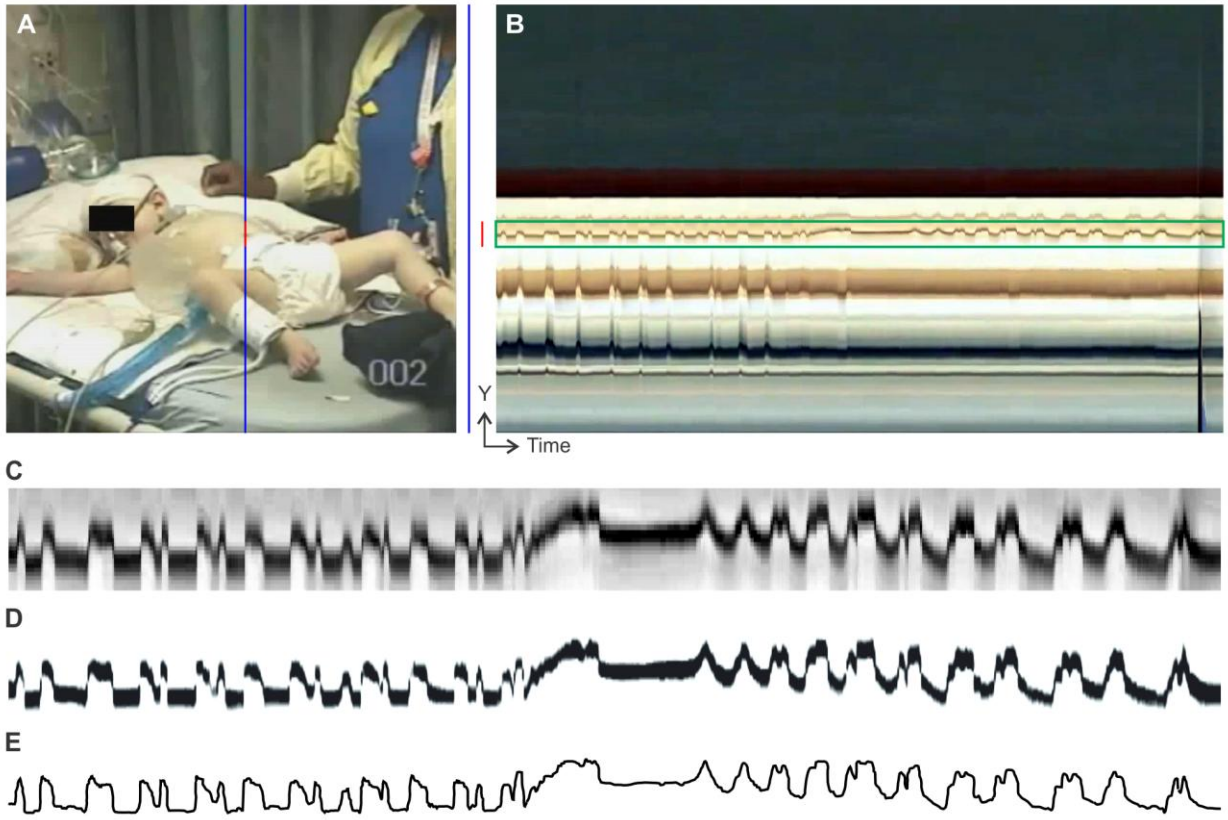
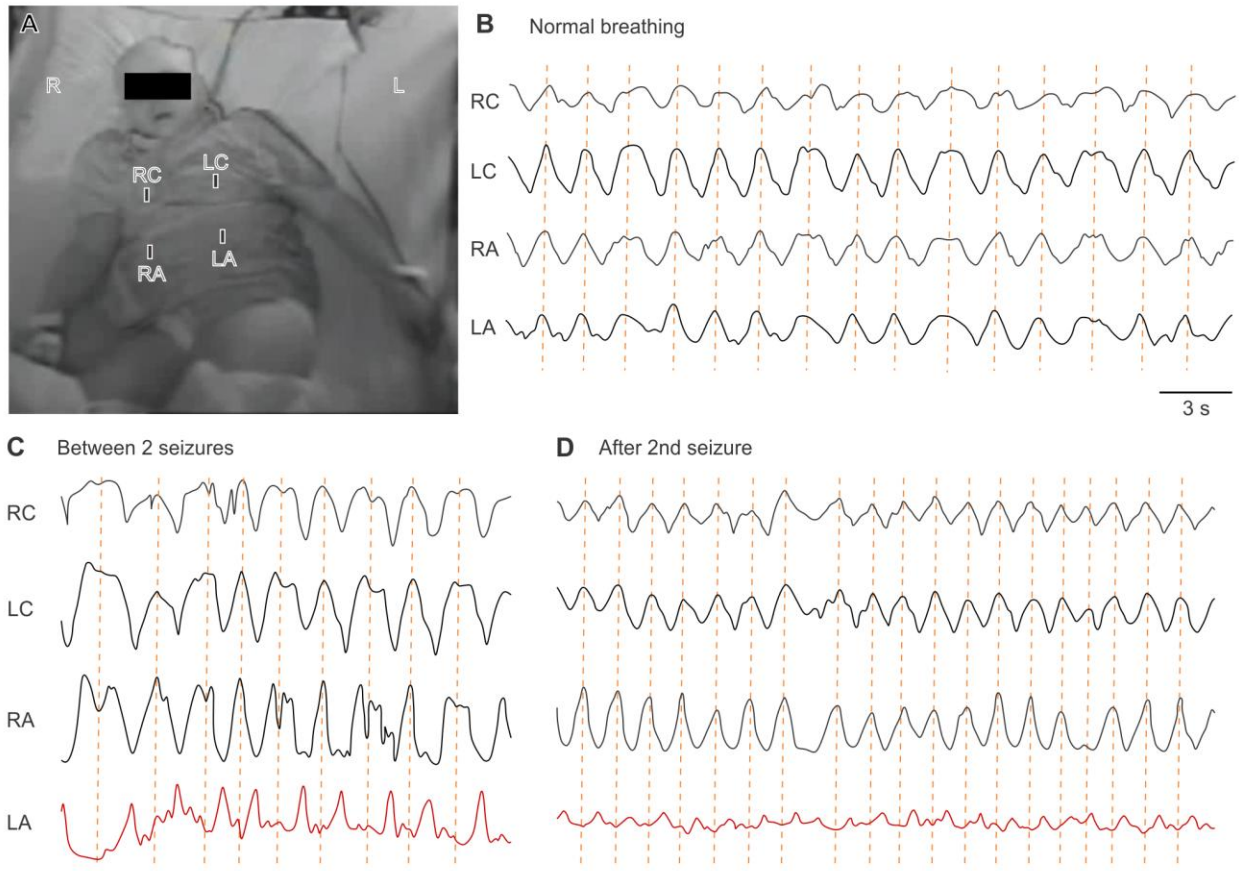
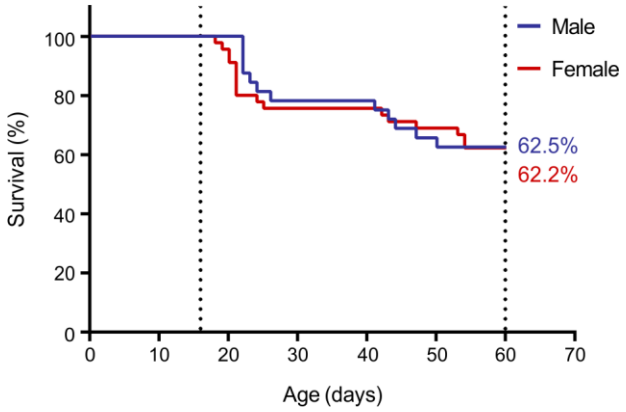
Supplemental data



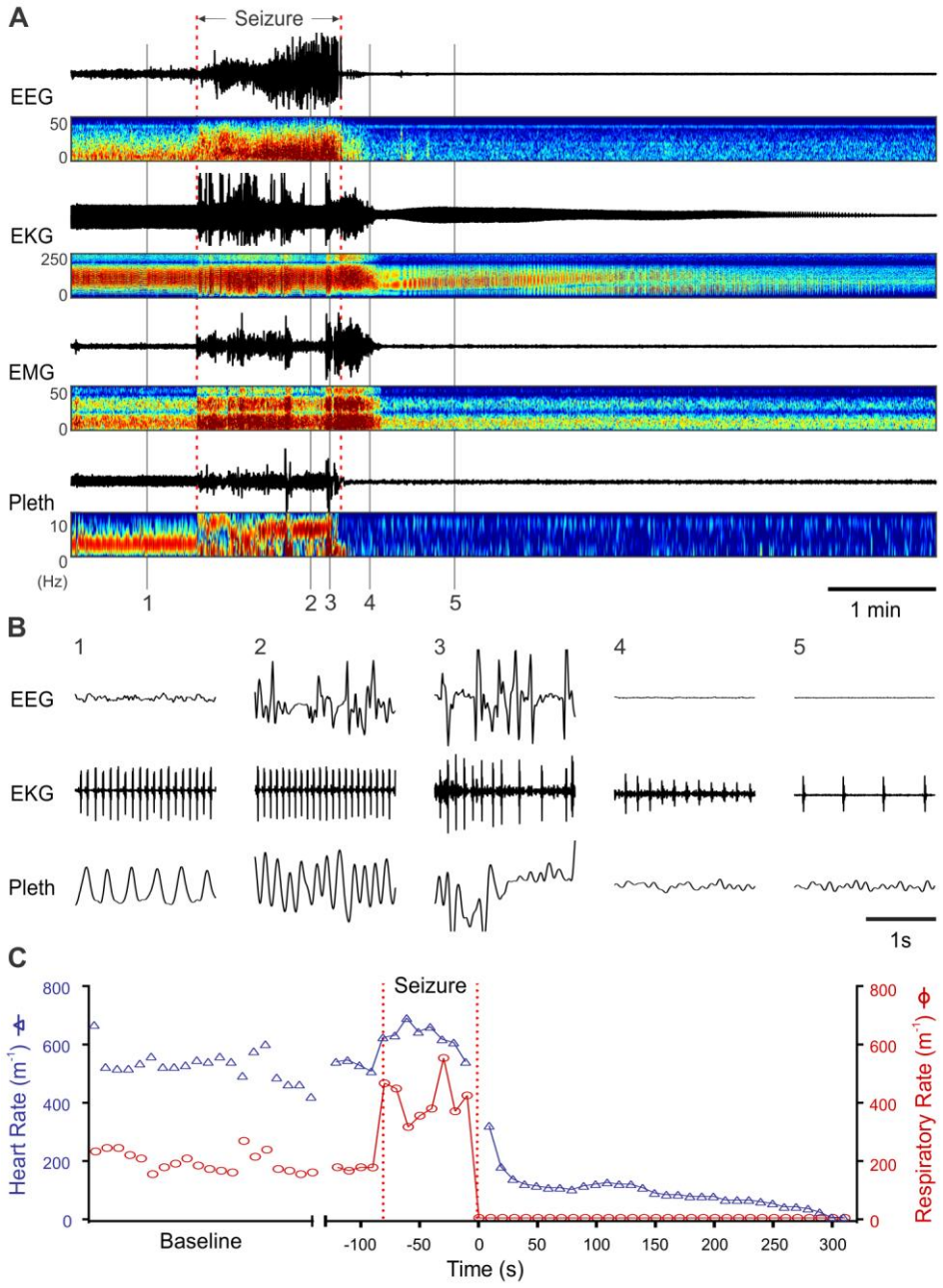
Supplemental Figure 1. Method used to analyze respiratory movements in videos of Dravet patients. (A) A region of interest was chosen from a frame of a video image (in this case a vertical line from Supplemental Video 1). This patient image is the same as that shown in Figure 1A. (B) A plot was generated with the y-axis representing the color values extracted for each pixel along the region of interest, and the x-axis representing successive video frames of the video (or time with video frame rate of 24 Hz). A band was then chosen where respiratory movements were maximized (in this case the box drawn around the umbilicus, which moved up and down with each breath). (C) Enlargement of the chosen band after conversion to grayscale image and contrast adjustment. (D) Movement of umbilicus clarified by cropping of surrounding image and conversion to black and white. (E) A line was drawn down the middle of the black region in D to obtain a line drawing of breathing movements.



