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# Individual Differences in Some (But Not All) Medial Prefrontal Regions Reflect Cognitive Demand While Regulating Unpleasant Emotion

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## Abstract

The present study investigated the premise that individual differences in autonomic physiology could be used to specify the nature and consequences of information processing taking place in medial prefrontal regions during cognitive reappraisal of unpleasant emotion. Neural (blood oxygenation level-dependent functional magnetic resonance imaging) and autonomic (electrodermal, pupil diameter, cardiac acceleration) signals were recorded simultaneously as twenty-six older people (ages 64-66 years) used reappraisal to increase, maintain, or decrease their responses to unpleasant pictures. EDA was higher when increasing and lower when decreasing compared to maintaining. This suggested modulation of emotional arousal by reappraisal. By contrast, pupil diameter and cardiac acceleration were higher when increasing and decreasing compared to maintaining. This suggested modulation of cognitive demand. Importantly, reappraisal-related activation (increase, decrease > maintain) in two medial prefrontal regions (dorsal medial frontal gyrus and dorsal cingulate cortex) was correlated with greater cardiac acceleration (increase, decrease > maintain) and monotonic changes in EDA (increase > maintain > decrease). These data indicate that these two medial prefrontal regions are involved in the allocation of cognitive resources to regulate unpleasant emotion, and that they modulate emotional arousal in accordance with the regulatory goal. The emotional arousal effects were mediated by the right amygdala. Reappraisal-related activation in a third medial prefrontal region (subgenual anterior cingulate cortex) was not associated with similar patterns of change in any of the autonomic measures, thus highlighting regional specificity in the degree to which cognitive demand is reflected in medial prefrontal activation during reappraisal.

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**Keywords**

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Emotions are intense, short-lived changes in how we feel and in what the brain and body do in response to salient events. They interrupt ongoing behavior and engender the energy we need to make an appropriate behavioral response. Emotions that are too weak or too intense, or whose duration is too short or too long, may not be as effective in serving these functions. Being able to tailor our emotional states, therefore, provides one pathway by which humans avoid ill-being and attain high levels of well-being (John & Gross, 2004).

The ability to tailor our emotional states is known as emotion regulation, which has been defined as “the extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goals” (Thompson, 1994, p. 27-28). There are many ways of regulating our emotional responses, including situation selection, situation modification, attentional deployment, cognitive change, and response modulation (Gross & Thompson, 2007). We focus here on cognitive change, specifically cognitive reappraisal, which refers to reinterpreting events in such a way as to amplify or attenuate their emotional impact. Because of the potential importance of emotion regulation processes like reappraisal to psychological and physical health, there has been a recent push to better understand the brain and body correlates of this ability.

Mostly using functional magnetic resonance imaging (fMRI), neuroimaging studies have implicated lateral ventral, ventromedial, dorsomedial, and dorsolateral regions of prefrontal cortex (PFC) when using reappraisal to decrease (Banks et al., 2007; 2001; Bechara, 2004; Eippert et al., 2007; Goldin et al., 2008; Harenski & Hamann, 2006; Johnstone et al., 2007; Kalisch et al., 2006; Kim & Hamann, 2007; Levesque et al., 2003; Ochsner et al., 2002; Ochsner et al., 2004; Ohira et al., 2006; Phan et al., 2005; Urry et al., 2006; van Reekum et al., 2007; Wager et al., 2008) and increase (Eippert et al., 2007; Ochsner et al., 2004; Urry et al., 2006; van Reekum et al., 2007) negative emotion compared to a control condition. Because the negative emotion is being regulated in opposite directions, regions of PFC that show greater activation both when decreasing and increasing negative emotion compared to a control condition *may* belie the cognitive demand necessary to achieve this regulation. However, the simple presence of greater brain activation when using reappraisal to increase and decrease negative emotion compared to a control condition is by itself insufficient for concluding that the information processing taking place in that region reflects cognitive demand. Associations between these regions and validated measures of cognitive demand would provide converging evidence for this conclusion.

Most emotion researchers recognize that emotional responses involve changes not only in the brain, but also in autonomic physiology. In studies examining spontaneous reactions to unpleasant pictures, a typical pattern of physiological change involves increased electrodermal (sweat gland) activity (EDA), enlarged pupil diameters, and changes in cardiovascular activity (Bradley et al., 2008). Thus, reappraisal processes that are invoked to modulate emotional responses would be expected to modulate this pattern of autonomic physiology as well. However, the findings are mixed with respect to whether the autonomic physiological changes index emotional arousal or cognitive demand.

On the one hand, early work in this area demonstrated that providing denial or detachment commentaries with an unpleasant film clip reduces heart rate and EDA relative to passive

viewing of the clip (Lazarus & Alfert, 1964; Speisman et al., 1964). In addition, reappraisals focused on decreasing negative emotion reduce accelerative aspects of heart rate compared to a control condition (Kalisch et al., 2005). These results suggest that reappraisal-related changes in autonomic physiology index emotional arousal. On the other hand, other studies indicate that reappraisals focused on increasing (Johnstone et al., 2007; Urry et al., 2006; van Reekum et al., 2007) and decreasing (Johnstone et al., 2007; Urry et al., 2006; van Reekum et al., 2007) negative emotion potentiate pupil dilation compared to a control condition. Reappraisals focused on increasing (Sheppes et al., 2009) and decreasing (Eippert et al., 2007) negative emotion also potentiate EDA compared to a control condition. These studies collectively suggest that reappraisal-related changes in autonomic physiology might reflect the allocation of cognitive resources required to reappraise. More studies are needed that include two active reappraisal conditions and multiple indicators of autonomic physiology to better parse the contributions of emotional arousal and cognitive demand.

Medial prefrontal brain regions, which have been implicated in reappraisal as noted previously, are likely to be crucial in modulating patterns of autonomic physiology underlying emotion. Medial prefrontal regions project to both the hypothalamus and the periaqueductal gray (PAG) (Ongur & Price, 2000), thus providing a neuroanatomical basis for correspondence between medial prefrontal activation and autonomic responding. Moreover, functional links between ventral and dorsal medial prefrontal regions and physiology have also been documented. For instance, pharmacological blockade of ventromedial prefrontal cortex (VMPFC) attenuated cardiovascular responses (arterial blood pressure and heart rate) in rats re-exposed to a particular context, regardless of whether they had been conditioned to fear that context (Resstel et al., 2006). Consistent with this, in a study with humans, Critchley and colleagues (2000) reported that activation in ventromedial prefrontal and orbitofrontal regions covaried with amplitude of EDA in a decision-making task involving monetary rewards and punishments. In other human studies, activation in VMPFC has been shown to be inversely associated with heart rate (Gianaros et al., 2004; Wong et al., 2007) and electrodermal activity (Nagai et al., 2004).

With respect to dorsal medial prefrontal regions, Napadow and colleagues (2008) reported a positive association between dorsomedial prefrontal cortex activation and high frequency heart rate variability. A similar result was reported by Lane and colleagues (2001), who also showed a similar positive association in rostral anterior cingulate cortex. Finally, in a meta-analysis of human studies of emotion, Kober and colleagues (2008) recently demonstrated that activation in dorsomedial prefrontal cortex is often co-activated with the hypothalamus and that this co-activation is completely mediated by the PAG. These relations between medial prefrontal regions and autonomic physiology (or with regions known to influence autonomic physiology like the PAG) suggest that activation in medial prefrontal regions during reappraisal should be associated with changes in autonomic physiology.

Only a couple of studies have directly examined correlations between reappraisal-related neural activation and autonomic physiology. Using an individual-difference approach, Urry and colleagues (2006), for example, reported that participants exhibiting greater activation in the left superior and inferior frontal gyri when decreasing negative affect relative to a control condition exhibited larger pupil diameter, an index of cognitive demand (Kahneman & Beatty, 1966). By contrast, there was a trend for participants exhibiting lower activation in the amygdala when decreasing relative to a control condition to exhibit larger pupil diameters. Johnstone and colleagues (2007) reported the same inverse association between pupil diameter and amygdala activation in a non-depressed group. Such individual-difference correlations between frontal activation during reappraisal and pupil diameter support the idea that the information processing taking place in these frontal circuits reflects cognitive demand, or the allocation of cognitive resources required for reappraisal. Moreover, they highlight the role of

the amygdala in potentiating autonomic responses. Medial PFC regions exhibit interconnections with the amygdala, which sends efferent projections to regions like the hypothalamus and PAG that modulate autonomic activity (see review by Price, 2005). Finally, the correlation between activation in frontal circuits and pupil dilation suggests that down-regulation of the amygdala when decreasing negative emotion using reappraisal was most successful amongst people who allocated the most resources to the task. Recent work, however, indicates that pupil diameter may also track emotional arousal (Bradley et al., 2008). Thus, unfortunately, the use of only a single autonomic measure in these studies limits the specificity with which autonomic changes can be explained as the result of cognitive demands involved in reappraisal versus resulting changes in emotional arousal.

