Supporting Information

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SI Materials and Methods

Computer Simulations. Suprachiasmatic nuclei (SCN) and food-entrainable oscillators (FEO) and methamphetamine-sensitive circadian oscillators (MASCO) were simulated by coupled Pittendrigh–Pavlidis equations, forced by light/dark (L) or restricted feeding (F) zeitgebers, respectively, where R and S are the state variables, and a, b, c, and d are parameters. These equations differ from the Pavlidis equations (1) by a parameter K, which is a small, nonlinear term ($K = 1/[1 + 100\ R^2]$) that ensures numerical smoothness. The R variables are explicitly constrained to be positive. Parameters C_{LF} and C_{LS} set the coupling strengths of oscillator SCN to FEO/MASCO and of oscillator FEO/MASCO to SCN, respectively. Both zeitgebers, L and F, are represented by square-wave functions.

$$\text{Oscillator SCN: } dR_L/dt = R_L - c_L S_L - b_L S_L^2 + (d_L\text{-}L) + K$$
$$dS_L/dt = R_L - a_L S_L + C_{FL} S_F$$

$$\text{Oscillator FEO/MASCO: } dR_F/dt = R_F - c_F S_F - b_F S_F^2$$
$$+ (d_F\text{-}F) + K$$
$$dS_F/dt = R_F - a_F S_F + C_{LF} S_L$$

In all simulations, zeitgeber L had a 1-h duration and amplitude *1*, and zeitgeber F had amplitude 0.3 and 1-h duration. A fixed 12-h phase relationship was set between zeitgebers L and F. To attain a damped SCN oscillator, the parameter set values were chosen so as to leave the oscillator out of the self-sustainment domain. Simulations were performed using CircadianDynamix software (www.neurodynamix.net), which is an extension of Neurodynamix II (2). We used the Euler method for numerical integration, with 1,000 integration steps per 24-h d. Simulated light/dark-driven locomotor activity, or the FAA/MASCO rhythm, occurred every time the S variable in oscillator SCN or oscillator FEO/MASCO, respectively, rose above a threshold value, set at two-thirds of the maximum amplitude of this variable.

Group-Average Activity Profiles. ClockLab software was used to generate group-average activity profiles by averaging the counts per 5-min bin for all mice in each group. The SDs in the mean activity profile graphs represent the variability among the mice in the group. The average activity profiles during restricted feeding were generated by averaging the activity of each mouse during days 1–10 (Fig. S8*A*), days 1–9 (Fig. S8 *B* and *C*), or cycles 1–12 (Fig. S8*D*) of restricted feeding. The first and second days (Fig. S8 *A–C*) or cycles (Fig. S8*D*) of food deprivation were averaged separately and plotted.

1. Pavlidis T (1967) A mathematical model for the light affected system in the Drosophila eclosion rhythm. *Bull Math Biophys* 29:291–310.

2. Friesen WO, Friesen JA (2009) *Neurodynamix II. Concepts in Neurophysiology Illustrated by Computer Simulations* (Oxford Univ Press, New York).

Fig. S1. Characterization of circadian behavior of *Per1⁻/⁻/Per2⁻/⁻/Per3⁻/⁻* mice. (*A–J*) Double-plotted actograms of wheel-running activity (5-min bins) of *Per1⁻/⁻/Per2⁻/⁻/Per3⁻/⁻* mice maintained in 12L:12D (light indicated by yellow shading) for 6 d and then released into constant darkness. *Per1⁻/⁻/Per2⁻/⁻/Per3⁻/⁻* mice appear rhythmic in the light/dark cycle (with activity onset occurring ∼2 h before lights off), but their circadian rhythms are abolished upon release into constant darkness. Fast Fourier transform (FFT) analyses of activity in constant darkness showed that all mice have a dominant period in the ultradian range. The rhythm appeared to persist for several days in constant darkness in the animal shown in *I*, although FFT analysis showed a dominant period of 3.46 h. The data shown in *D* are also shown in Fig. 1*B*.

Fig. S2. Methamphetamine-induced wheel-running rhythms in wild-type and $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ mice. Double-plotted actograms of wheel-running activity (5-min bins) of wild-type (A) and $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ (B) mice maintained in constant darkness (indicated by black bars above actograms) and administered 0.005% methamphetamine (methamphetamine administration indicated by dashed vertical lines; days 1–33 of methamphetamine treatment are shown). Records from all mice are shown in this figure. The periods (mean ± SD) (C) of the methamphetamine-induced locomotor activity rhythms in wild-type ($n = 3$) and $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ ($n = 6$) mice were determined by χ^2 periodogram analyses. The days used for χ^2 periodogram analysis (shown by the solid vertical lines on the y-axes of the actograms; the first χ^2 periodogram value was used to calculate the mean) varied for each animal due to spontaneous changes in the phase of the rhythm (indicated by arrows) or disturbances caused by cage changes (indicated by red asterisks). *$P < 0.01$. The first actograms in A and B and are also shown in Fig. 1 C and D, respectively.