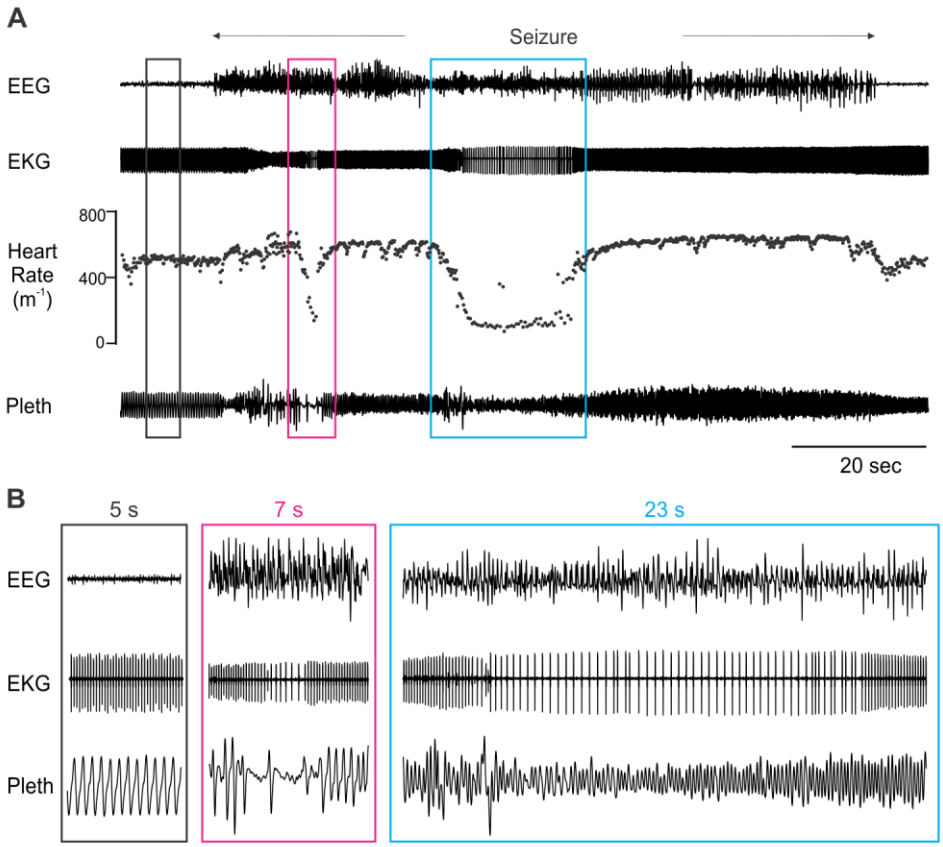
Supplemental Figure 2. Seizures induced paradoxical breathing in a DS patient. (A) Video frame illustrating four separate regions of interest for analysis of respiratory movements. (B) Normal breathing movements from the four regions of interest. Analysis was performed as illustrated in Supplemental Figure 1, except that a single line was used to illustrate breathing movement for each region of interest. Note that breathing occurs in phase for each quadrant of the torso (vertical dashed lines). (C) Breathing between two convulsive seizures. Note that breathing is irregular and erratic, and that movements at LA are 180 degrees out of phase with the other three quadrants. (D) Breathing after second convulsive seizure. Note that the LA movements are now much smaller and remain out of phase. RC & LC – Right and left chest. RA & LA – Right and left abdomen. The video of this patient can be played from Supplemental Video 2.



