Supporting Online Material for

Neurobiological Substrates of Dread

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Supporting Online Material

Subjects: A total of 33 people were scanned in the fMRI study, but due to incomplete data, one subject had to be discarded, leaving N=32 for the scanning (18 male, 14 female; ages: 19-49). SCR's were collected on a subset of these, of which 12 had data unaffected by scanner artifact, so an additional 10 people (4 male, 6 female; ages: 19-37) were studied outside the scanner for the SCR data. All participants gave written, informed consent for a protocol approved by Emory University's IRB.

Experimental Procedures: Cutaneous electrical shocks were delivered using a Grass SD-9 stimulator (West Warwick, RI) through shielded, gold electrodes placed 2-4 cm apart on the dorsum of the left foot. Each shock was a monophasic pulse of 10-20 ms duration. The Grass stimulator was modified by attaching a servo-controlled motor to the voltage potentiometer. The motor allowed for computer-control of the voltage level without comprising the safety of the electrical isolation in the stimulator. The motor was controlled by a laptop through a serial interface.

Prior to scanning, the voltage range was titrated for each participant. The detection threshold was determined by delivering pulses starting at zero volts and increasing the voltage until the individual could feel them. The voltage was increased further, while each participant was instructed, "When you feel that you absolutely cannot bear any stronger shock, let us know – this will be set as your maximum; we will not use this value for the experiment, but rather to establish a scale. You will never receive a shock of maximum value." The minimum voltage ranged across individuals from 20 to

49 volts, and the maximum ranged from 47 to 98 volts. Subsequent voltage levels were defined as a percentage of each individual's range: $(V - V_{min})/(V_{max} - V_{min})*100$.

After the voltage titration, the scanning phase began. The software package, COGENT 2000 (FIL, University College London), was used for stimulus presentation and response acquisition. Each trial began with a cue indicating the upcoming voltage level (expressed as a percent of the range) and the time, in seconds, to wait. The cues stayed on the screen for the duration of the waiting period, and, to prevent conditioning to its offset, the cue stayed on for 1 s after the shock. Following each trial, a visual analog scale (VAS) appeared, and the subject was asked to rate the preceding experience, including the waiting period. Specifically, subjects were instructed, "Tell us how pleasant or unpleasant this waiting and shock combination was." Four different voltage levels (10%, 30%, 60%, and 90%) were presented in combination with four different delays (1 s, 3 s, 9 s, and 27 s). These intervals were chosen because we hypothesized that the relative effects of time would follow either an exponential or hyperbolic form (S*1, 2*). All 16 combinations of voltage and delay were presented in random order, each combination repeated 6 times, for a total of 96 trials.

Following the scanning phase, a series of choice pairs was presented. Each choice was of the form, "30% in 27 sec OR 60% in 9 sec." Although there was a total of 120 possible pairings, it was not possible to present all of these choices in a reasonable period of time. Consequently, we selectively presented 36 choices, picked to sample the choices in a way that would maximize the information obtained. For example, we assumed that at a given delay, subjects would always choose the lower voltage, so these were not presented. At each specific voltage, however, several choices of different

delays were offered. In addition, choices were offered in which a higher voltage was paired with a shorter delay (we reasoned that most people would not choose a higher voltage at a longer delay, but we included 2 choices of this type to make sure – and none did). This category is critical for determining how much more voltage and individual is willing to take to get a trial over with quickly. So that there was no advantage to speeding up the process, the next choice pair appeared after the longest delay of the preceding trial. Individuals received the actual voltage/delay chosen on each trial.

FMRI measurements: Scanning was conducted on a Siemens 3T Trio whole-body scanner. After acquisition of a high-resolution T1-weighted scan, fMRI of the BOLD response was performed (TR = 2350ms, TE = 30 ms, 64X64 matrix, 35 axial slices, 3 mm^3 cubic voxels). To prevent electrical artifacts in the fMRI signal due to shock deliveries, the latter occurred during a 50 ms pause after each volume, yielding an effective TR = 2400 ms. Three runs of 32 trials were performed, for a total scan time of approximately 45 minutes.

SCR measurements: Skin conductance responses (SCR) were acquired with a Biopac MP150 digital converter (Biopac Systems, Goleta, CA) and fed into AcqKnowledge 3.7 recording software. A TTL-generator box was interfaced to the serial port of the computer running COGENT, allowing for the generation of digital timestamps for each stimulus on the Biopac channel recordings. The SCR data were sampled at 125 Hz, and a 1 Hz low-pass filter and 0.05 Hz high-pass filter were applied to the data during acquisition. Due to high rates of scanner artifacts in the SCR's, we obtained useable data on only 12 subjects. Therefore, we collected SCR's on an additional 10 subjects outside of the scanner, for a total of 22 subjects.