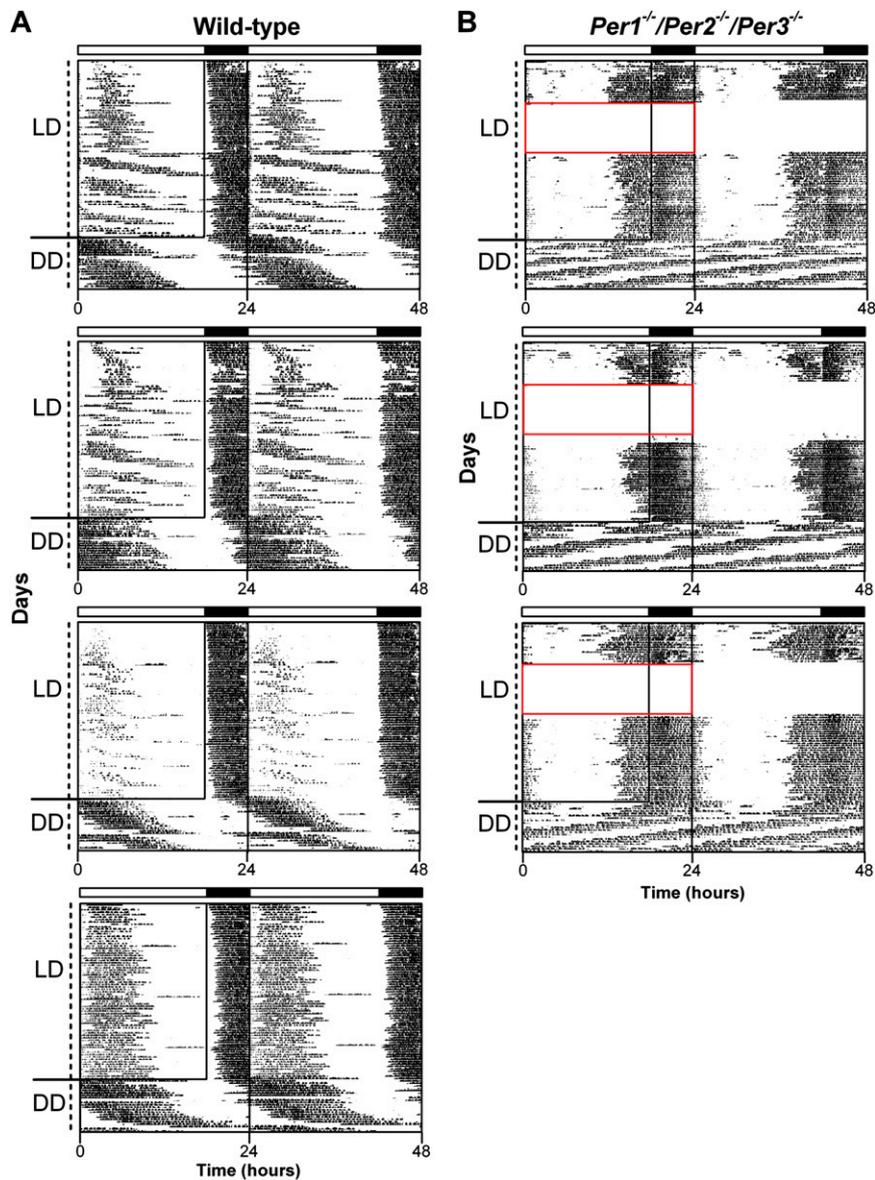
Fig. S3. The MASCO rhythm in *Per1^−/−/Per2^−/−/Per3^−/−* mice does not dissociate from SCN-controlled activity in the light/dark cycle. Double-plotted actograms of wheel-running activity (5-min bins) of wild-type (*A*) and *Per1^−/−/Per2^−/−/Per3^−/−* (*B*) mice administered 0.005% methamphetamine (indicated by dashed vertical line) for the entire experiment. The mice were maintained in 18L:6D (light and dark indicated by white and black bars, respectively, above actograms) for 78 d (LD) and then released into constant darkness (DD) for 21 d. The time when the mice were released into DD is indicated by the solid horizontal line. During the days outlined by the red box in *B*, the data were inadvertently copied over during saving (the mice were maintained in identical conditions in 18L:6D during this time). The time of darkness is outlined on the left half of the actograms. The data shown in the second panel of *A* and the third panel of *B* are also shown in Fig. 1 *E* and *F*, respectively.