The aim of this study was to examine medial prefrontal-autonomic physiology associations as participants used reappraisal to regulate unpleasant emotion. Older people were recruited for this effort as part of an ongoing longitudinal study focused on determining whether regulation-induced changes in brain function predict health and well-being in subsequent longitudinal follow-ups. We recorded blood oxygenation level-dependent (BOLD) signal using fMRI and three separate measures of autonomic physiology (cardiac acceleration, pupil diameter, and EDA) while participants used cognitive reappraisal to increase, maintain, or decrease their responses to unpleasant photographs. The use of three different measures of autonomic physiology was expected to allow us to parse reappraisal effects reflecting changes in emotional arousal from those reflecting changes in cognitive demand.

Based on prior studies supporting their ability to index cognitive demand, we expected that both pupil diameter (Siegle et al., 2008) and cardiac acceleration (Backs, 1997) would show reappraisal-related activation (increase, decrease > maintain), thus demonstrating the cognitive demand associated with the *process* of reappraising. As an index of relatively pure sympathetic activation of the autonomic nervous system (Dawson, Schell, & Filion, 2007), we expected that EDA would show a monotonic pattern of decreasing activation across reappraisal conditions (increase > maintain > decrease), thus demonstrating the *outcome* of reappraisal on emotional arousal.

In addition to these patterns of change in autonomic physiology, we further expected that medial prefrontal regions would exhibit reappraisal-related activation (increase, decrease > maintain). Adopting an individual-difference perspective, we expected that variation in reappraisal-related activation in at least some of these medial prefrontal regions would be correlated with pupil diameter and cardiac acceleration, suggesting that the information processing taking place in these medial prefrontal regions reflects cognitive demand. We further expected that reappraisal-related activation in medial prefrontal regions would be correlated with monotonic change in EDA across reappraisal conditions (increase > maintain > decrease). This would suggest that the cognitive demand operations supported by medial prefrontal regions modulate the outcome of reappraisal (changes in emotional arousal) in accordance with the regulatory goal.

## Method

### Participants

The participants in this research were recruited from the Wisconsin Longitudinal Study (WLS), a longstanding effort to comprehensively describe the sociodemographic and psychological trajectories of approximately 10,000 men and women who were Wisconsin high school seniors in 1957 (see http://www.ssc.wisc.edu/~wls for more information). In a wave of data collection from 2003-2005, the original high school graduates completed a 1-hour telephone interview and a 48-page mail survey. A subset of 273 graduates randomly selected from the earliest replicates of respondents who had completed both the interview and mail surveys were invited

by letter to consider participating in an overnight study on the University of Wisconsin-Madison campus. Thirty people met entrance criteria, agreed to participate, stayed overnight in Madison and completed the MRI scan. Of the remaining 243 people receiving invitation letters, 138 declined to participate, 53 were ineligible, and 52 did not respond to our letters. The present sample is independent of both the WLS sample studied by Urry et al. (2006) and the sample of older people studied by van Reekum et al. (2007).

Our final analytic sample size was $n = 26$ (15 females) for the MR, pupil diameter, EDA, and subjective ratings data. Data from three participants (females) were excluded due to excessive movement during the scan, and from one participant (male) due to data acquisition error. For analyses involving IBI, $n = 25$ (14 females) because IBI data were not acquired for one female participant. Ages ranged from 64 – 66 years at the time of the scan with a mean age of 64.8 ($SD = 0.5$) years. Informed consent was obtained and the rights of participants were protected according to the procedures set forth by the UW-Madison Health Sciences Institutional Review Board. Participants received USD$70 for their participation in the MRI session.

Participants completed the Visual Paired Associates (VPA) and Visual Reproduction (VR)—both Immediate (I) and Delayed (II)—subtests of verbal and visual recall and recognition from the Wechsler Memory Scale-III (Pearson Education, San Antonio, TX). Mean performance on all subtests suggested intact cognitive abilities relative to age-appropriate norms (raw scores: VPA I recall $M = 19.69$, $SD = 6.94$, VPA II recall $M = 6.58$, $SD = 1.72$, VPA II recognition $M = 23.92$, $SD = .39$, VR I recall $M = 77.62$, $SD = 11.48$, VR II recall $M = 54.42$, $SD = 17.28$, VR II, recognition $M = 43.08$, $SD = 3.84$). In addition, participants reported no history of neurological issues or contraindications for MRI scanning (e.g., implanted cardiac or ferrous metal devices).

## Affect-Laden Picture Stimuli

During their scan session, participants viewed a set of 54 unpleasant digital color photographs from the International Affective Picture System (IAPS; for recent information about this set of stimuli, see Lang et al., 2008). Pictures were selected on the basis of IAPS normative data for all subjects, i.e., across men and women.[1] These unpleasant pictures were highly arousing, arousal $M = 6.05$, $SD = .77$, on a 1 to 9 scale where 9 signifies completely aroused, and highly unpleasant, valence $M = 2.13$, $SD = .47$, on a 1 to 9 scale where 9 signifies completely happy. Participants first viewed all pictures in a spontaneous emotion reactivity task (data not reported). The pictures were then presented a second time in an emotion regulation task in which participants were asked to modulate (increase, maintain, or decrease) their affective response using reappraisal.

## Reappraisal Task

Using a variant of the paradigm originally validated by Jackson and colleagues (2000), participants were trained to follow one of three situation-focused reappraisal instructions during each picture trial: *increase*, *decrease*, or *maintain*. The instruction to *increase*, presented via pneumatic headphones (Avotec, Inc., Stuart, FL), served as a cue to amplify the intensity of their negative emotion (participants heard the word “enhance”). For this task, participants were trained to imagine a worse outcome than the one depicted (e.g., in response to a picture of a ferocious dog, a participant might imagine that the dog's leash broke and so the dog is about to bite them). Conversely, the instruction to *decrease* signified the cue to reduce the

[1]The following pictures from the IAPS set, listed by catalog number, were used: 2053, 2205, 2800, 2900, 3000, 3030, 3051, 3053, 3060, 3061, 3062, 3064, 3080, 3100, 3102, 3130, 3150, 3160, 3168, 3170, 3181, 3220, 3230, 3261, 3266, 3300, 3301, 3350, 3400, 3530, 6200, 6213, 6230, 6300, 6313, 6350, 6560, 6570, 7380, 8230, 9040, 9180, 9253, 9300, 9320, 9405, 9421, 9561, 9611, 9630, 9800, 9810, 9910, and 9921.

intensity of their negative emotion, for which they were trained to imagine that the situation being depicted had a better outcome than the one suggested (e.g., victims of a car accident survived and healed well) (participants heard the word “suppress”). Alternatively, on *maintain* trials, participants were instructed to maintain their negative emotional experience by holding in mind their initial impression of the picture. Presentation of reappraisal goals was pseudorandomized such that all three conditions followed one another with equal frequency. Three different condition orders were generated, one for each scan run. Orders were counterbalanced across participants, and pictures were randomly assigned to these predetermined orders thus the picture order was unique for each participant.

## Trial Structure

The reappraisal task was presented in three blocks of 18 trials. As shown in Figure 1, at the beginning of each trial, a white fixation cross was presented in the center of a black screen for 1 second. The fixation cross was followed by presentation of a picture for 12 seconds. The reappraisal instruction (increase, maintain, or decrease) was delivered 4 seconds after picture onset, a design feature that provided time for unregulated affect to be elicited prior to applying voluntary regulatory strategies. Participants were instructed to continue following the task instruction until the picture was removed from the screen, a total of 8 seconds of active regulation. The picture was replaced by a black screen with a central white fixation dot which lasted from 5 – 10 seconds, thus reappraisal trials ranged in duration from 18 – 23 seconds.

## Procedures

Participants completed the laboratory portion of this experiment at the University of Wisconsin-Madison in two sessions separated by one day. At the first session, participants underwent a “mock” scan to become acclimated to the sights, sounds, and procedures of the scanning environment, and to train them to complete the reappraisal task using a standard set of instructions presented via an E-Prime stimulus presentation program (Psychology Software Tools, Pittsburgh, PA). Participants were positioned inside the bore of an inactive MRI scanner shell, complete with bed, head coil, response box, and goggles, so they could practice the task. Simulated scanner sounds and task instructions were piped through ear bud headphones. The practice blocks were succeeded by follow-up queries to determine whether participants were utilizing the strategies as instructed and to shape as necessary.

The actual MRI scan session occurred from 10:00am to 12:00pm on the morning following the mock session. Prior to completing the scan, the experimenter reviewed task instructions again to consolidate participant understanding of the reappraisal task. Next s/he affixed the skin conductance electrodes and positioned the participant inside the bore of the magnet. A vacuum pillow was used to stabilize head position, and goggles were arranged to permit clear viewing of the visual stimuli and measurement of pupil diameter. The pulse oximetry sensor and skin conductance electrodes were connected, and eye tracking/pupil calibration was then performed. FMRI data were collected as participants first completed an emotion reactivity task (data not reported) and then as they completed the reappraisal task, again presented via E-Prime. Subjective ratings of difficulty, effort, and success were collected at the end of each functional run. Anatomical images were collected after the functional runs.

