aligned} \Delta V_{max} &= \max(V(t)) - \min(V(t)) && (12)\\ &\approx 2\pi (2 r_0 d_0 r_m + r_0^2 d_m). && (13) \end{aligned}$$

1.3 Deriving an expression for d_m

We imagine a cylindrical abdominal compartment beneath the lung compartment with the diaphragm serving as a shared wall. We imagine that the vertical displacement of the diaphragm $\tilde{d}_A(t) = -\tilde{d}(t)$ will increase the radius of the abdomen $r_A(t)$. We therefore derive an expression to infer diaphragm displacement $\tilde{d}(t)$ from the abdominal radius $r_A(t)$.

We can define the abdominal volume in a similar fashion as above,

$$V_A(t) = \pi r_A(t)^2 d_A(t). \tag{14}$$

with the important distinction that V_A(t) is considered constant in time (i.e., no compression of abdominal volume).

Both the radius and height can be characterized in a similar fashion as above (eqns: 3 and 4):

$$r_A(t) = r_{A0} + \tilde{r}_A(t),\ \tilde{r}_A(t) = r_{Am}\cos\omega t,\ \frac{r_{Am}}{r_{A0}} \ll 1 \tag{15}$$

$$d_A(t) = d_{A0} + \tilde{d_A}(t),\ \tilde{d_A}(t) = -d_m\cos\omega t,\ \frac{d_m}{d_{A0}} \ll 1 \tag{16}$$

Here the negative sign in front of $\tilde{d}(t)$ reflects the compression of the abdomen.

1.4 Estimating d_m

Since V_A is constant,

$$\begin{aligned}
\frac{dV_A}{dt} &= 0 && (17)\\
&= \pi(2r_A(t)d_A(t)r'_A(t) + r_A(t)^2 d'_A(t)) && (18)\\
&= \pi(2r_A(t)d_A(t)(-r_{Am}\sin\omega t) + r_A(t)^2(d_m\sin\omega t)) && (19)\\
\Rightarrow\ & 2r_A(t)r_{Am}(d_{A0} - d_m\cos\omega t) = r_A(t)^2 d_m && (20)\\
\Rightarrow\ & 2r_A(t)r_{Am}d_{A0} = (2r_A(t)r_{Am}\cos\omega t + r_A(t)^2)d_m. && (21)
\end{aligned}$$

We set aside the time-dependence for clarity and solve for d_m:

$$\begin{aligned}
d_m &= \frac{2r_A d_{A0} r_{Am}}{(2r_A\tilde{r}_A + r_A^2)} && (22)\\
&= \frac{2d_{A0}r_{Am}}{(2\tilde{r}_A + r_A)} && (23)\\
&= \frac{2d_{A0}r_{Am}}{(3\tilde{r}_A + r_{A0})} && (24)\\
&= \frac{2d_{A0}\frac{r_{Am}}{r_{A0}}}{\frac{(3\tilde{r}_A + r_{A0})}{r_{A0}}} && (25)\\
&\approx 2d_{A0}\frac{r_{Am}}{r_{A0}} \text{ since } \frac{r_{Am}}{r_{A0}} \ll 1. && (26)
\end{aligned}$$

1.5 Estimating Minute Ventilation

Now that we have expressions for d_m and V_{max}, we can write V_{max} in terms of r_m and r_{Am}:

$$\begin{aligned}
\Delta V_{max} &\approx 2\pi(2r_0 d_0 r_m + r_0^2 d_m) && (27)\\
&\approx 2\pi(2r_0 d_0 r_m + \frac{2r_0^2 d_{A0}}{r_{A0}} r_{Am}). && (28)
\end{aligned}$$

And we can now estimate minute ventilation as:

$$\Psi = \Delta V_{max}\cdot\omega \approx (K_c r_m + K_a r_{Am})\cdot\omega. \tag{29}$$

where

$$K_c = 4\pi r_0 d_0 \tag{30}$$

$$K_a = \frac{4\pi r_0^2 d_{A0}}{r_{A0}}. \tag{31}$$

As we will show below, it is possible to obtain time-varying estimates of r_m, r_{Am}, and ω, which can be used in the above formula to obtain a time-varying estimate of minute ventilation:

$$\Psi(t) = \Delta V_{max}(t) \cdot \omega(t) \approx (K_c r_m(t) + K_a r_{Am}(t)) \cdot \omega(t). \tag{32}$$