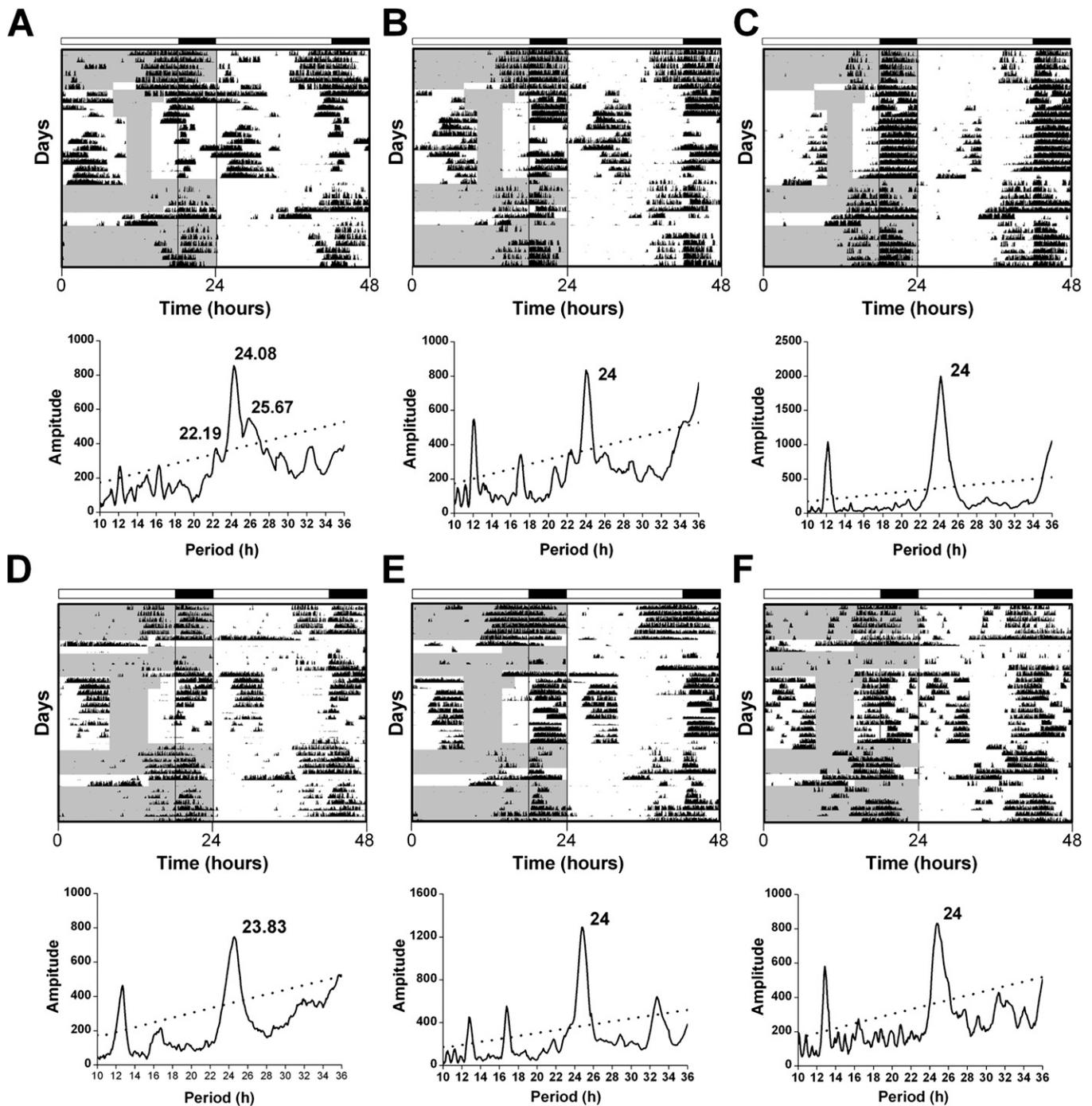
Fig. S4. Food anticipatory activity during daily (24-h) restricted feeding of $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ mice in the light/dark cycle. (*A–E Upper*) Double-plotted actograms of wheel-running activity (5-min bins) of $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ mice maintained in the light/dark cycle (18L:6D, light/dark conditions indicated by white and black bars, respectively, above actograms, and the dark phase is outlined with a black box on the left half of each actogram). The time when food was available is shown by gray shading on the left half of each actogram. Mice were fed ad libitum for 5 d, then 8 h/d for 2 d, 6 h/d for 2 d, and 4 h/d for 9 d (mice were fed 4 h per 24-h d in *A–C* and 6 h per 24-h d in *D–F*). On the 10th day of restricted feeding, food was left in the cage and mice ate ad libitum for 3 d. Mice were then fasted for 48 h and returned to ad libitum feeding for 6 d. (*A–E Lower*) χ^2 periodogram analyses were performed on days 1–9 of restricted feeding. The dotted line in the periodogram shows the significance level $P = 0.001$. The data shown in *E* are also shown in Fig. 2.