## Autonomic Physiology

**Electrodermal Activity—**Two Ag/AgCl electrodes (8 mm) filled with isotonic paste were attached to the distal phalanges of the index and middle fingers on the left hand. Electrodermal activity (EDA) was acquired at a sampling rate of 500 Hz using an isolated coupler (Coulbourn Instruments, Allentown, PA) with DC coupling and constant voltage electrode excitation (sensitivity = 1K). The data were downsampled to 20 Hz offline, averaged across trials within each condition in 1-s time bins, and linearly detrended for each participant by trial block (24

trials for the regulation task). Regulation-related change in EDA was captured by subtracting EDA during the 4-s picture period from each of eight 1-s time bins following delivery of the reappraisal instruction. An area-under-the-curve index of EDA was computed by summing across all time points within each of three time intervals, early, middle, and late, as described below for the pupil diameter measure.

Because we averaged EDA across all trials within conditions (within 1-s time bins), including trials for which there was no measurable discrete response, our index of EDA activity is a measure of magnitude. As noted by Dawson, Schell, and Filion (2007), "A magnitude measure can create the impression that the response size is changing when, in fact, it is response frequency that is changing" (p. 165). As a result, some advocate using a measure of EDA amplitude, i.e., mean EDA for each condition based only on those trials on which a measurable response occurred. EDA amplitude measures have the advantage of providing information about response size that is unconfounded with response frequency. However, they result in variation across people in the number of trials that contribute to the average in each condition. Moreover, participants with no discrete responses would be eliminated altogether. In the present study, we therefore supplemented our EDA magnitude measure with a measure of the number of skin conductance responses (SCR) in each condition. SCRs were defined as a deflection of at least 0.03 μS occurring from 1 – 3 seconds after stimulus onset. Number of SCRs for each reappraisal goal was then entered as covariates in a multivariate GLM computed to assess the effects of reappraisal goal (increase, maintain, decrease) and time (early [1-2 s post-instruction average], middle [3-5 s post-instruction], and late [6-8 s post-instruction]) on EDA magnitude.

**Interbeat Interval—**Pulse oximetry was acquired continuously at 500 Hz with a photoplethysmogram transducer attached to the third finger of the nondominant hand. Estimates of the time elapsed between successive heart beats (i.e., interbeat interval [IBI]) were determined for each participant for each condition. Second by second estimates of IBI were calculated using a weighted average of measured IBIs that fell at least partially within each one-second window, with weights for each measured interval based upon the proportion of that interval falling within the one-second window (cf., Hugdahl, 1995). Reappraisal-related change in IBI was captured by subtracting IBI during the 4-s picture period from each of eight 1-s time bins following delivery of the reappraisal instruction. Analyses focused on rate of change in IBI, which was computed by calculating the slope of change in IBI for each condition for each participant, with smaller (more negative) values indicating cardiac acceleration. A multivariate General Linear Model (GLM) was computed to assess the effect of reappraisal goal (increase, maintain, decrease) on mean change in IBI slope.

**Pupil Diameter—**Pupil diameter was acquired continuously during the scan session (sampling rate = 60 Hz) using an iView X system (v. 1.3.31) with a remote eye-tracking device (SensoMotoric Instruments, Teltow, Germany) interfaced with the fiber optic goggle system (Avotec, Inc., Stuart, FL). The pupil dilation data were cleaned and processed using Matlab (The Mathworks, Inc., Natick, MA) algorithms designed by Siegle, Granholm, & Steinhauer (2002, unpublished Matlab code) that were adapted for use in the Davidson laboratory (L.L. Greischar, 2003, unpublished Matlab code). Blinks were identified and eliminated using local regression slopes and amplitude thresholds. Missing data points were then estimated using linear interpolation. A 5-sample rolling average was calculated to smooth the signal, and slow, irrelevant drifts in the pupil diameter data over the course of the scan session were removed via linear detrending over blocks of 24 trials. As with the fMRI data, trials requiring more than 50% interpolation during the picture presentation period, suggesting suboptimal viewing of the picture, were eliminated. Pupil diameter was aggregated into 500-ms bins, then range-corrected within subjects [(current pupil diameter- minimum pupil diameter) ÷ (maximum pupil diameter -minimum pupil diameter)], and then aggregated within conditions across trials.

Change in pupil diameter was calculated by subtracting mean diameter for the 500 ms bin immediately prior to the reappraisal instruction from the 500-ms mean pupil diameter bins following instruction until picture offset (a total of 8 seconds) within each condition. A multivariate GLM was computed to assess the effect of reappraisal goal and time (early [0.5-3.0 s post-instruction average], middle [3.5-5.5 s post-instruction], and late [6.0-8.0 s post-instruction]) on pupil diameter.

## MRI Data Acquisition and Reduction

**Image Acquisition—**Whole brain functional and anatomical images were acquired using a 3.0 Tesla GE Signa MRI scanner (GE Medical Systems, Waukesha, WI) with LX software (version VH2), a transmit-receive quadrature birdcage coil, and Nvi (40 mT/m; slew rate = 150 mT/m/ms) gradients. Functional images were acquired using a T2*-weighted gradient-echo echo-planar imaging (EPI) pulse sequence with 30 4-mm sagittal slices (interslice gap = 1 mm; TE = 30.0 ms; TR = 2000.0 ms; flip angle = 60°; FOV = 240 × 240 mm; 64 × 64 data acquisition matrix). High resolution 3D T1-weighted inversion recovery fast gradient echo anatomical images were collected in 124 contiguous 1.2-mm axial slices (TE = 1.8 ms; TR = 8.9 ms; flip angle = 10°; FOV = 240 mm; 256 × 256 data acquisition matrix) thus enabling localization of functional effects.

**Image Preprocessing—**The functional MRI data were processed using the Analysis of Functional NeuroImages (AFNI) suite of image analysis routines (Cox, 1996). During offline reconstruction, the first 5 whole-brain images were discarded from each of five scan runs to ensure steady-state magnetization. Because ventral locations are subject to susceptibility-related signal dropout, we limited our single subject time series analyses to voxels meeting a signal threshold of at least ~1% of the whole-brain maximum signal value for the last time point. The raw EPI data were converted to AFNI format with correction for slice timing differences due to interleaved acquisition. Using six rigid body motion parameters, each time point was then registered to the one closest in time to collection of our anatomical images. We applied a high-pass filter (0.02 Hz) to remove slow drift in the signal over time.

**Single-Subject Analyses—**The three regulation scan runs were concatenated into one data set for each participant. Single-subject General Linear Models (GLMs) using full deconvolution (B.D. Ward, *Deconvolution Analysis of MRI time Series Data*, http://afni.nimh.nih.gov/afni) were then performed to estimate the shape of the hemodynamic response for the conditions of interest. To account for motion-related change in BOLD signal, we also modeled six motion predictors obtained during volume registration. Trials containing time points where motion estimates exceeded 2 mm or exhibited shifts from one time point to the next that exceeded 0.5 mm were eliminated (0.2% of all time points). Trials for which the pupil diameter data were missing for more than 50% of the total trial length, likely indicating suboptimal viewing of the picture, were also eliminated (an additional 3% of all time points). BOLD signal estimates were expressed as % signal change (100 * estimated response amplitude / baseline). An area-under-the-curve (AUC) metric was then calculated by summing estimates of % signal change chosen to correspond to the period of peak response (6 to 17 seconds post picture onset). The AUC metric has the benefit of capturing the peak of the estimated hemodynamic response even if the peak of the response varies temporally as a function of brain region and/or condition. Additionally, it eliminates variation in the hemodynamic response that occurs with the rise and fall of the response. AUC images were transformed into Talairach space and resampled to 2 $mm^3$. AUC estimates were spatially blurred with a 5-mm FWHM Gaussian filter to allow for variability across subjects in brain anatomy.

**Groupwise Analyses—**Voxelwise repeated measures ANOVAs ($n$ = 26) were performed to identify regions exhibiting a main effect of reappraisal goal (increase, maintain, decrease) with subjects modeled as random effects. Statistically-defined clusters of activation were identified using Monte Carlo simulations (AFNI's AlphaSim program) to achieve a corrected cluster threshold of $p < 0.05$. For each statistically-defined cluster, mean AUC estimates across all voxels were extracted for each subject for follow-up analyses in SPSS (SPSS, Inc., Chicago, IL). Mean AUC estimates were also extracted for each subject from left and right amygdala regions-of-interest defined using the Talairach Daemon (Lancaster et al., 2000). Groupwise functional effects were superimposed on a high resolution T1 anatomical image, averaged across the 26 participants, for localization purposes.

To answer our focused question about associations between medial prefrontal regions and autonomic physiology, we concentrated on three functionally-defined medial prefrontal regions of interest (ROI) that demonstrated a quadratic pattern of activation (increase, decrease > maintain) in the analyses described above. These regions are depicted in Figure 3 as follows: dorsal medial frontal gyrus (BA 6; shown as cluster #9), dorsal cingulate cortex (cluster #4), and subgenual anterior cingulate cortex (BA 25; sACC, cluster #5). From each of these three functionally-defined clusters, we extracted mean estimates of BOLD signal across all voxels and then submitted these estimates to multiple regression analyses in SPSS to examine the relation between brain activation and autonomic responses. The full results of the voxelwise ANOVAs are reported and discussed in the Supplementary Material.