1.6 Estimating an Instantaneous Respiratory Amplitude and Frequency using a State Space Oscillator Model.

We use the state space oscillator model described in Matsuda and Komaki (2) in a multivariable form to represent thoracic and abdominal respiratory waveforms $x_c(t)$ and $x_a(t)$, respectively:

$$x_c(t) = \begin{bmatrix} x_c^{(1)}(t) \\ x_c^{(2)}(t) \end{bmatrix}, x_a(t) = \begin{bmatrix} x_a^{(1)}(t) \\ x_a^{(2)}(t) \end{bmatrix} \tag{33}$$

$$\begin{bmatrix} x_c(t) \\ x_a(t) \end{bmatrix} = \begin{bmatrix} a_c R & 0 \\ 0 & a_a R \end{bmatrix} \begin{bmatrix} x_c(t-1) \\ x_a(t-1) \end{bmatrix} + v_t \tag{34}$$

$$y(t) = \begin{bmatrix} 1 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} x_c^{(1)}(t) \\ x_c^{(2)}(t) \\ x_a^{(1)}(t) \\ x_a^{(2)}(t) \end{bmatrix} + w_t \tag{35}$$

where:

$$R = \begin{bmatrix} cos(\omega_0 \Delta t) & -sin(\omega_0 \Delta t) \\ sin(\omega_0 \Delta t) & cos(\omega_0 \Delta t) \end{bmatrix}, v_t \sim N\left(0, \begin{bmatrix} \sigma_{v,c}^2 & 0 \\ 0 & \sigma_{v,a}^2 \end{bmatrix}\right), w_t \sim N(0, \sigma_w^2), \Delta t = \frac{1}{F_s}. \tag{36}$$

where F_s is the sampling frequency. We assume that the respiratory waveforms share the same underlying frequency ω_0. We used a Von Mises distribution to represent the prior density on the frequency parameter

$$f(\omega_0 | \mu, \kappa) = \frac{e^{\kappa cos(\omega_0 - \mu)}}{2\pi I_0(\kappa)} \tag{37}$$

where I_0 is a Bessel function of order 0, the concentration parameter was set to κ = 1000, and μ = 0.3 Hz, which corresponds to 18 breathing cycles/minute. We used the EM algorithm to obtain maximum *a posteriori* estimates of the parameters ω_0, a_c, a_a, $\sigma_{v,c}^2$, $\sigma_{v,a}^2$, and σ_v^2 as well as the hidden states $x_c(t)$ and $x_a(t)$ (1; 4; 3).

The instantaneous time-varying respiratory amplitudes can then be calculated as

$$r_m(t) = \sqrt{x_c^{(1)}(t|n)^2 + x_c^{(2)}(t|n)^2} \tag{38}$$

$$r_{Am}(t) = \sqrt{x_a^{(1)}(t|n)^2 + x_a^{(2)}(t|n)^2} \tag{39}$$

where

$$x_j^{(i)}(t|n) \equiv E\left[x_j^{(i)}(t) | y(1), y(2), ..., y(n)\right]. \tag{40}$$

and n indicates the length of the time series.

To estimate an instantaneous time-varying frequency, we first estimated the phase at each point in time

$$\Phi_a(t) = \tan^{-1}\left(\frac{x_a^{(2)}(t|n)}{x_a^{(1)}(t|n)}\right). \tag{41}$$

In general, the instantaneous frequency is defined as the time derivative of the time-varying phase, in this case $\Phi_a(t)$. However, since we are working with sampled discrete-time data, we could not directly evaluate the time derivative of the phase. Moreover, because our phase estimates are noisy, a direct approximation of this time derivative, such as a first difference, might further amplify noise. In addition, we could expect that the respiratory frequency in this study would vary over a time scale of minutes, tracking the changes in fentanyl concentration, a time-scale that is much slower than the sampling interval for the respiratory data (2 msec downsampled to 40 msec). Taking this all into account, we represented the time-varying frequency as a random walk observed in noise:

$$\omega(t) = \omega(t-1) + \eta(t) \tag{42}$$

$$\alpha(t) = \omega(t) + \gamma(t) \tag{43}$$

$$\eta(t) \sim N(0, \sigma_\eta^2), \gamma(t) \sim N(0, \sigma_\gamma^2). \tag{44}$$