SCR Analysis: The SCR data were first detrended. Average responses were computed in a peristimulus window aligned to the shock. We then used the (peak – prestimulus) amplitude as the measure of SCR response (Fig. S1). The shock-SCR showed a monotonically increasing effect of voltage, as would be expected with the increased arousal associated with more voltage. Apart from the shortest delays, in which the SCR contains both the cue and shock response, the effect of delay was seen to increase the shock-SCR. This suggests that one effect of waiting is to increase "gain" of the autonomic nervous system (S*3*).

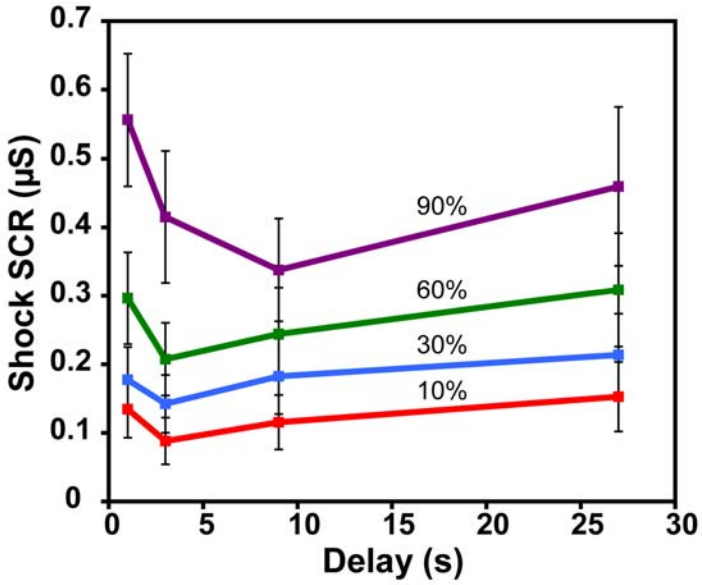

Fig. S1. Skin conductance response (SCR) to the shock (± s.e.m. across subjects) as a function of voltage and delay. Repeated measures ANOVA confirmed that there was a significant effect on SCR of both voltage [$F(3,63)=18.2$, $P<0.0001$] and delay [$F(3,63)=5.9$, $P<0.001$]. The responses with delays of 1s and 3s are higher because they contain the response to both the cue and the shock, whereas the other delays are the response to only the shock.

Construction of Utility Curves from Choices: Because we sparsely sampled the matrix of possible pairings during the choice procedure, we estimated the utility curves based on a method derived from Laplace's "rule of succession," known as the Colley Matrix

Method, which has been used in the derivation of college football team rankings in the Bowl Championship Series (BCS) (S*4*). We view each choice as analogous to a "match," with the goal of determining for each subject the relative rankings of the 16 combinations of voltage and delay ("teams"). If every possible match were played, then the rankings could be determined simply from the winning percentages, but since they were not, the rankings must be adjusted for the relative importance of each match. Following Laplace, Colley uses the ratio:

$$r = \frac{1 + n_w}{2 + n_{tot}}, \tag{1}$$

where r is the estimated ranking, given n_w wins out of n_{tot} matches. The rankings must be adjusted for the strength of the schedule:

$$n_{w,i}^{eff} = n_{w,i} + \sum_{j=1}^{n_{tot,i}} r_j^i \tag{2}$$

where n_w^{eff} is the effective number of wins, adjusted by the rankings of the teams played. This leads to a set of equations that must be solved simultaneously for r. In matrix notation:

$$\mathbf{C}\,\mathbf{r} = \mathbf{b} \tag{3}$$

where $b_i = 1 + (n_{w,i} - n_{l,i})/2$, and the elements of C, the Colley matrix, are defined:

$$\begin{aligned} c_{ii} &= 2 + n_{tot,i} \\ c_{ij} &= -n_{j,i} \end{aligned} \tag{4}$$

where $n_{j,i}$ is the number of times team i has played team j. Solving Eq. 3 for **r**, by Cholesky decomposition yields the rankings of the 16 voltage-delay combinations.

Determination of Marginal Rate of Substitution (MRS): Using the voltage-delay ranking derived from Eq. 3, we determined the marginal rate of substitution between volts and seconds. The preference rankings can be used as a proxy for utility (*U*), the two of which are related by a monotonic transformation (but the nature of which is irrelevant for the calculation of MRS). By visual inspection of the ranking curves, we see that the curves are approximately linear in voltage and exponential in time. With only 4 different delays it was not possible to meaningfully distinguish between exponential and hyperbolic discounting. Although a hyperbolic equation is commonly used to describe intertemporal choice (S*1*), the advantages over an exponential form are modest (S*5*), and so we opted for the more more easily linearized exponential form. Because these represent ordinal rankings, there will always be a separation between the curves, even at long delays. Interestingly, the effects of voltage and time appeared additive in the sense that the different voltage levels didn't converge to a single value at large delays, as would be expected if the effect of delay was multiplicative with voltage. This implies that there may be a fixed cost to waiting, regardless of what one is waiting for. Consequently, we fit a function that was linear in voltage and additive with an exponential delay term:

$$U(V,d) = a(1-V) + b\,e^{-r\,d} + c \tag{5}$$

where V is relative voltage, d is delay, and a, b, r, and c are constants. The constants were fit to each individual's preference curves by a mixed-model linear regression, using SPSS 12.0 (SPSS, Inc., Chicago, IL). On average, this model correctly predicted subjects' choices on 86.6% of the trials. The MRS is defined by the ratio of partial derivatives (S*6*):

$$MRS = \frac{\partial U}{\partial d} \Big/ \frac{\partial U}{\partial V} \tag{6}$$

or,

$$MRS = \left. \frac{b r e^{-r d}}{a} \right|_{d=0} = \frac{b r}{a} \tag{7}$$

The MRS, evaluated at d = 0 s, tells us the rate at which the voltage level would need to be decreased to make a delayed shock as appealing as an instantaneous one.

We used the MRS values to divide the cohort into 2 groups: mild dreaders and extreme dreaders. The higher the MRS, the more averse a person is to waiting. Using the KMEANS clustering procedure in Matlab 6.5 (Mathworks, Natick, MA), the cohort of 32 subjects was divided into 9 extreme dreaders and 23 mild dreaders (Fig. S2).

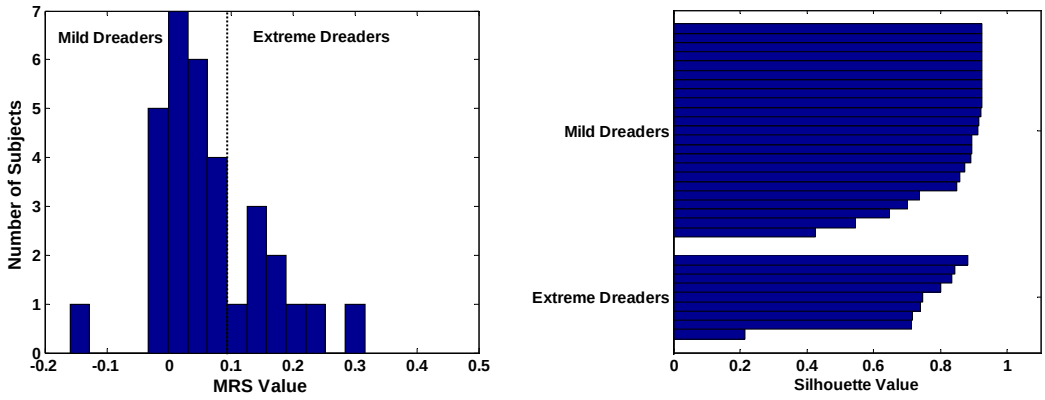

Fig. S2. Histogram of MRS values (*left*) and silhouette values of derived clusters (*right*). The histogram was suggestive of a bimodal distribution and this was confirmed by the silhouette values, which are measures of how similar each point is to other members of its cluster and ranges from -1 to +1. A silhouette value of 0 means that a point could belong equally well to either cluster, whereas positive values mean it belongs in its own cluster. As shown, all but one point in each cluster had silhouette values >0.5, implying a good clustering.

FMRI Analyses: FMRI data were initially analyzed with SPM2. Standard preprocessing was used, including motion correction, slice timing correction, and normalization to the MNI template brain in Talairach orientation. Statistical inferences were made at the

second level. Because of the different lengths of time associated with each type of trial, a combination of impulse functions and variable duration events was used to construct the 1st-level design matrix (Table S1). For example, 1 s – trials were modeled as a single event comprised of both the cue and shock; whereas 9 s and 27 s – trials were modeled with three types of events: the cue onset, the waiting period, and the shock. In this fashion, each voltage level was modeled separately. The VAS was modeled as a variable duration event. Thus, there were 37 conditions per run. The six motion parameters were also included.

Table S1. Summary of how the elements of each type of trial were modeled. Each element was convolved with a standard hemodynamic response function.

Trial Type	**Cue Onset**	**Waiting Period**	**Shock**
1 s – trials	Impulse		
3 s – trials	Impulse	None	Impulse
9 s – trials	Impulse	Variable Duration	Impulse
27 s – trials	Impulse	Variable Duration	Impulse

To identify regions of the putative "pain matrix," we used a contrast of shock responses that increased linearly by voltage level. This was averaged across the 3, 9, and 27 s trials (the 1s trial was excluded from this contrast because it contained the cue) and thresholded at $P<0.001$ ($k>5$). Although this type of contrast is not specific for "pain," it provides for the minimum requirement that regions that code some aspect of pain should show a positive relationship to voltage. ROI's were based on this functional map for the following regions, which were drawn from the generally accepted definition of the

cortical "pain matrix" (S*7-9*), somatosensory areas for the foot (S*10, 11*), and the amygdala (S*12*):

- SI (8 mm sphere centered at 6, -39, 57)
- SII (8 mm sphere at 60, -30, 21)
- insula – defined by the intersection with the corresponding PickAtlas mask and then subdivided into posterior (8 mm sphere at 36, -18, 15) and anterior (8 mm sphere at 39, 9, 3) portions
- ACC – defined by the intersection with the PickAtlas (S*13*) mask for BAs 24 and 32 and then subdivided into 3 parts: caudal ACC (8 mm sphere at 3, -3, 42), mid ACC (8 mm sphere at 3, 18, 33), and rostral ACC (8 mm sphere at 3, 36, 15).
- Amygdala – defined by the anatomical mask in the PickAtlas.