## Results

### Overview of Results

We begin by presenting the effects of reappraisal goal on autonomic physiology. One goal of these analyses was to determine whether EDA would exhibit a monotonic pattern of reappraisal effects (increase > maintain > decrease), signifying an effect of emotional arousal. A second goal was to determine if pupil diameter and cardiac acceleration would each exhibit greater reappraisal-related activation (increase, decrease > maintain), signifying an effect of cognitive demand. We then report individual-difference regression analyses to reveal associations between BOLD signal extracted from functionally-defined medial prefrontal regions and autonomic physiology.

To keep this report focused on the main question of brain-physiology associations, we report the following additional information as Supplementary Material: 1) the effects of reappraisal goal on BOLD signal as measured using fMRI, findings that replicate previous studies; 2) the effects of reappraisal goal on ratings of difficulty, resource allocation, and success; and 3) the effects of reappraisal goal on gaze duration as measured using eye tracking.

### Effects of Reappraisal on Autonomic Physiology

Figure 2 depicts change in EDA (panel a), pupil diameter (panel b), and IBI (panel c) over time following delivery of increase, maintain, and decrease instructions on negative picture trials across all participants. Panel d presents the IBI slopes as a bar graph. The IBI slopes are also overlaid as dotted trend lines in the IBI peristimulus plots in panel c.

**Emotional Arousal—**EDA exhibited a monotonic pattern of change (increase > maintain > decrease), with significant differences between the increase and maintain, and the maintain and decrease conditions. This was revealed through significant interactions between reappraisal goal, time, and SCR frequency in the increase, maintain, and decrease conditions (which were entered as covariates), all $p$s < .05 (see footnote for F statistics).[2] The significant interactions were decomposed with simple main effects of reappraisal goal at each of the three

time points, all *p*s < .05. During the middle, *M* = 0.44, *SE* = .13, and late, *M* = 0.35, *SE* = .18, time points, increasing negative emotion led to higher EDA compared to maintaining, *M* = 0.12, *SE* = .10, *p* = .007 and *M* = -0.09, *SE* = .14, *p* = .021, respectively. During the early, *M* = 0.03, *SE* = .04, and middle, *M* = -0.09, *SE* = .08, time points, decreasing negative emotion led to lower EDA compared to maintaining, *M* = 0.13, *SE* = .04, *p* = .044, and *M* = 0.12, *SE* = .10, *p* = .061, respectively.

**Cognitive Demand—**IBI slope and pupil diameter exhibited reappraisal-related effects (increase, decrease > maintain), with significant differences between the increase and maintain, and between the decrease and maintain conditions.

For IBI slope, a main effect of reappraisal goal, $F(2,23) = 8.80$, $p = .001$, $\eta_P^2 = .43$, revealed more negative IBI slopes (faster cardiac acceleration) for increasing negative emotion, *M* = -2.89, *SE* = .60, compared to maintaining, *M* = -0.70, *SE* = .42, *p* < .001. More negative IBI slopes (faster cardiac acceleration) were also evident for decreasing negative emotion, *M* = -2.37, *SE* = .57, compared to maintaining, *p* = .010. Increasing and decreasing displayed similar acceleration, *p* = .287.

For pupil diameter, the significant interaction between reappraisal goal and time, $F(4,22) = 4.89$, $p = .006$, $\eta_P^2 = .47$, was decomposed with simple main effects analyses of reappraisal goal at each time interval. These were significant at the middle and late intervals, *p*s < .05, when increasing negative emotion, *M* = 0.07, *SE* = 0.01, and *M* = 0.07, *SE* = 0.01, resulted in larger pupil diameter compared to maintaining, *M* = 0.03, *SE* = 0.01, *p* = 0.003 and *M* = 0.03, *SE* = 0.01, *p* = 0.001, respectively. Decreasing negative emotion, *M* = 0.06, *SE* = 0.01 and *M* = 0.05, *SE* = 0.01, respectively, resulted in larger pupil diameter compared to maintaining at the middle, *p* = 0.046, and late, *p* = 0.041, time intervals too. There was no difference between increasing and decreasing negative emotion, both *p*s > .05.

From the above results for autonomic physiology, we conclude that reappraisals produced monotonic changes in emotional arousal, as evidenced by EDA, and that increase and decrease reappraisals exacted greater cognitive demand than maintain appraisals, as evidenced by the IBI slope and pupil diameter measures.

## Linear and Quadratic Contrast Scores for Autonomic Physiology

For later use in regression analyses, linear and quadratic contrast scores (also known as L-scores) were calculated for each participant according to the method described by Rosenthal, Rosnow, and Rubin (2000).

Linear contrast scores were of interest for EDA in light of the monotonic pattern reported above across reappraisal conditions (increase > maintain > decrease). Linear contrast scores were calculated across time intervals by multiplying each participant's mean EDA score for the increase and decrease conditions by +1 and -1, respectively, while the mean EDA score for the maintain condition was multiplied by 0. As expected given the pattern described above, the linear contrast for EDA was significant across all participants, $t(25) = 2.58$, $p = .016$ (test value = 0).

Quadratic contrast scores were of interest for IBI slope and pupil diameter given the reappraisal-related pattern of activation (increase, decrease > maintain). For IBI slope and pupil diameter,

[2]F statistics for the interactions between reappraisal, time, and SCR frequency for the three reappraisal conditions are as follows: increase SCR frequency $F(2,21) = 12.28$, $p < .001$, $\eta_P^2 = .54$, maintain SCR frequency $F(2,21) = 16.57$, $p < .001$, $\eta_P^2 = .61$, and decrease SCR frequency $F(2,21) = 9.10$, $p = .001$, $\eta_P^2 = .46$. Without including these SCR frequency covariates, the reappraisal main effect was borderline significant, $p = .055$, and the reappraisal by time interaction was not significant, $p = .104$.

quadratic contrast scores were calculated by multiplying each participant's mean scores for the increase and decrease conditions by +1 (-1 for IBI slope since smaller numbers indicate greater activation), while the mean score for the maintain condition was multiplied by -2 (+2 for IBI slope). As expected given the pattern described above, the quadratic contrasts for IBI slope and pupil diameter were significant across all participants, $t(24) = 3.82$, $p = .001$ and $t(25) = 2.98$, $p = .006$, respectively.

## Individual Differences in Neural Activation and Autonomic Physiology

**Cognitive Demand—**We expected that reappraisal-related activation in functionally-defined medial prefrontal regions (increase, decrease > maintain) would be associated with pupil diameter and IBI slope, thus suggesting that the information processing taking place in those regions signifies greater cognitive demand.

As described above for the IBI slope and pupil diameter measures, we calculated a quadratic contrast score for the medial prefrontal regions referenced earlier (see Figure 3), all three of which exhibited reappraisal-related activation (increase, decrease > maintain) in tests of the reappraisal main effect. For each participant for each medial prefrontal region, mean BOLD signal estimates for the increase and decrease conditions were both multiplied by +1 while mean BOLD signal estimates for the maintain condition were multiplied by -2.

These quadratic contrast scores were used as criterion variables in a series of multiple regressions in which the quadratic contrast scores for IBI slope and pupil diameter were entered as predictors. Positive associations between quadratic contrast scores for IBI slope and/or pupil diameter and quadratic contrast scores for medial prefrontal activation would suggest that greater reappraisal-related neural activation is associated with greater cognitive demand.

In the first regression, IBI slope and pupil diameter quadratic contrast scores as a set explained 40% of the variance in dorsal cingulate activation, $F(2,22) = 7.42$, $p = .003$. The standardized regression coefficient for IBI slope was positive and significant, $\beta = .63$, $t(22) = 3.84$, $p = .001$, indicating that participants producing greater cardiac acceleration during the reappraisal period exhibited greater activation in dorsal cingulate. The standardized regression coefficient for the pupil diameter contrast score was not significant, $\beta = .10$, $t(22) = 0.60$, $p = .553$.

In the second regression, IBI slope and pupil diameter quadratic contrast scores as a set explained 25% of the variance in dorsal medial frontal gyrus activation, $F(2,22) = 3.65$, $p = .043$. The standardized regression coefficient for IBI slope was positive and significant, $\beta = .45$, $t(22) = 2.41$, $p = .025$, indicating that participants producing greater cardiac acceleration during the reappraisal period exhibited greater activation in dorsal medial frontal gyrus. The standardized regression coefficient for the pupil diameter contrast score was not significant, $\beta = .19$, $t(22) = 1.05$, $p = .306$.

In the third regression, IBI slope and pupil diameter contrast scores as a set did not explain significant variance in sACC activation, $F(2,22) = .65$, $p = .534$, $R^2 = .06$. Moreover, neither of the standardized regression coefficients were significant, $\beta = .21$, $t(22) = 1.00$, $p = .327$ and $\beta = -.13$, $t(22) = -.61$, $p = .551$, respectively.

As a whole, this pattern of regression results suggests that the information processing taking place in dorsal cingulate and medial frontal gyri (but not in sACC) reflects cognitive demand, as indexed by IBI slope.