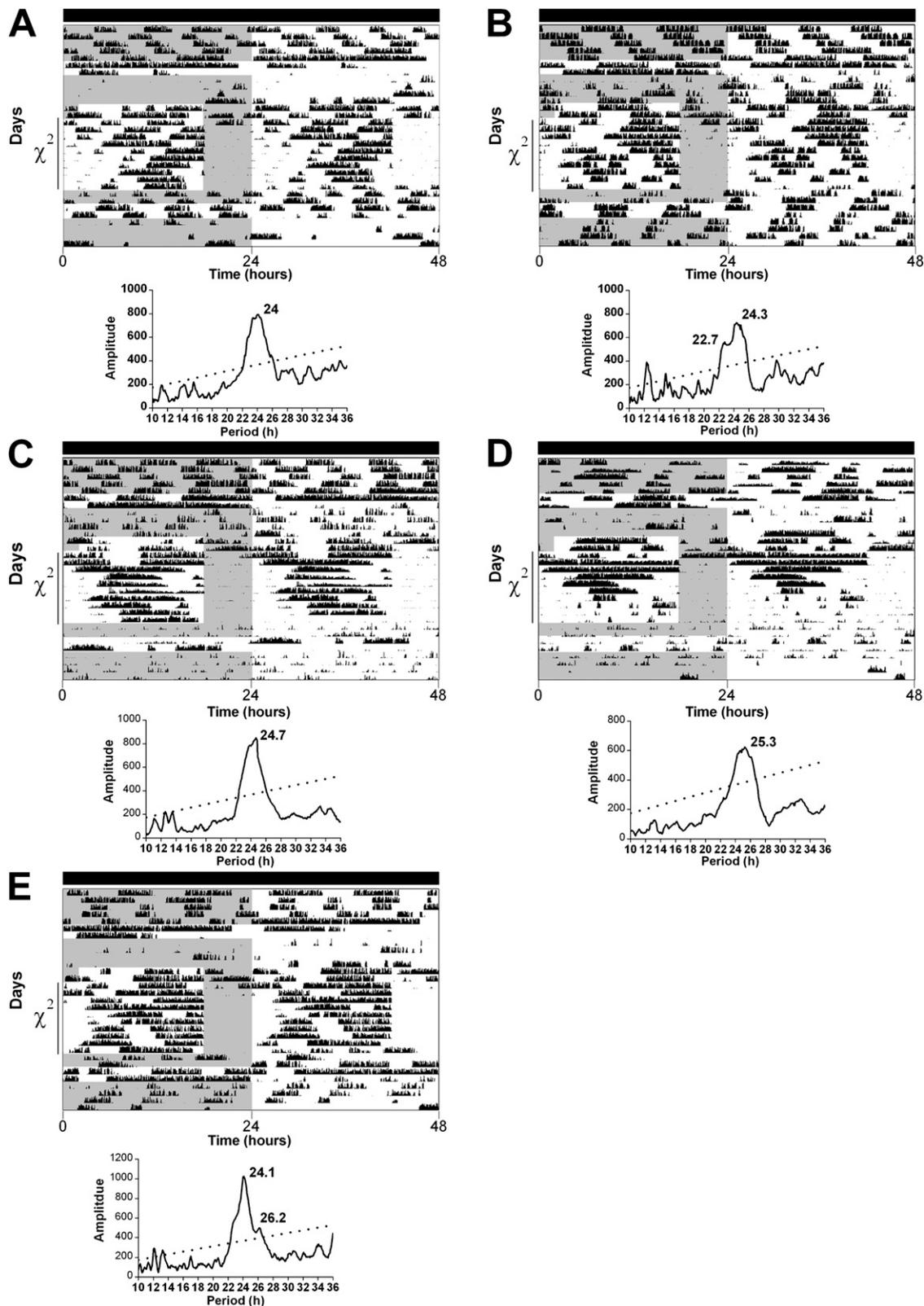
Fig. S5. T24 (daily) restricted feeding in constant darkness I. Variable patterns of food anticipatory activity during daily restricted feeding of *Per1⁻/⁻/Per2⁻/⁻/Per3⁻/⁻* mice in constant darkness: 6 h/d (T24) restricted feeding with 2 d ad libitum food before food deprivation. Representative double-plotted actograms (*A–E Upper*; 5-min bins) of wheel-running activity of *Per1⁻/⁻/Per2⁻/⁻/Per3⁻/⁻* mice maintained in constant darkness (indicated by black bars above actograms). Gray shading on left halves of the actograms indicates when food was available. Mice were fed ad libitum for 5 d, then fasted for 48 h to characterize activity during fasting before restricted feeding. Mice were then returned to ad libitum feeding for 3 d, fed 8 h/d for 2 d, and then 6 h/day for 9 d. On the 10th day of restricted feeding, food was left in the cage, and mice ate ad libitum for 2 d. Mice were then fasted for 48 h and returned to ad libitum feeding for 4 d. (*A–E Lower*) χ² periodogram analyses were performed on days 1–10 of restricted feeding, as indicated on the *y* axes of the actograms. The dotted line in the periodogram shows the significance level *P* = 0.001. The data shown in *A* are also shown in Fig. 3 *A* and *B*.