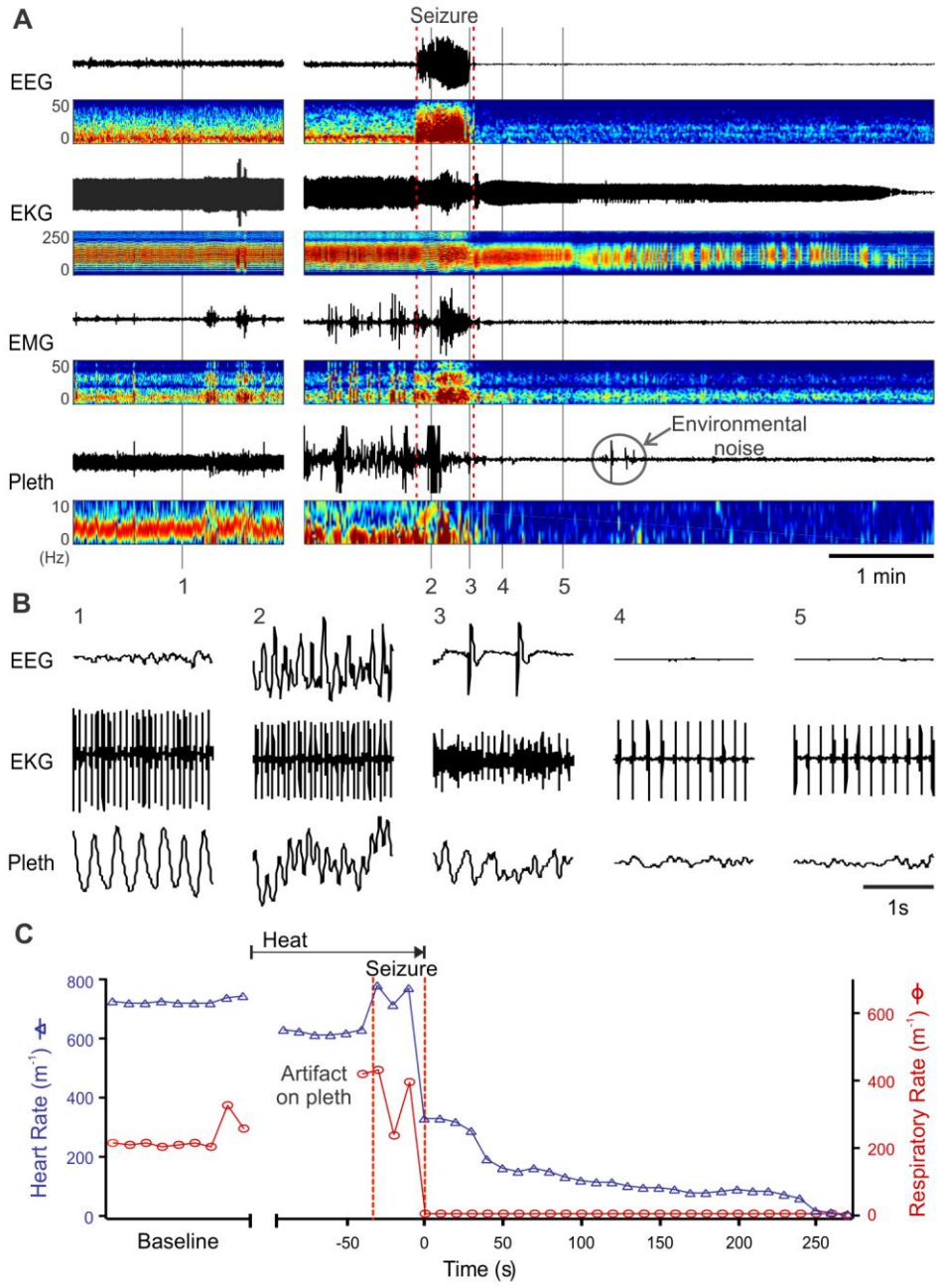
Supplemental Figure3. Survival curves for male (n=32) and female (n=45)*Scn1a*$^{R1407X/+}$ mice. Methods are the same as those used for Figure 3. There was no gender difference in survival(p=0.871; Log-rank Mantel-Cox test)



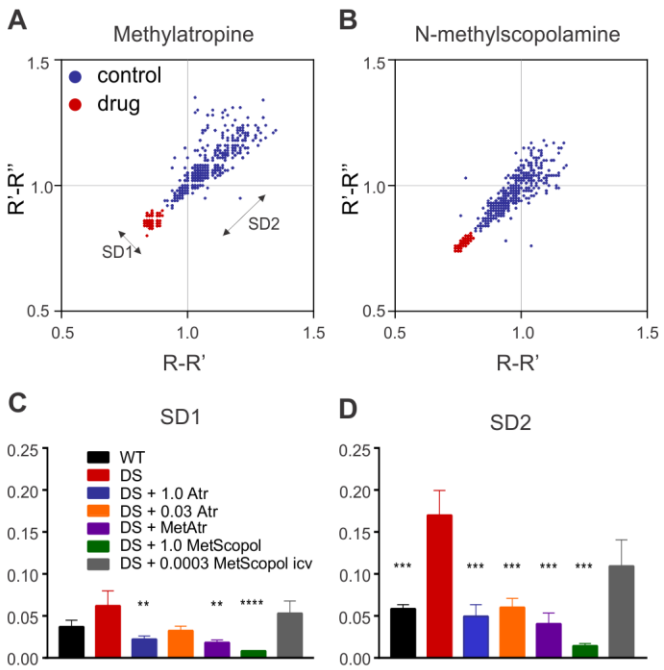
Supplemental Figure4. Postictal death after a spontaneous seizure in a 2nd *Scn1a*$^{R1407X/+}$ mouse(P24). (A) Physiological recordings with corresponding power spectrum heat maps (using same format as Figure 4) showing events leading to death. Breathing became disrupted during the seizure and ceased at the end of the seizure. In contrast, bradycardia began later and terminal asystole did not occur until nearly 5 minutes after the end of the seizure. (B) Expanded traces of EEG, EKG and plethysmography from times marked by vertical lines labelled in A as 1-5.(C) Plot of breathing and heart rate for the data in A.



Supplemental Figure5. Spontaneous non-fatal seizure in an *Scn1a*$^{R1407X/+}$mousethat died 5.5 hours later from a spontaneous seizure. (A) Physiological recordings duringa spontaneous non-fatal seizure showing EEG, EKG instantaneous heart rate and plethysmography. This non-fatal seizure was associated with disruption of breathing, including apnea. During the second, longer episode breathing frequency was increased but tidal volume was greatly decreased. During both episodes bradycardia also occurred, but followed the onset of abnormal breathing. The apnea and bradycardia were both less severe than during the fatal seizure that occurred later. This is the same mouse as that shown in Figure 4. (B) Expanded traces from times designated in A by the colored boxes.