**Emotional Arousal—**We expected that reappraisal-related activation in medial prefrontal regions (increase, decrease > maintain) would be associated with monotonic change in EDA across reappraisal conditions (increase > maintain > decrease). We computed a set of three

bivariate regression analyses that paralleled those reported above, one each with the quadratic contrast score for dorsal cingulate cortex, dorsal medial frontal gyrus, or sACC serving as the criterion variable. This time, however, the predictor in each analysis was the linear contrast score for EDA. Positive associations between linear contrast scores for EDA and quadratic contrast scores for medial prefrontal activation would suggest that greater neural activation is associated with modulation of emotional arousal in accordance with regulatory goals.

In the first regression, the linear EDA contrast score explained 23% of the variance in dorsal cingulate cortex activation, $F(1,24) = 7.28$, $p = .013$. The standardized regression coefficient was positive, $\beta = .48$, indicating that participants producing a stronger monotonic pattern of EDA (increase > maintain > decrease) exhibited greater activation in dorsal cingulate.

In the second regression, the linear EDA contrast score explained 17% of the variance in dorsal medial frontal gyrus activation, $F(1,24) = 4.87$, $p = .037$. The standardized regression coefficient was positive, $\beta = .41$, indicating that participants producing a stronger monotonic pattern of EDA (increase > maintain > decrease) exhibited greater activation in dorsal medial frontal gyrus.

In the third regression, the linear EDA contrast score did not explain significant variance in quadratic activation in the sACC, $\beta = .29$, $F(1,24) = 2.19$, $p = .152$, $R^2 = .08$.

As a whole, this pattern of regression results suggests that the information processing taking place in dorsal cingulate gyrus and dorsal medial frontal gyrus (but not in sACC) modulates emotional arousal in accordance with regulatory goal.

## Resolving Ambiguity in MPFC Information Processing

Activation in the dorsal medial frontal and cingulate gyrus regions is correlated with physiological indicators of both cognitive demand (quadratic contrast score for IBI slope) *and* emotional arousal (linear contrast score for EDA). This overlap of associations prompts an important question: How should we understand the information processing taking place in dorsal medial frontal and cingulate gyri? We took two tactics to resolve this interpretive ambiguity.

First, in a follow-up set of two regression analyses, we entered EDA and IBI slope as simultaneous predictors of dorsal MFG and dorsal cingulate activation. In both cases, the IBI slope quadratic contrast score predicted unique activation, $\beta = .52$, $p = .008$ and $\beta = .34$, $p = .073$ (one-tailed), respectively, but the linear contrast score for EDA did not, $\beta = .19$, $p = .167$ and $\beta = .22$, $p = .164$ (one-tailed), respectively. These results suggest that the information processing taking place in these medial prefrontal regions uniquely reflected the cognitive demand associated with implementing reappraisals.

Second, we assessed whether the correlation between medial prefrontal activation and emotional arousal is mediated by another brain region. Given the literature reviewed in the introduction, we tested whether monotonic change in the amygdala, as indexed by the linear contrast score (increase > maintain > decrease), served this role. We computed two simple mediation analyses using a product-of-coefficients strategy (Preacher & Hayes, 2008), as implemented in the SPSS macro command set written by A. F. Hayes (version 3, May 16, 2007, retrieved from http://www.comm.ohio-state.edu/ahayes/SPSS%20programs/indirect.htm on September 9, 2008). In brief, this analysis provides estimates of the effect of an independent variable on a mediator (*a*), the effect of a mediator on a dependent variable (*b*), the direct effect of an independent variable on a dependent variable (*c'*), and of the indirect effect of an independent variable on a dependent variable by way of a mediator (*ab*).

The first mediation analysis revealed a significant indirect effect of dorsal medial frontal gyrus on EDA by way of the right amygdala, *ab* = .04, *SE* = .02, *Z* = 1.92, *p* = .027 (one-tailed). Higher activation in dorsal medial frontal gyrus was associated with higher linear contrast scores in the right amygdala, *a* = .34, *SE* = .14, *t*(23) = 2.42, *p* = .012 (one-tailed). In turn, higher linear contrast scores in the right amygdala were associated with higher linear contrast scores for EDA, *b* = .13, *SE* = .04, *t*(23) = 2.95, *p* = .004 (one-tailed). Importantly, the direct pathway between dorsal MFG and EDA was not significant, *c′* = .03, *SE* = .03, *t*(23) = .97, *p* = .172 (one-tailed), thus this association was fully mediated by the right amygdala.

Similarly, the second mediation analysis revealed a significant indirect effect of dorsal cingulate on EDA by way of the right amygdala, *ab* = .04, *SE* = .02, *Z* = 1.66, *p* = .048 (one-tailed). Higher activation in dorsal cingulate was associated with higher linear contrast scores in the right amygdala, *a* = .32, *SE* = .17, *t*(23) = 1.92, *p* = .034 (one-tailed). In turn, higher linear contrast scores in the right amygdala were associated with higher linear contrast scores for EDA, *b* = .12, *SE* = .04, *t*(23) = 3.02, *p* = .003 (one-tailed). In this case, the direct pathway between dorsal cingulate and EDA was still significant, *c′* = .06, *SE* = .03, *t*(23) = 1.81, *p* = .042 (one-tailed), thus this association was partially mediated by the right amygdala.

## Discussion

In this study, we used individual-difference associations between medial prefrontal regions and autonomic physiology to make inferences about the nature and consequences of the information processing taking place in those medial prefrontal regions. Here we moved beyond the basic question of which brain regions control which physiological responses. Instead, we used the brain-physiology associations to understand one important psychological process, voluntary emotion regulation. We focused on reappraisal, a cognitive change strategy for regulating emotion that involves changing one's interpretation of a situation in order to modulate its emotional impact. A pattern of neural activation in which reappraisals generated to increase and decrease negative emotion lead to greater activation compared to a control condition (e.g., attend or maintain) might indicate the involvement of those regions in the cognitive demand associated with generating and implementing reappraisals. This report uses multiple indicators of autonomic physiology to contribute the novel observation that this may be true for some (dorsal cingulate cortex, dorsal medial frontal gyrus) but not all (subgenual anterior cingulate cortex) medial prefrontal regions. We discuss our results further below.

### Autonomic changes during reappraisal

We asked whether reappraisals used to increase, maintain, or decrease negative emotion would impact autonomic physiology, as indexed by EDA, cardiac acceleration (IBI slope), and pupil diameter. We used multiple measures of autonomic physiology because these measures can reflect distinct processes (emotional arousal versus cognitive demand), which might be differentially affected by the act of reappraising. We reasoned that pupil diameter and IBI slope measures of autonomic physiology would be maximal during the two active reappraisal conditions compared to the maintain control condition (increase, decrease > maintain), signifying changes in cognitive demand. By contrast, we reasoned that successful reappraisal would yield a monotonic pattern of decreases in EDA (increase > maintain > decrease), signifying changes in emotional arousal.

As we have shown previously (Johnstone et al., 2007; Urry et al., 2006; van Reekum et al., 2007), pupil diameters were larger when both increasing and decreasing negative emotion relative to the maintain control condition. Pupil diameters grow larger when attentional or memory resources are being allocated, or when exposed to difficult material (Siegle et al., 2008). While pupil dilation has also been associated with emotional arousal (Bradley et al., 2008; Partala & Surakka, 2003), there is some indication that the effects of cognitive demand

on pupil dilation take precedence over effects of emotional arousal (Stanners et al., 1979). Moreover, if pupil diameter were sensitive to emotional arousal in this context, we would have expected to see smaller rather than larger pupils when decreasing negative emotion. Our findings are therefore consistent with the idea that both types of reappraisals require greater demands on processing resources than maintaining, and this occurs regardless of whether the emotional response is altered to be experienced as more versus less negative.

The pattern of reappraisal-related change in pupil diameter was mirrored with the IBI slope data, for which cardiac acceleration was more pronounced when increasing and decreasing negative emotion compared to maintaining. In response to unpleasant images, it is typical for the heart to exhibit an initial deceleration, which is thought to represent attentional orienting (Bradley & Lang, 2007). Such an initial deceleration was evident across all three reappraisal conditions for approximately the first two seconds, as shown in Figure 2b. After that, reappraisals focused on increasing and decreasing negative emotion both led to cardiac acceleration. Backs (1997) proposed that phasic cardiac acceleration indexes effort and is sensitive to attentional allocation. Moreover, Bradley and Lang (2007) proposed that cardiac acceleration reflects somatic activity that prepares the body for action, at least in laboratory paradigms involving imagery. These observations are consistent with the idea that somatic preparation for action was a consequence of engaging in the thought processes that transformed unpleasant emotion to be more or less intense in this effortful reappraisal task.