The observed frequency $\alpha(t)$ was obtained by taking the first difference of the instantaneous phase estmate $\Phi_a(t)$:

$$\alpha(t) = \frac{\Phi_a(t) - \Phi_a(t-1)}{\Delta t}. \tag{45}$$

We then used the EM algorithm to estimate the unknown parameters σ_η^2 and σ_γ^2 as well as the instantaneous frequency $\omega(t)$:

$$\omega(t|n) \equiv E\left[\omega(t)|\alpha(1), \alpha(2), ..., \alpha(n)\right]. \tag{46}$$

2 Supplementary Figures S1 to S3

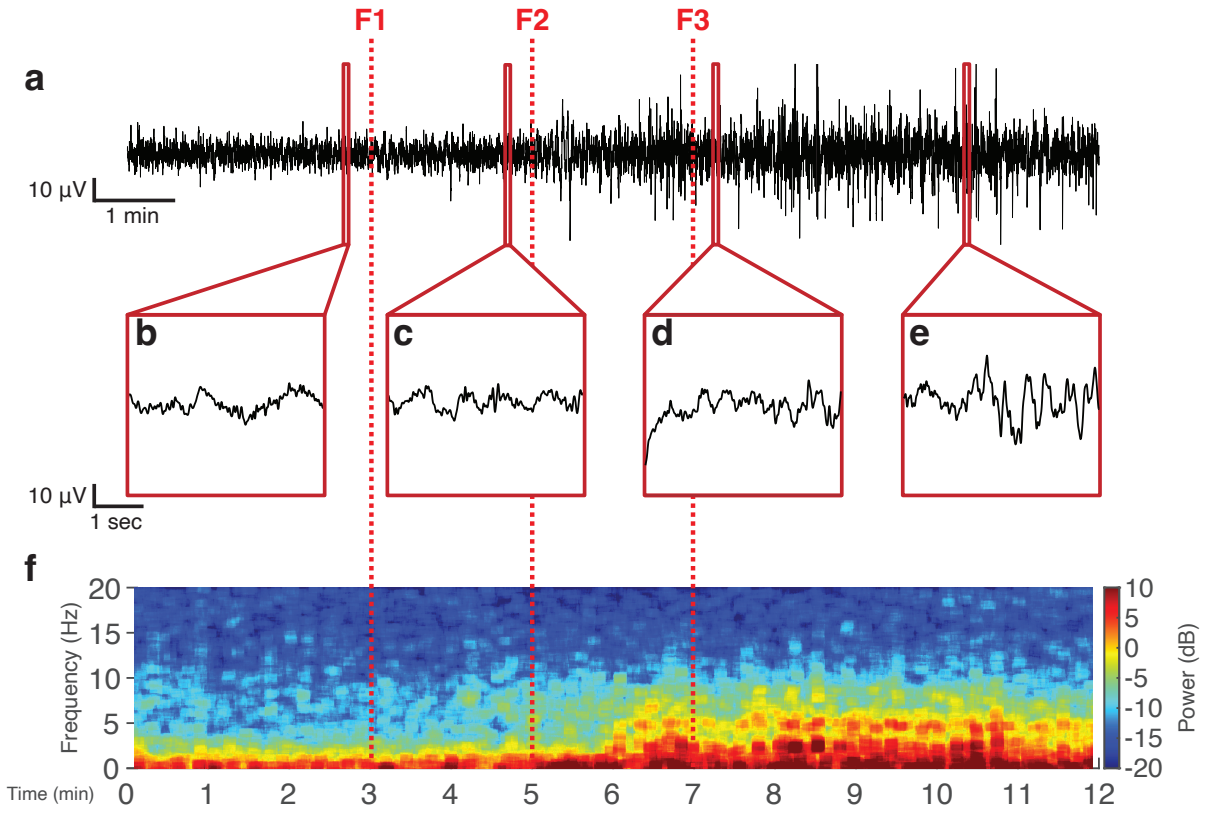

Fig. S1: (A) Filtered EEG waveform across the protocol (12 minutes) of a representative subject. The dashed lines correspond to the times of administration of fentanyl. We took samples of the evolution of this waveform after baseline (B), administration of the first fentanyl bolus (B), just before the second bolus (C), after the third bolus (D) and reaching the end of the protocol (E). In (F) we show the multitaper spectrogram.