The average beta values for the shock in the 16 voltage-delay combinations were extracted for these ROI's, and a 2-factor mixed-model repeated measures ANOVA was performed with SPSS for the effects of voltage, delay, and group (mild dreaders vs. extreme dreaders; Table S2).

Timecourses of activation were extracted from regions of interest with use of custom software that modifies the SPM2 design matrix stucture (Fig. S3). Events of interest – in this case the cue, waiting period, and shock – were replaced with dummy events for a user-specified number of scans before and after the shock. This created a hybrid design matrix with FIR elements surrounding the effect of interest while still adjusting for the other effects, including the VAS and motion parameters. We used spm_get_data to load the unfiltered data from each subject and a portion of spm_regions to extract the 1st principal component of activation within each ROI for each subject. The

1st principal component was then regressed against the aforementioned hybrid design matrix, and the coefficients corresponding to the dummy FIR elements were averaged across subjects in the two groups. Because the 27s-trials provided the most data points during the waiting period, we restricted our attention to this trial type. To improve the signal-to-noise ratio, we averaged the two highest voltage levels to obtain the timecourse estimate.

Table S2. Summary of repeated measures ANOVA on shock response in the ROI's.

Region	**MNI Coordinates**	**Voltage**	**Delay**	**Group X Voltage**	**Group X Delay**
R SI	6, -39, 57	$P<0.0001$	NS	NS	NS
R SII	60, -30, 21	$P<0.0001$	$P<0.001$*	NS	$P=0.003$*
R Post Insula	36, -18, 15	$P<0.0001$	NS	NS	NS
R Ant Insula	39, 9, 3	$P<0.0001$	$P=0.012$	NS	NS
R Amygdala	24, 0, -21	$P<0.0001$	NS	NS	NS
L SII	-6, -39, 57	$P<0.0001$	$P=0.039$	NS	NS
L Post Insula	-36, -18, 15	$P<0.0001$	$P=0.049$	NS	NS
L Ant Insula	-39, 9, 3	$P<0.0001$	$P=0.021$	NS	NS
L Amygdala	-21, 0, -21	$P=0.001$	NS	NS	NS
ACC (Caudal)	3, -3, 42	$P<0.0001$	NS	NS	NS
ACC (Mid)	3, 18, 33	$P<0.0001$	NS	NS	NS
ACC (Rostral)	3, 36, 15	$P<0.0001$	$P=0.048$	NS	NS

* Significant after Bonferroni correction for 12 ROI's.