We also observed that, relative to maintaining, increasing negative emotion produced higher EDA levels while decreasing produced lower EDA levels, a monotonic pattern of mean differences. In the GLM analyses, these differences were more apparent when we treated the frequency of discrete SCRs in each condition as covariates in the analysis. Previous studies mostly reported EDA levels without taking into account frequency of SCRs, thus this may be one reason for the failure to observe significant differences in those studies. That EDA was lower for decreasing than maintaining makes sense if using reappraisal to decrease emotional responses reduces the arousal component of those responses, which is consistent with early appraisal studies by Lazarus and colleagues. Interestingly, a recent study showed that EDA and pupil diameter both exhibit increased activity in response to emotionally-arousing pleasant and unpleasant pictures relative to neutral pictures (Bradley et al., 2008). Thus, the fact that EDA was lower and pupil dilation higher when decreasing compared to maintaining indicates that EDA and pupil dilation can reflect different processes in this particular reappraisal task (emotional arousal versus cognitive demand, respectively), but this may be context-dependent.

### Brain-autonomic physiology associations

Using an individual-difference approach, we found that neural activation when using reappraisal to regulate unpleasant emotion was associated with autonomic physiology. Specifically, people exhibiting greater cardiac acceleration when increasing and decreasing negative emotion relative to maintaining were more apt to exhibit reappraisal-related activation in dorsal medial frontal gyrus and dorsal cingulate gyrus. In addition, people exhibiting greater EDA when increasing and lower EDA when decreasing relative to maintaining were also more apt to exhibit reappraisal-related activation in dorsal medial frontal gyrus and dorsal cingulate gyrus.

These two sets of associations imposed interpretive ambiguity, leading us to puzzle over how to understand the information processing taking place in dorsal medial frontal and cingulate gyri when activation in these regions is correlated with physiological indicators of both cognitive demand *and* emotional arousal. Using regression analyses, we demonstrated that the physiological indicator of cognitive demand and not emotional arousal explained unique variance in these medial prefrontal regions. Moreover, using mediation analyses, we demonstrated that the correlations we observed between these regions and emotional arousal

were fully (dorsal medial frontal gyrus) or partially (dorsal cingulate gyrus) mediated by the right amygdala. Collectively, these analyses resolved the ambiguity and suggested a simple framework, as shown in Figure 4.

We propose that reappraisal-related activation in these medial prefrontal regions (increase, decrease > maintain) carries out information processing reflecting the cognitive demand involved in reappraisal. This medial prefrontal activation leads to monotonic change in the right amygdala, which monitors the need for energy mobilization due to changes in motivational state. Amygdala changes then facilitate sympathetic nervous system (SNS) output, signifying changes in emotional arousal that accord with the regulatory goal. It is important to note that although the pattern described above is consistent with a top-down process, the correlational nature of these associations and the bidirectional anatomical connectivity necessarily precludes such causal inference. In addition, this simple framework is not meant to suggest that the right amygdala has an exclusive mediating role. Rather, this is the only mediated relationship we tested. It is quite possible, and even likely, that other regions are contributing to correlation between dorsal medial prefrontal regions and emotional arousal. The periaqueductal gray (PAG) in the brainstem is one candidate region which is well-connected with medial prefrontal regions, as noted in the introduction. Interestingly, the left amygdala did not show the same pattern of mediation (data not shown). The reason for this hemispheric asymmetry is unclear.

Notably, only cardiac acceleration and not the pupil diameter measure explained unique variance in the individual-difference associations we observed between dorsal medial frontal gyrus and dorsal cingulate cortex and autonomic physiology. In keeping with the idea that cardiac acceleration reflects effort and somatic activity that prepares the body for action, this suggests that the information processing taking place in those two medial prefrontal regions reflected action preparatory aspects of cognitive demand. As highlighted by Critchley, Tang, Glaser, Butterworth and Dolan (2005), different sections of the medial PFC, particularly around the ACC, are associated with separate aspects of autonomic arousal. According to this view, dorsal ACC regions are more associated with cardiovascular arousal, which is consistent with the pattern described here.

A meta-analysis by Seitz and colleagues (2006) implicates these regions in attention to action and sensation, movement preparation, and self-referencing of action, processes these authors link to empathy. Dorsal cingulate cortex is also implicated in interference resolution during response selection as measured in tasks like the Stroop and flanker interference tasks (Nee et al., 2007), while the posterior medial prefrontal cortex, including dorsal medial frontal gyrus, is also associated with signaling a need to make adjustments in the face of errors (Klein et al., 2007). All of these processes are likely to be relevant to generating, implementing, and monitoring the success of reappraisals, and the associated pattern of autonomic activation supports the resource-intensive nature of these processes.

### What should we make of sACC activation in this study?

Reappraisal-related sACC activation was not correlated with autonomic physiology in the same way as the dorsal medial frontal and dorsal cingulate gyrus regions described above. This hints that this particular sACC region may reflect neither the cognitive demand associated with reappraising nor the modulation of emotional arousal. However, our measures of cognitive demand and emotional arousal are physiological. It remains possible that sACC reflects cognitive demand and emotional arousal processes that do not have physiological correlates. Moreover, we focused on a targeted quadratic contrast of activation in sACC (increase, decrease > maintain) and a linear contrast of EDA (increase > maintain > decrease). There may be cognitive demand and/or emotional arousal information processing taking place in sACC which is not captured by these contrasts of *a priori* interest.

Aside from cognitive demand or emotional arousal, what other types of information processing might be taking place in sACC during reappraisal? Kross, Davidson, Weber, and Ochsner (2009) recently found that sACC was more active in a condition in which participants were asked to focus on the feelings associated with an unpleasant autobiographical experience relative to a condition in which they were asked to accept their feelings. Reappraisal-related sACC activation might therefore signify that the increase and decrease reappraisal conditions involve self-relevant processing or concentration on one's feeling state to a greater degree than the maintain condition. This interpretation has important clinical implications for the treatment of mood disorders, which are associated with abnormal sACC volumes and functional activity (see review by Drevets & Savitz, 2008). Mayberg and her colleagues (Lozano et al., 2008; Mayberg et al., 2005) have reported, for example, that deep brain stimulation of subgenual anterior cingulate successfully ameliorates treatment-resistant depression. It is worth noting here, however, that the sACC region in this study is ventral to the location targeted by Mayberg and colleagues for deep brain stimulation. Nevertheless, from the standpoint of psychotherapeutic treatments, our findings suggest that people diagnosed with mood disorders who exhibit abnormal functioning in the region of sACC highlighted herein might respond best to psychotherapies that specifically target self-relevant processing and attention to feeling states. Future research is needed to directly address this possibility.

Finally, Kross, Davidson, Weber, and Ochsner (2009) reported that the sACC difference noted between focusing on and accepting feelings in their study was correlated with greater increases in reported negative emotion. Such findings are consistent with a study in which activity in this region, measured using positron emission tomography, was shown to be positively correlated with reports of negative affect (Zald et al., 2002). One might be tempted to conclude, then, that the pattern shown in the present study, in which increasing and decreasing negative emotion produced greater sACC activation than maintaining signifies *greater* rather than *reduced* negative emotional experience when decreasing. However, EDA magnitude was lower rather than higher when decreasing, a reduction in sympathetically-mediated emotional arousal that is inconsistent with greater negative emotional experience.

### Using pictures to induce emotion

Although pictures reliably elicit emotions in predictable and potent ways, it is likely that these emotional states are different in important ways from emotional states emerging from situations with clear personal relevance. Moreover using pictures to prompt emotion enables an alternative emotion regulation strategy for regulating emotional responses: Attentional deployment towards or away from the emotionally-salient aspects of a picture. As we have documented (van Reekum et al., 2007), substantial variance in reappraisal-related brain function may be explained by an attentional deployment strategy, as measured using eye tracking to quantify gaze behavior. Indeed, as reported by Xing and Isaacowitz (2006), when asked to manage their emotional states, participants spend less time looking at unpleasant images compared to a condition in which they are given no such management instructions. In addition, attending to emotional versus neutral information has been shown in previous work to influence electrophysiological indices of emotional arousal (Dunning & Hajcak, 2009; Hajcak et al., in press) and subjective mood states (See et al., 2009; MacLeod et al., 2002).

Interestingly, older people have been shown to direct their attention more to positive than negative emotional information (Isaacowitz et al., 2006). Here the older age of the present sample is of clear relevance. Indeed, as described in the Supplementary Material, we found that time spent looking at the emotional areas of these negative pictures declined over time when our older participants used decrease reappraisals, but not when participants used increase or maintain reappraisals. Importantly, this difference in visual attentional deployment did not explain the reappraisal effects in BOLD responses we observed in this study. Nevertheless, as

discussed in depth in the Supplementary Material by Urry et al. (2006), there may indeed be age-related changes in the neural and autonomic correlates of emotion regulation (see, e.g., Phillips et al., 2008). It would be of great interest to compare younger and older people to determine how the neural and autonomic correlates of emotion regulation change in later life.