Supplemental Figure6. Death of *Scn1a*$^{R1407X/+}$ mice after heat-induced seizures was also due to respiratory arrest followed by bradycardia. (A) Events leading to death of a mouse during a heat-induced seizure. Data are shown in same format as in Figure 4. Traces are discontinuous to show baseline recordings prior to hyperthermia. At the time indicated, a seizure occurred after the animal's temperature had increased to 38.9 degrees C. After the seizure, PGES was seen on the EEG. Towards the end of the seizure, breathing became erratic, and then respiratory activity suddenly ceased. The EKG showed a rapid decrease in heart rate at the end of the seizure, after which the frequency and amplitude slowly decreased over the next four minutes. (B) Expanded traces of EEG, EKG and plethysmography at the times labelled 1-5. (C) Respiratory rate and heart rate for the data shown in A & B. Data points are discontinuous prior to the seizure due to movement artifact.



Supplemental Figure7. Effect of atropine and quaternary ammonium derivatives on HRV.(A-B)Poincaré plots demonstrate that methylatropine (1 mg/kg) and N-methylscopolamine (1 mg/kg) both reduced HRV in *Scn1a*$^{R1407X/+}$mice. The plots in parts A & B are from two individual animals. Summary data for replicate animals for these experiments are shown in parts C & D. Number of replicates was 6 for part A and 7 for part B. (C) Short-term HRV for each group from panels A-B, Figure 6and Figure 7. (D) Long-term HRV for each group from panels A-B, Figure 6and Figure 7. Number of animals for each experiment are (for bars from right to left): 7, 10, 6, 6, 6, 7, 4. Symbols represent p-values compared to DS group (Mann-Whitney U Test). * - $p<0.01$; ** - $p<0.001$; *** - $p<0.0001$.

Supplemental Video 1. Video of a Dravet Syndrome patient during and after a seizure. Panel on left is the original video. Panel on right was processed with phase-based Eulerian video magnification motion processing to enhance respiratory movements (4X; 0.05-3 Hz).

Supplemental Video 2. Video of a second Dravet Syndrome patient during and after a seizure. Video was processed with Eulerian video magnification to enhance respiratory movements (10X; 0.05-3 Hz).