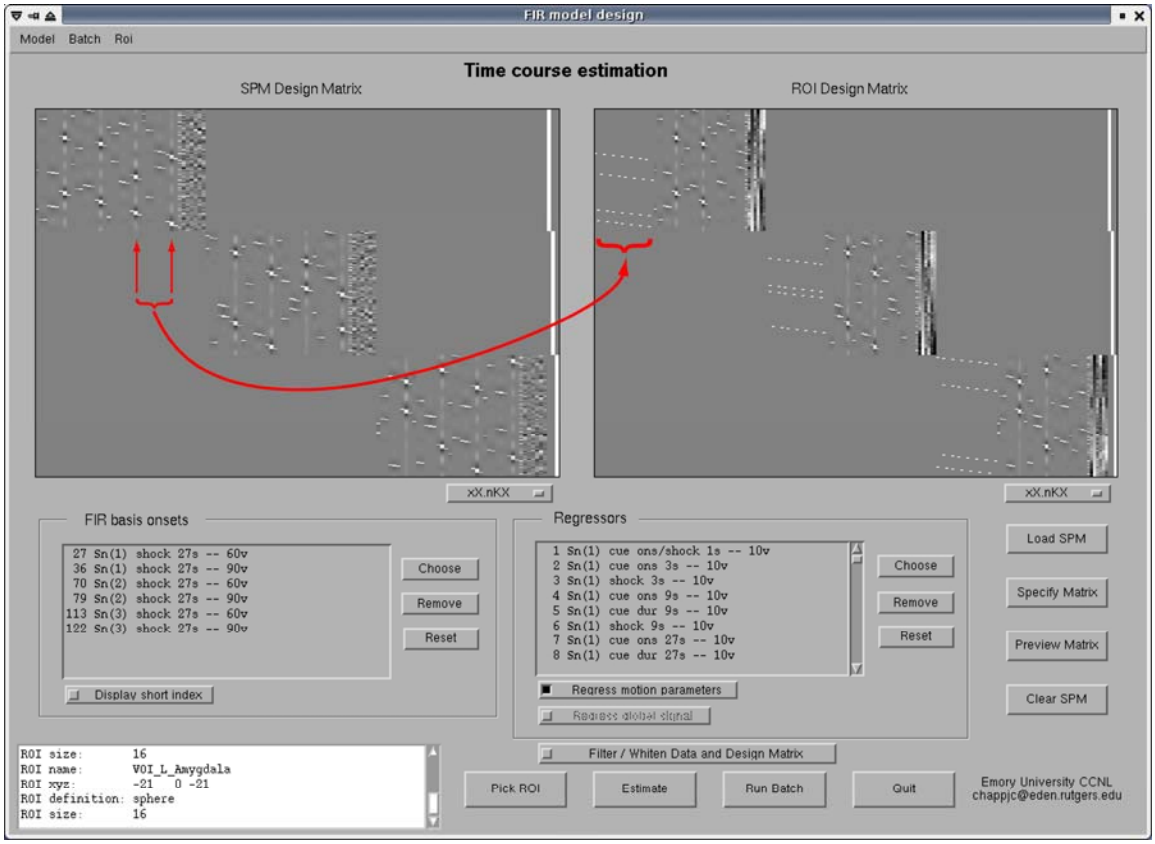

Fig. S3. Screenshot of graphical user interface for modifying SPM design matrix with user-specified FIR basis functions. The original 1st-level design matrix is shown on the left. The two red arrows denote the 60V and 90V trials of 27s duration. These have been replaced with a series of delta functions in a window stradling the times of the original events (*right*). The other effects remain unchanged, and the motion parameters are also included for each run. The new model is then applied to a user-specified ROI and can be run in a batch mode for a user-supplied list of subjects.

Model of anticipation (dread) and consumption: We used Loewenstein's model for the utility of anticipation to fit the timeseries extracted from the ROI's (S*14*). This model lends itself naturally to the imaging experiment. Loewenstein suggested that the present value of a delayed act of consumption can be divided into two components: the utility from anticipation and the utility from consumption. The value of future consumption is simply the utility of consumption, U, time-discounted by an exponential function (S*15*).

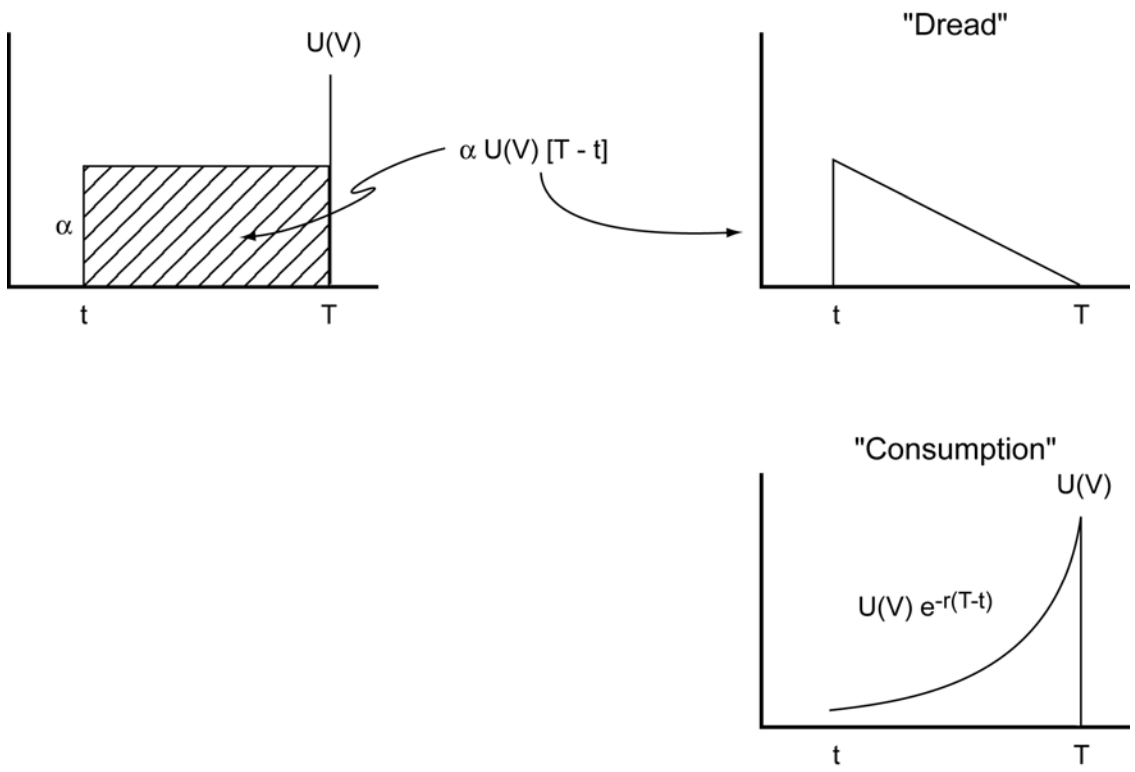

Fig S4. Theoretical framework for the utility of anticipation and consumption. Dread is defined as the forward-looking integral from the present (t) to the shock at time, T. We assume the shock is instantaneously consumed with utility, U(V), which is a function of the voltage, V. The integral is scaled by the dread factor, α. The utility of future consumption is defined by the standard discounted utility model with a discount rate, r. The sum of the "Dread" and "Consumption" terms yields the net present value of a future shock.