### Limitations

Although we have made a novel contribution in specifying the nature and consequences of the information processing taking place in medial prefrontal regions during reappraisal, there are some limitations worth nothing. First, we used unpleasant pictures to which participants had previously been exposed in a spontaneous reactivity task immediately before the reappraisal task. This approach may have reduced responding and/or introduced variation in brain responses as a function of memory retrieval processes during the reappraisal task that were not evident in prior studies. Second, the individual-difference approach adopted in this study does not allow us to form conclusions about the extent to which neural signals during reappraisal track changes in autonomic physiology over time within participants. Further analyses of these data treating the autonomic measures as predictors of neural activation at the single-subject level would be needed. We used an individual-difference perspective as a starting place because, as stated cogently by Underwood (1974), individual differences "may be used as a crucible in nomothetic theory construction," an approach that "provides a critical test of theories as they are being born…" (p. 6). Third, we did not collect reports of subjective emotional experience, thus, despite the monotonic decrease in EDA that accords with the regulatory goal, we cannot say whether subjective experience of unpleasant emotion changed accordingly as well.

## Conclusion

Voluntarily regulating responses to affect-laden visual stimuli using reappraisal relies in part on the medial prefrontal network, and has consequences for autonomic physiology. Increasing and decreasing negative emotion using reappraisal prompts larger pupil diameter and greater cardiac acceleration compared to maintaining negative emotion. These autonomic measures are sensitive to the cognitive demand required of reappraisal, regardless of the direction in which emotion is regulated. By contrast, changes in electrodermal activity reflected changes in emotional arousal. Increasing negative emotion prompts increases in EDA while decreasing negative emotion prompts decreases in EDA compared to maintaining negative emotion. We further demonstrated that reappraisal-related changes in cardiac acceleration signifying cognitive demand are associated with activation in some (but not all) of the medial prefrontal regions implicated in cognitive reappraisal, including dorsal medial frontal gyrus and dorsal cingulate cortex. Reappraisal-related activation in these two medial prefrontal regions was also associated with greater monotonic modulation of emotional arousal in accordance with the regulatory goal, as measured using EDA. These associations were demonstrated across people, thus highlighting the utility of an individual-difference approach to learning about the information processing that takes place in the brain using autonomic signals that take place in the body.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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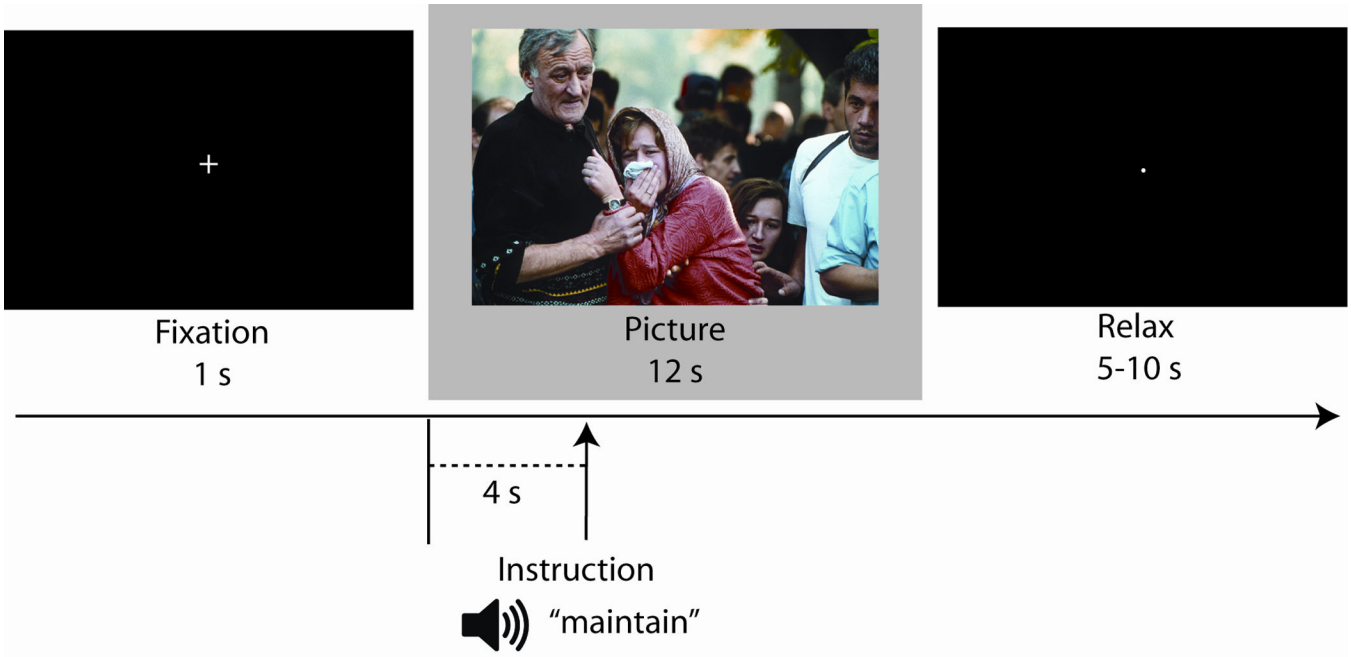


**Figure 1.**
Trial structure for the reappraisal task. One instruction (increase, maintain, decrease) was delivered 4 s after picture onset on each trial. This figure represents a "maintain" trial. Photo of mourning family by Mikhail Evstafiev retrieved from http://commons.wikimedia.org/wiki/Image:Evstafiev-bosnia-sarajevo-funeral-reaction.jpg on August 18, 2008. It is licensed under the Creative Commons Attribution ShareAlike 2.5 License, which allows reproduction (see license at http://creativecommons.org/licenses/by-sa/2.5).

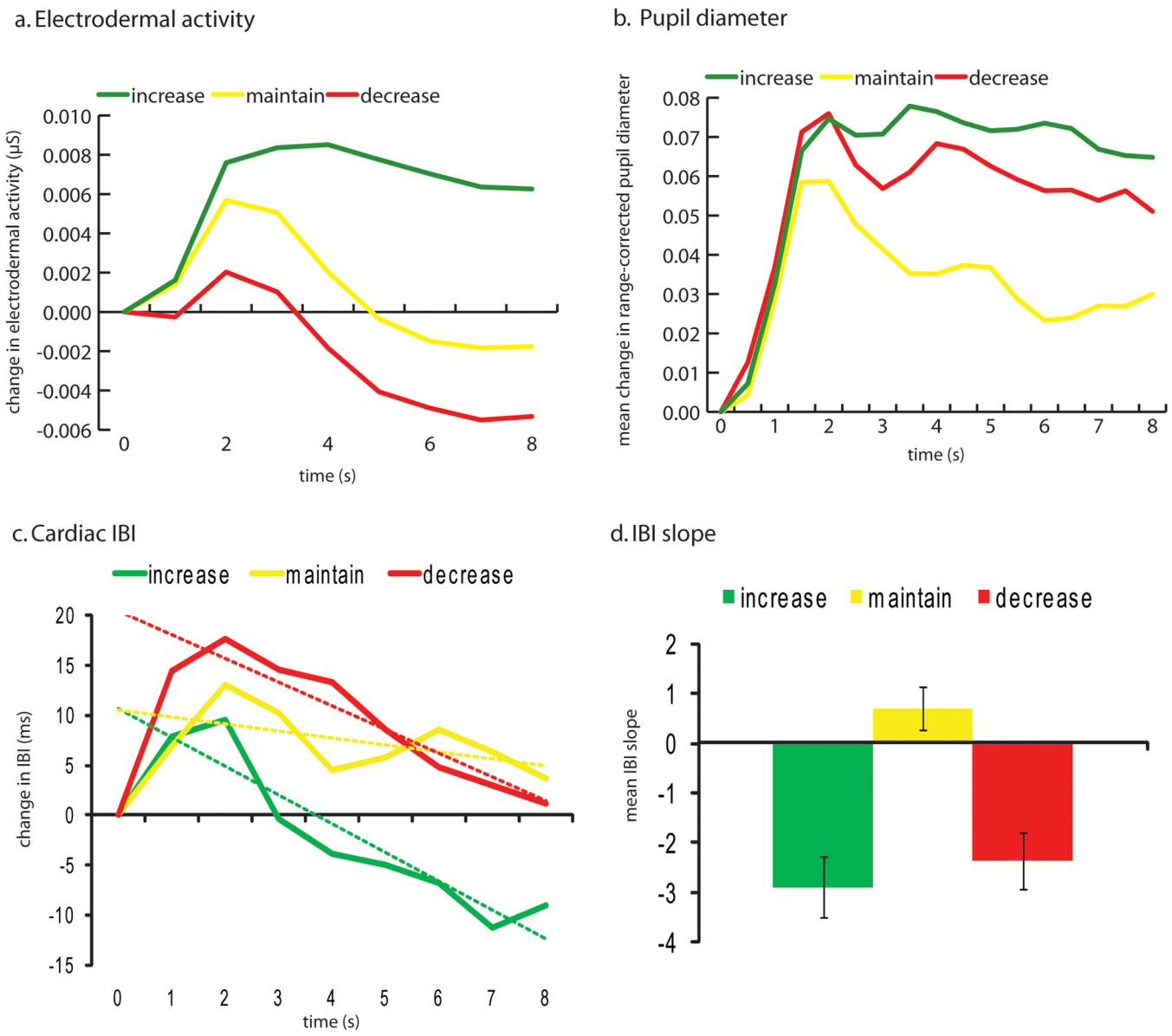


**Figure 2.**

Peristimulus time course of reappraisal effects on change in autonomic nervous system activity, specifically electrodermal activity (panel a), pupil diameter (panel b), and cardiac IBI (panel c). Increasing negative emotion is represented by the green line, decreasing by the red line, and maintaining by the yellow line. Panel d depicts mean cardiac acceleration, as measured using slope of change in the IBI series (depicted with dotted lines for each reappraisal condition in panel c).