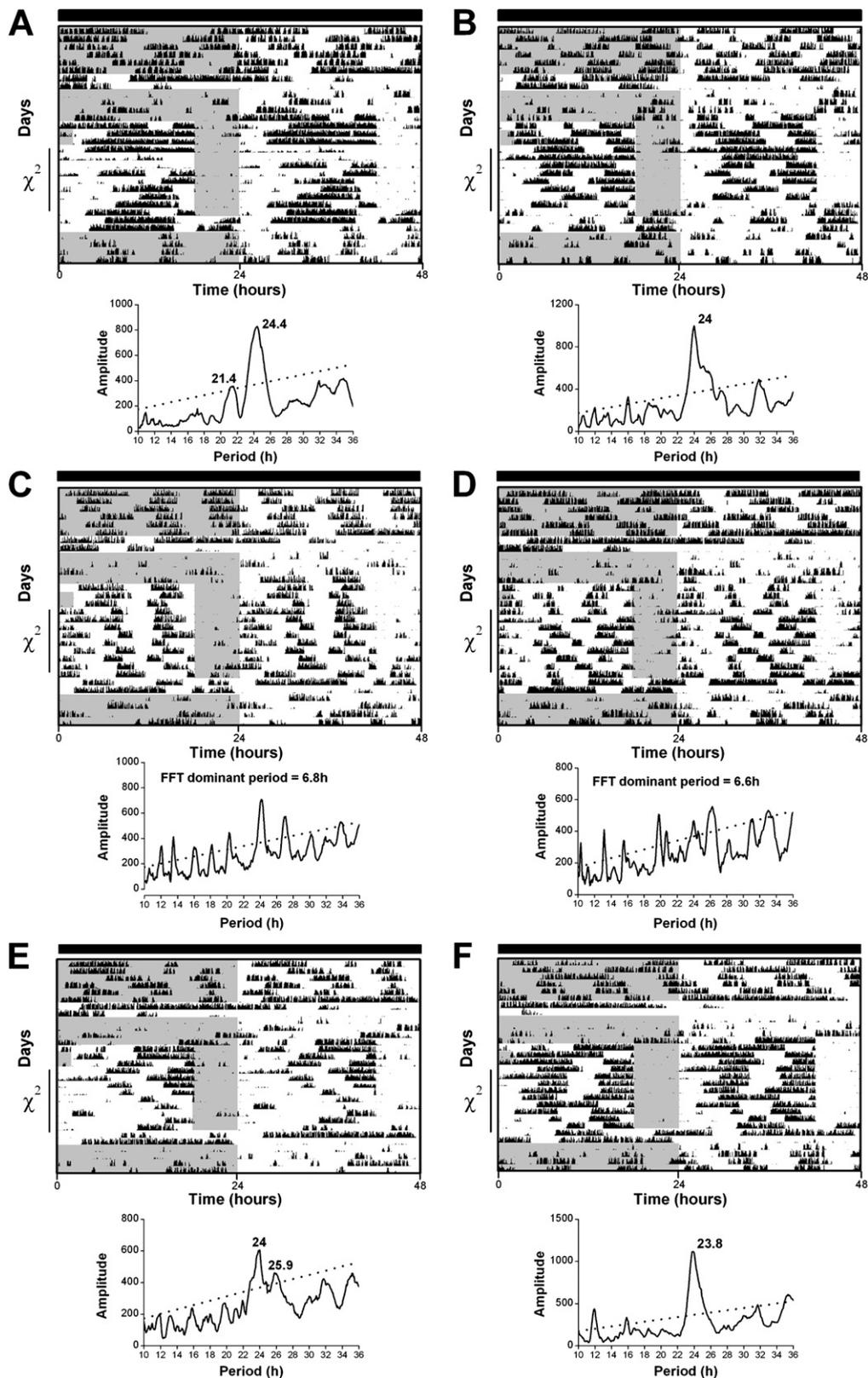
Fig. S6. T24 restricted feeding in constant darkness II. Variable patterns of food anticipatory activity during daily restricted feeding of $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ mice in constant darkness: 6 h/d (T24) restricted feeding and immediate release into food deprivation. Double-plotted actograms of wheel-running activity (*A–F Upper*; 5-min bins) of $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ mice maintained in constant darkness (indicated by the black bars above the actograms). The time when food was available is shown by gray shading on the left half of each actogram. Mice were fed ad libitum for 5 d, then fasted for 48 h to characterize activity during fasting before restricted feeding. Mice were then returned to ad libitum feeding for 3 d, then fed 8 h/d for 2 d and 6 h/d for 9 d. Mice were then immediately fasted (with no intervening ad libitum food) for 48 h and then provided food ad libitum for 4 d. (*A–F Lower*) χ^2 periodogram analysis was performed on days 1–9 of 6 h/d restricted feeding. The dotted line in the periodogram shows the significance level $P = 0.001$.