In addition to this standard, discounted, utility, Loewenstein proposed that anticipation itself conferred some utility. This utility was calculated as the integral of a "waiting function" from the present moment until the act of consumption. In the case of aversive outcomes, this term captures the feeling of "dread."

In order to reduce the number of parameters for better fitting to the fMRI data, we simplified Loewenstein's model in two respects. First, we assumed that consumption was instantaneous, and we modeled consumption by a scaled delta function – a reasonable assumption given the fact that the shock lasted less than 20 ms. Second, we

assumed that there was no discounting of anticipation, and so we modeled the utility of dread as the forward-looking integral of a constant. The value of this constant is a direct measure of the amount of dread a person experiences. This term is maximal at the onset of a trial and decreases linearly to zero as the shock approaches (Fig. S4). Thus, a person who dreads waiting more than the shock itself will have the highest value at the beginning of a trial (for this person, the shock provides relief from waiting), whereas a person who doesn't mind waiting will have the maximal value at the moment of shock. For the consumption term, we used standard exponential discounting with discount rate, *r*. The sum of the anticipation (dread) and consumption terms yields the present value as a function of time:

$$U(V,t) = \begin{cases} U(V)[\alpha(T-t) + e^{-r(T-t)}] & t \le T \\ 0 & t > T \end{cases} \quad (8)$$

<u>*Fitting the model to fMRI timeseries*</u>: We performed nonlinear regression to fit the model described above to the ROI timeseries data. But in order to fit the fMRI data, the model had to be convolved with a hemodynamic response function. We used the gamma-variate function described by Buxton et al. (S*16*),

$$h(t) = \frac{1}{k\tau_h(k-1)!}\left(\frac{t}{\tau_h}\right)^k e^{-t/\tau_h} \quad (9)$$

with the following parameters: $k = 3$, $\tau_h = .968$ s, and an additional lag = 2.5 s. After convolution, an additional parameter, *c*, was included to account for a nonzero baseline.

Thus, the full model was:

$$
\begin{aligned}
y_i(t) &= h(t) \otimes \begin{Bmatrix} U_i[\alpha_i(T-t) + e^{-r_i(T-t)}] & t \le T \\ 0 & t > T \end{Bmatrix} + c_i \\
U_i &= \hat{U} + \beta_U g_i + \eta_{Ui} \\
\alpha_i &= \hat{\alpha} + \beta_\alpha g_i + \eta_{\alpha i} \\
r_i &= \hat{r} + \eta_{ri} \\
c_i &= \hat{c} + \eta_{ci}
\end{aligned}
\tag{10}
$$

where $y_i(t)$ was the activation of subject i at time, t; g was a dummy variable that coded group (mild dreader=0 and extreme dreader=1). The parameter estimates for each subject represented the combination of a fixed effect, e.g. $\hat{U}$, and a subjectwise random error, e.g. η_{Ui}. The parameters, β_U and β_α represented the random effect of group on the respective fixed effects, U and α.

In particular, we were interested in β_α because when it is significant, this implies that mild and extreme dreaders have a different dread factor. By coding mild and extreme dreaders as in Eq. 10, the maximum likelihood estimate of β_α represents the additional amount to be added to extreme dreaders' α to account for whatever difference might exist between the two groups. In other words, $\alpha_{mild\ dreader} = \alpha$ and $\alpha_{extreme\ dreader} = \alpha+\beta_\alpha$. To perform the regression, we used the Matlab software package MONOLIX v 1.1 (Modèles Non Linéaires à effets mIXtes, courtesy Marc Lavielle, Laboratoire de Mathématiques, Université Paris-Sud) (S*17-19*), which implements maximum likelihood estimation of nonlinear mixed-effect models and, by virtue of running in Matlab, allowed us to implement the convolution in Eq. 10 efficiently within a Matlab function. Although we were primarily interested in the effect of group on the dread factor, we also allowed

group to interact with U. This controlled for the possibility that the two groups might have different overall magnitudes of shock response. Moreover, in nonlinear regression, the parameters may not be independent of each each other. In our model, the discount rate, r, and the dread factor, α, are candidates for collinearity because an early rise in activity could be partially accounted for by either a small discount rate or a large dread factor. To control for this possibility, we specified a covariance matrix that had nonzero off diagonal terms for these two parameters. The following initial values (and variances) were used: α: 0.01 (0.005), r: 0.2 (0.01), U: 0.01 (0.005), c: 0 (0.005). A total of 700 iterations was performed for each region with 400 of fixed step size and 300 of decreasing step size. Parameter significance was estimated based on sampling the gaussian distribution of values near the maximum likelihood estimates (S*19*). Significance of the random effects, β_U and β_α, was assessed with the Wald test (Table S3). As a final check, we compared the paramter estimates with those obtained by the LSQCURVEFIT routine in MatLab 6.5. The latter was performed separately on the average timeseries for the mild and extreme dreaders for each ROI, which provided a qualitative assessment that MONOLIX was, in fact, providing good estimates for the parameters.