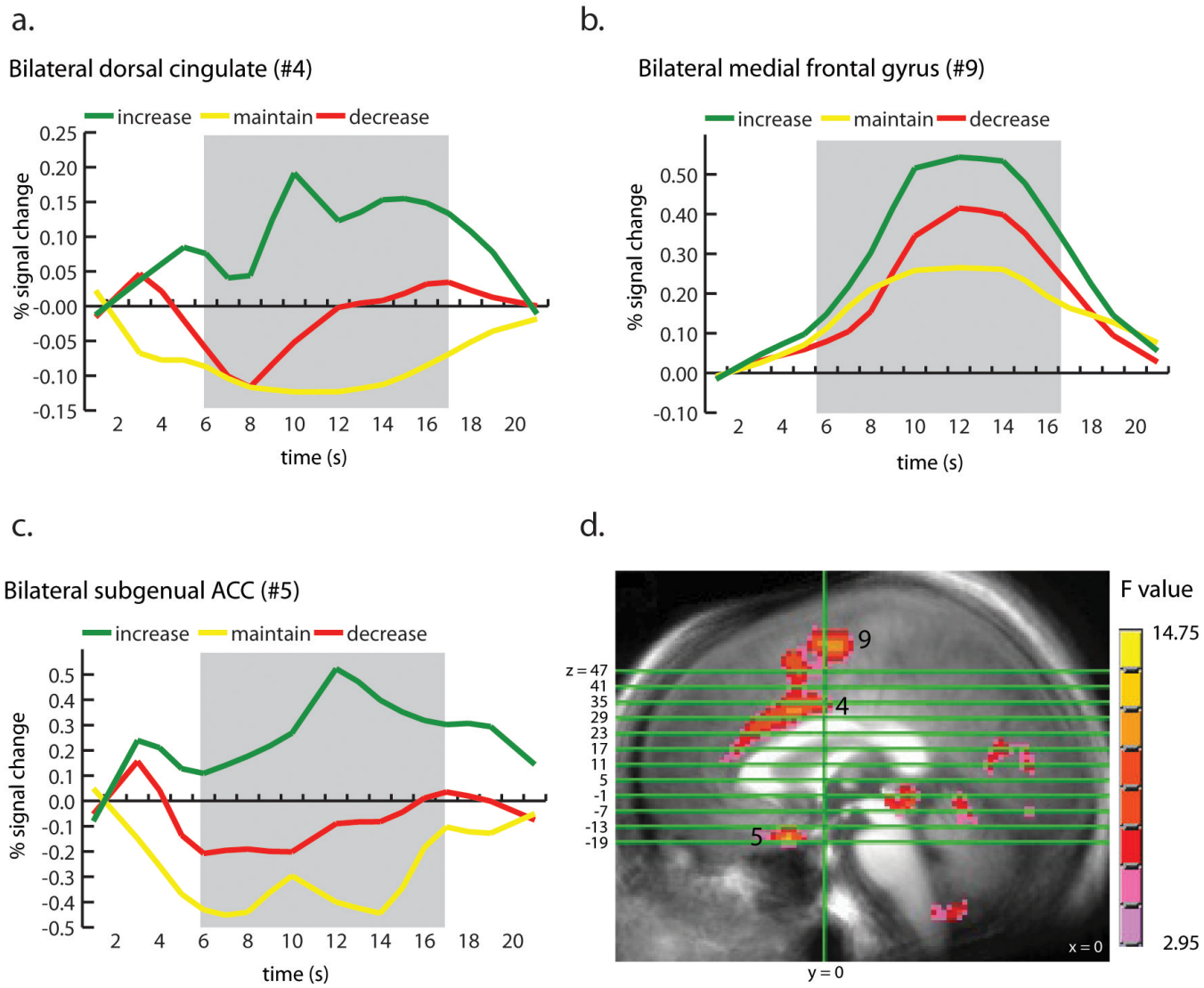


**Figure 3.**

In panels a, b, and c, we show the peristimulus time courses for three medial prefrontal clusters identified via voxelwise repeated measures ANOVAs comparing increasing, maintaining, and decreasing responses to negative pictures. Increasing responses to negative pictures is represented by the green lines, maintaining by the yellow lines, and decreasing by the red lines. The shaded area represents the time points that were summed to produce mean AUC signal estimates for analysis, which themselves are not shown. Panel d depicts these three medial prefrontal regions overlaid on the average high resolution, Talairach-transformed T1 image computed across all 26 participants, shown in radiological convention (R = L). The colors within each cluster represent uncorrected F values for the test of the regulation main effect, with yellow values indicating the voxels with the strongest effects, thresholded at $p < .01$. The numbers next to each cluster refer to the # recorded in the first column of Supplemental Table 1.

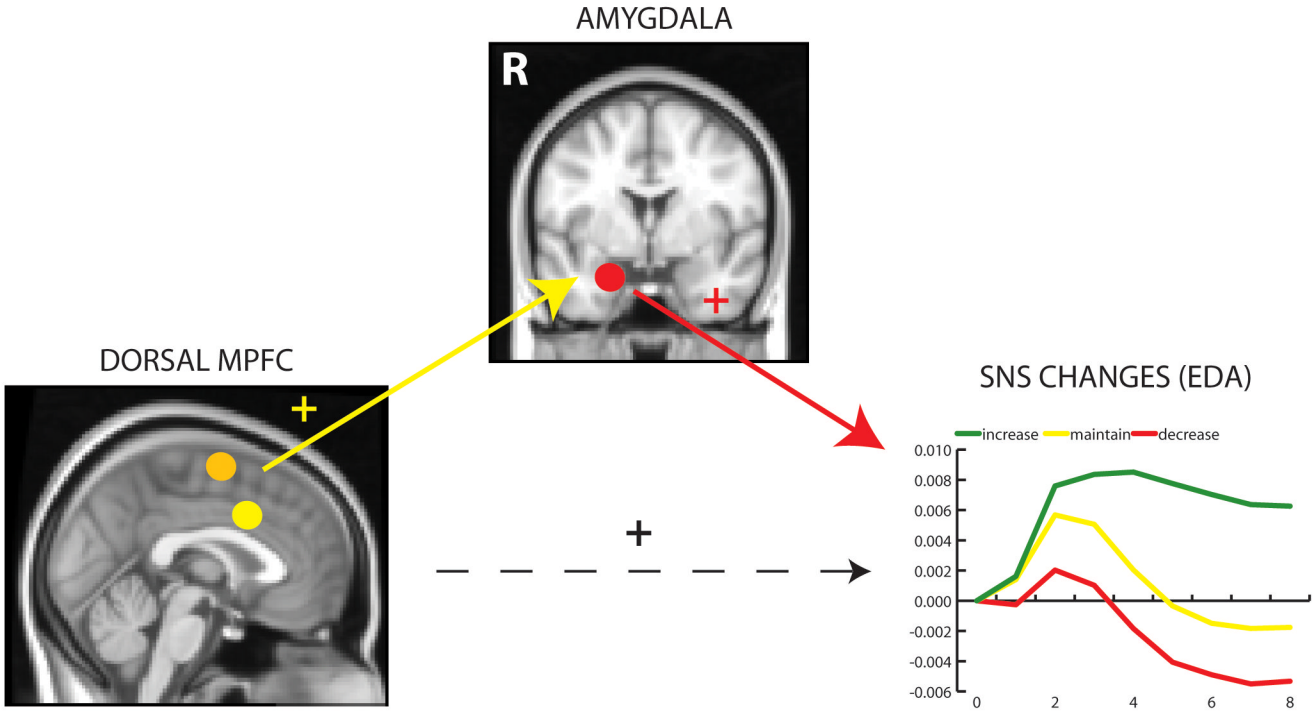


**Figure 4.**

This simple framework depicts the information processing taking place during reappraisal and its associated medial prefrontal neural correlates in the present study, as supported by mediation analyses. We propose that reappraisal-related activation in two regions of dorsal medial prefrontal cortex (MPFC; shown with yellow circles: dorsal medial frontal gyrus, top circle, and dorsal cingulate gyrus, bottom circle) (increase, decrease > maintain) carries out information processing associated with the cognitive demand involved in reappraisal. This activation produces monotonic change in the right amygdala (linear contrast score: increase > maintain > decrease; shown with red circle), which monitors the need for energy mobilization due to changes in motivational state. Amygdala changes then facilitate sympathetic nervous system (SNS) output, signifying changes in emotional arousal (also using linear contrast score) that accord with the regulatory goal. The black arrow connecting dorsal MPFC with SNS activation is broken so as to communicate the fact that this direct association is reduced or eliminated when taking the amygdala into account.