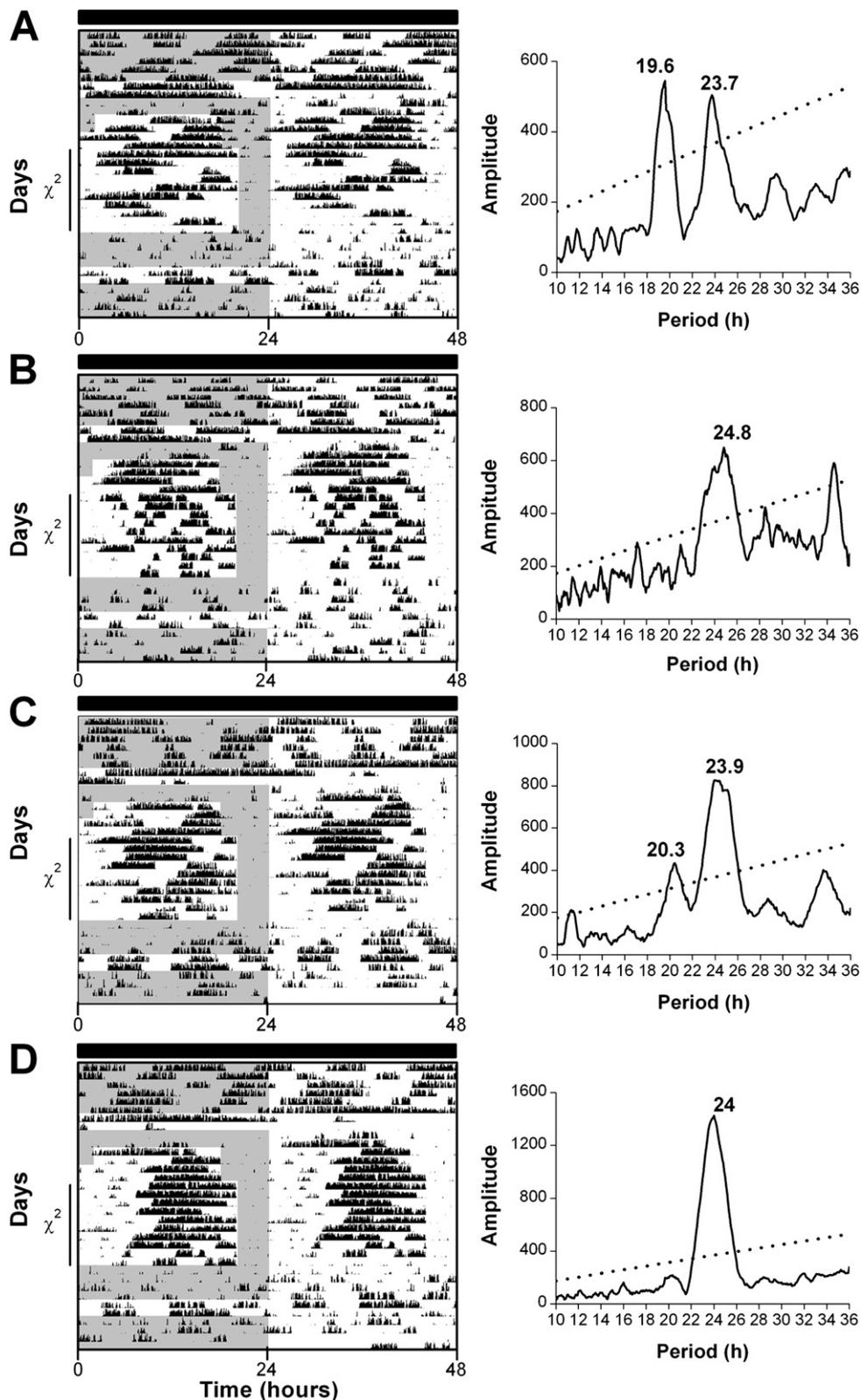
Fig. S7. T24 restricted feeding in constant darkness III. Variable patterns of food anticipatory activity during daily restricted feeding of $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ mice in constant darkness: 4 h/d (T24) restricted feeding. Double-plotted actograms of wheel-running activity (*A–D Left*; 5-min bins) of $Per1^{-/-}/Per2^{-/-}/Per3^{-/-}$ mice maintained in constant darkness (indicated by the black bars above the actograms). The time when food was available is shown by gray shading on the left half of each actogram. Mice were fed ad libitum for 5 d, then fasted for 48 h to characterize activity during fasting before restricted feeding. Mice were then returned to ad libitum feeding for 3 d, then fed 8 h/d for 2 d, 6 h/d for 2 d, and 4 h/d for 9 d. On the 10th day of restricted feeding, food was left in the cage and mice ate ad libitum for 3 d. Mice were then fasted for 48 h and returned to ad libitum feeding for 4 d. (*A–D Right*) χ^2 periodogram analysis was performed on days 1–9 of 4 h/d restricted feeding. The dotted line in the periodogram shows the significance level $P = 0.001$. The data shown in *C* are also shown in Fig. 3 *C* and *D*.