Table S3. Model parameters fit to ROI timeseries. Many of the ROI's had significant dread factors (α), those that had significantly different dread factors for mild and extreme dreaders were found mainly in the posterior elements of the pain matrix. None of the regions had significant group effects on U, indicating that both groups had similar magnitudes of response to the shock itself. See Fig. S5 for data and fits.

Region	$\boldsymbol{\alpha}$ (x 10^{-3})	$\boldsymbol{\beta_\alpha}$ (x 10^{-3})	$\boldsymbol{U}$ (x 10^{-3})	$\boldsymbol{\beta_U}$ (x 10^{-3})	$\boldsymbol{r}$	$\boldsymbol{c}$ (x 10^{-3})
R SI	4.1***	1.1***	7.4***	3.0	0.195***	-0.4**
R SII	3.2**	6.7***	8.8***	2.2	0.14***	-0.6***
R Post Insula	3.6***	3.0***	8.5***	1.7	0.137***	-0.6***
R Ant Insula	5.6***	-0.1	14.1***	-1.3	0.837***	-0.3***
R Amygdala	12.0**	-10.6	8.9***	0.5	0.243***	-0.4***
L SII	-1.3	0.6	12.5***	3.9	0.183***	-0.4***
L Post Insula	-12.1	3.9	4.6***	2.0	0.076***	-0.3***
L Ant Insula	-0.9	1.2***	10.8**	1.3	0.749***	-0.3
L Amygdala	-4.6	6.9	9.5***	-5.3	0.0933***	-0.1
ACC (Caudal)	2.5	4.3***	10.5***	0.6	0.120***	-0.4**
ACC (Mid)	9.5*	-10.1	9.1***	0.6	0.337***	-0.2***
ACC (Rostral)	69.8***	-82.9***	-0.9*	-0.1	0.117***	0.3***