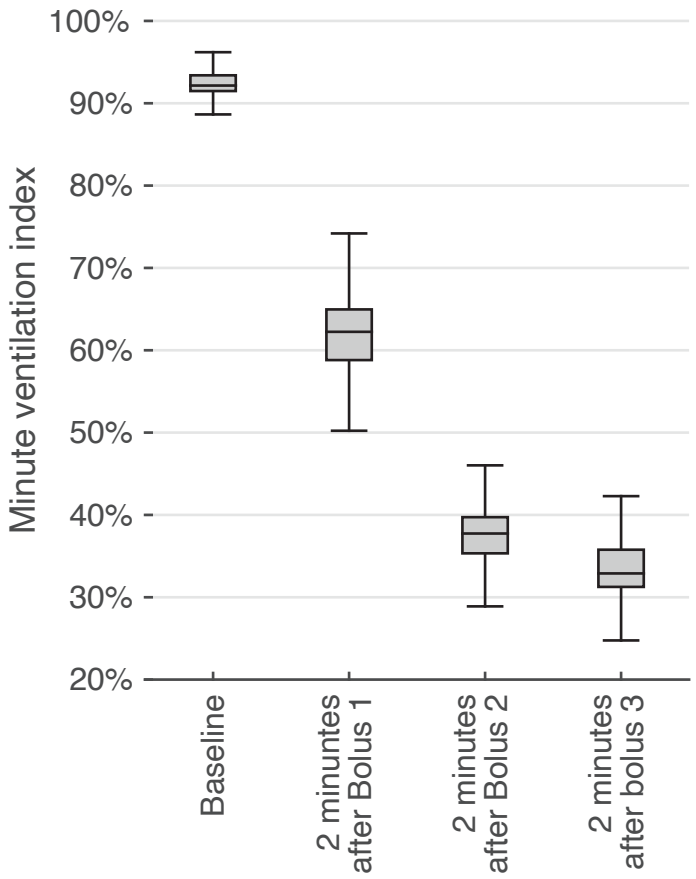

Fig. S2: Decline in minute ventilation occurs rapidly after exposure to fentanyl. A 10,000 sample bootstrap was conducted across subjects during the baseline period and 2 minutes after each bolus of fentanyl administered to characterize the average minute ventilation index. Subjects displayed a noticeable drop in minute ventilation even after 1 bolus, with progressive declines after subsequent boluses to the drug.