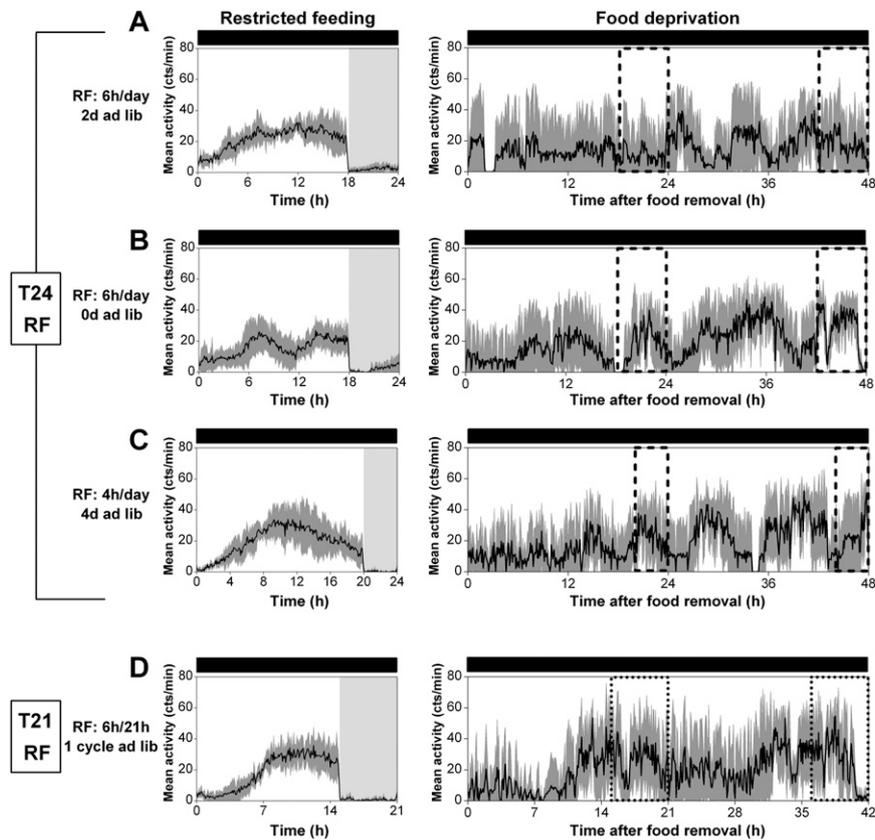
Fig. S8. Group average activity profiles during T24 and T21 restricted feeding and food deprivation of *Per1*^{−/−}/*Per2*^{−/−}/*Per3*^{−/−} mice. Group mean activity profiles were generated by averaging the number of wheel revolutions per 5-min bin (black line), and were plotted relative to time (24 h for *A–C* and 21 h for *D*). The SD, which represents the variability among mice, is shown in dark gray shading. *Per1*^{−/−}/*Per2*^{−/−}/*Per3*^{−/−} mice shown in Fig. S5 (*n* = 5), Fig. S6 (*n* = 6), Fig. S7 (*n* = 4), and Fig. S9 (*n* = 5; including the mouse that did not entrain to restricted feeding) were used to generate the activity profiles shown in *A–D*, respectively. The times when food was available are indicated by light gray shading in the activity profiles during restricted feeding (*Left*) and the times of previously scheduled food availability during food deprivation (*Right*) are indicated by black dashed lines. During restricted feeding (*A–D Left*), the activity of *Per1*^{−/−}/*Per2*^{−/−}/*Per3*^{−/−} mice is consolidated before the time of food availability when restricted feeding is performed on a 21-h cycle (T21) (*D*), whereas activity is dispersed across the day during daily (T24) restricted feeding (*A–C*). During food deprivation (*A–D Right*), the activity of *Per1*^{−/−}/*Per2*^{−/−}/*Per3*^{−/−} mice previously fed on a 21-h cycle increased before the time of previous food availability (*D*), whereas the activity of mice previously fed on a 24-h cycle was ultradian or showed no clear anticipation at the time of previous food availability (*A–C*).