*$P\leq0.05$ **$P\leq0.01$ ***$P\leq0.001$

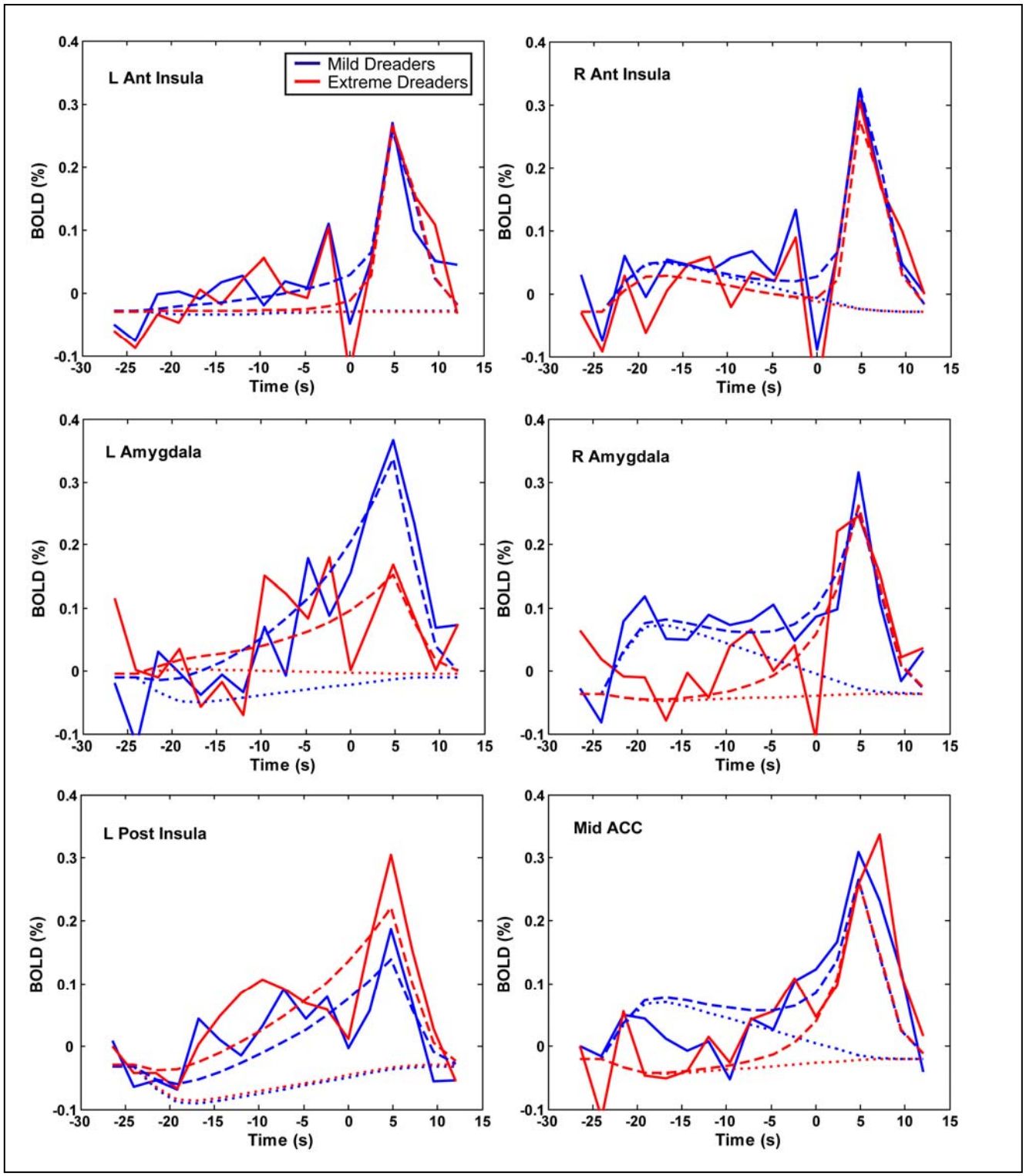

Fig. S5. Timecourses for extreme dreaders (*red*) and mild dreaders (*blue*) in other ROI's. Average of 60V and 90V for 27s-trials only. Dashed lines are derived from model fit (Eq. 10) and dotted lines are for only the dread term in Eq. 10.

Alternative Models: The aforementioned model, while derived from utility theory, is not unique in that alternative, simpler, models could be fit in the same fashion. For example, one model might not have the dread factor at all:

$$
\begin{aligned}
y_i(t) &= h(t) \otimes \begin{Bmatrix} U_i e^{-r_i(T-t)} & t \le T \\ 0 & t > T \end{Bmatrix} + c_i \\
U_i &= \hat{U} + \beta_U g_i + \eta_{Ui} \\
r_i &= \hat{r} + \beta_r g_i + \eta_{ri} \\
c_i &= \hat{c} + \eta_{ci}
\end{aligned}
\qquad (11)
$$

and where the discount rate, *r*, is allowed to take on different values between the groups. Using MONOLIX, we compared this model against that in Eq. 10 for the caudal ACC and right SII ROI's. The log-likelihood ratio test indicated that the model with the dread factor fit the data better (P=0.045 and P=0.008, respectively; see Fig. S6).

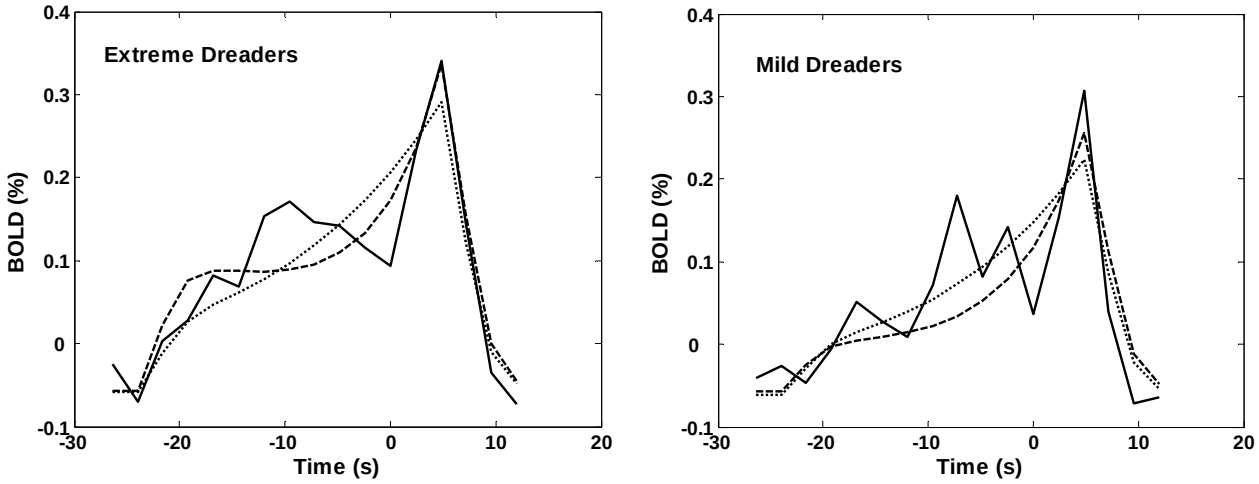

Fig. S6. Fit of alternative models in R SII for extreme dreaders (*left*) and mild dreaders (*right*). Solid lines are average data for the two groups. Dashed lines are for the full model (Eq. 10) and dotted lines are for the model without the dread term (Eq. 11).

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