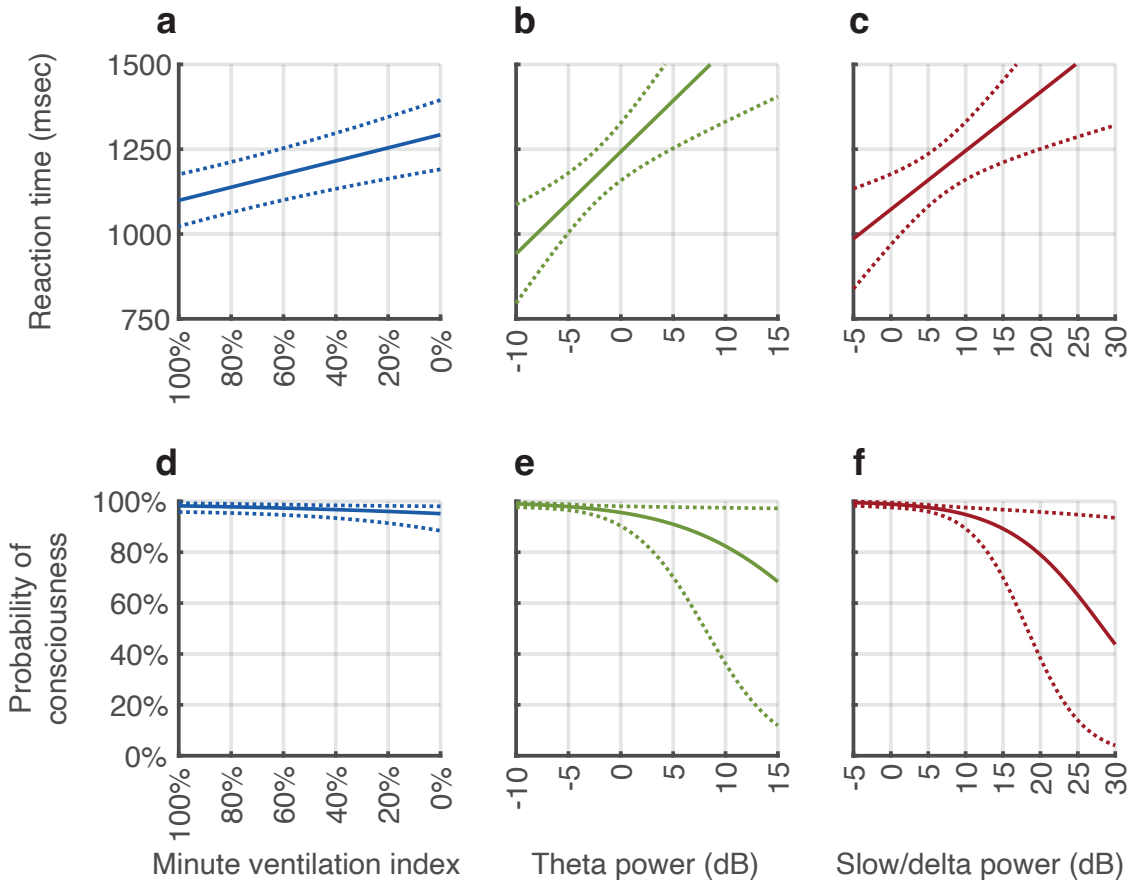

Fig. S3: Linear mixed effects models characterizing reaction time changes given changes in: (A) minute ventilation [Slope: -1.94 (-2.82, -1.06), Marginal R^2 = 0.013, Conditional R^2 = 0.18], (B) theta power [Slope: 30.11 (13.99, 46.22), Marginal R^2 = 0.065, Conditional R^2 = 0.313], (C) and Slow/Delta Power [Slope: 17.30 (6.24, 28.35), Marginal R^2 = 0.034, Conditional R^2 = 0.261]. In addition, we also constructed mixed effects logistic regressions to characterize changes in probability of consciousness given changes in: (D) Minute Ventilation Index [Odds Ratio: 0.99 (0.98, 1.00), Marginal R^2 = 0.016, Conditional R^2 = 0.499], (E) Theta Power [Odds Ratio: 0.86 (0.75, 0.98), Marginal R^2 = 0.059, Conditional R^2 = 0.570], (F) and Slow/Delta Power [Odds Ratio: 0.85 (0.76, 0.96), Marginal R^2 = 0.097, Conditional R^2 = 0.561]. Changes in reaction time and probability of consciousness appear to be relatively constant across a wide range of minute ventilation values and subjects are very likely to maintain consciousness even at dramatically low ventilation levels. In contrast, theta and slow/delta power appear to track both reaction time and loss of consciousness with greater sensitivity.

3 References

1 A. M. Beck, E. Stephen, and P. Purdon. State Space Oscillator Models for Neural Data Analysis. *2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2018.

2 Takeru Matsuda and Fumiyasu Komaki. Time Series Decomposition into Oscillation Components and Phase Estimation. *Neural Computation*, 29(2):332–367, February 2017.

3 Geoffrey J. McLachlan and Thriyambakam Krishnan. *The EM Algorithm and Extensions, 2E*. Wiley Series in Probability and Statistics. John Wiley & Sons, Inc., Hoboken, NJ, USA, February 2008.

4 R. H. Shumway and D. S. Stoffer. An Approach to Time Series Smoothing and Forecasting Using the Em Algorithm. *Journal of Time Series Analysis*, 3(4):253–264, 1982.