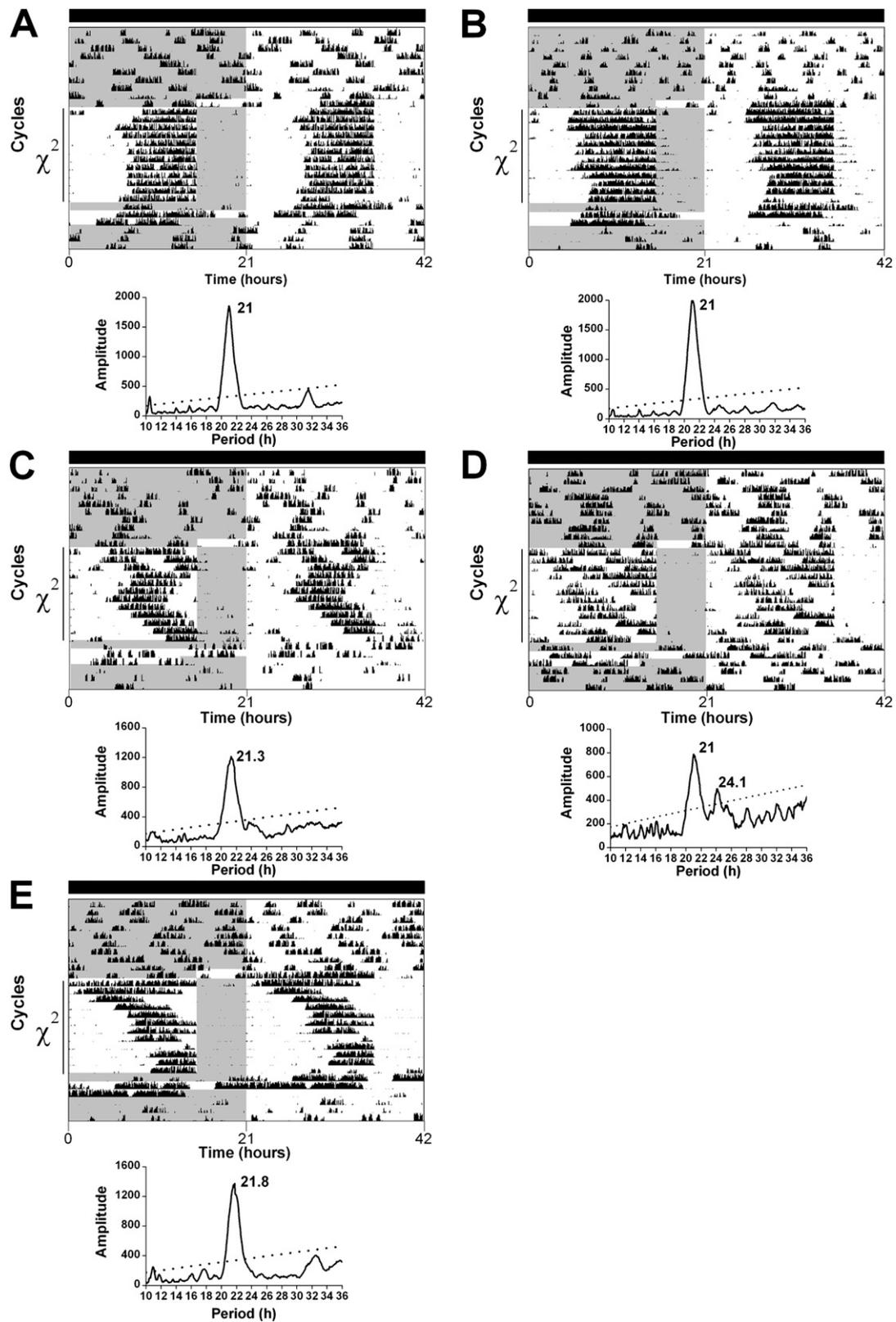
Fig. S9. *Per1*$^{-/-}$/*Per2*$^{-/-}$/*Per3*$^{-/-}$ mice entrain to a 21-h cycle (T21) of food availability. Actograms shown in *A–E* are replotted from Fig. 4 *A–E*, respectively. (*A–E Lower*) χ^2 periodogram analyses were performed on cycles 1–12 of restricted feeding (mice were fed 6 h per 21-h d). The dotted line in the periodogram shows the significance level *P* = 0.001.