Changes in Brain Function Through Repeated Emotion Regulation Training – Pilot Study

BACKGROUND/SIGNIFICANCE

Emotion Regulation (ER) involves cognitive processes that change the onset, duration, content, or intensity an emotional response [1, 2]. Although emotions can be regulated by avoiding or distracting oneself so that the full brunt of emotional reaction is not engaged, in the proposed pilot study, we are concerned with ER strategies designed to modify an already-initiated emotional response. Such strategies are arguably the most well-studied to date, likely because emotional experience is unavoidable. Further, exaggerated emotional reactions, which are reflective of emotional dysregulation, are implicated in numerous psychiatric disorders. Thus, understanding how to influence emotional experience likely will have the most immediate translational potential.

Over the past decade, the strategies people frequently use to regulate already-initiated emotional responses have been the topic of extensive research. One way to regulate emotions is through "re-appraisal" of a stimulus. Re-appraisal is often defined as an explicit ER strategy [3] that involves an alternative interpretation of a given stimulus or situation (in the form of thoughts or mental images) that alters or contradicts one's immediate spontaneous appraisal [4, 5]. For example, seeing a picture of an angry man pointing a gun typically elicits a fear reaction/autonomic fight-or-flight response and prompts negative beliefs, action plans, and interpretations. One can forestall or minimize such responses by ***reinterpreting*** the situation – e.g., realizing the man is a police officer pointing the gun at a dangerous criminal standing nearby. Experimental instructions to deliberately re-appraise the emotional experience of a scene involving threat of bodily harm, distress, etc. consistently lead to lower self-reports of negative emotion and lower emotion-related physiological reactions (e.g., electrodermal response or heart rate) [6-11]. In general, such re-appraisal tactics have been found to be more advantageous and linked to positive mental health compared to alternative response-focused ER strategies like suppression of emotional expression [12].

Another effective ER strategy to modify an already-initiated emotional response is called "***mindfulness***." Mindfulness emphasizes calm, non-judgmental observation of emotion. Although it was derived from Eastern philosophic traditions, modern Western scientific study has validated its theoretical distinctiveness, construct validity, and clinical utility (see reviews; [13, 14]). Mindfulness involves the cultivation of emotional awareness, moment-to-moment attention to emotion, and acceptance of all emotional reactions (positive or negative) through meditative practice. At the risk of theoretical over-simplification, while re-appraisal involves engaging cognitive resources in a different way to lower emotional response, mindfulness instead emphasizes non-engagement to accomplish a comparable reduction in emotional reaction. In terms of cognitively-controlled ER processes, they are similar with respect to recognition of negative affect, but differ in the need to re-establish stimulus-outcome associations with emotional arousal.

Table 1. ER Brain regions and their theorized cognitive relevance

Amygdala (**AMYG**)	Personal relevance detection that biases other brain region processing, usually seen w/emotion
Ventromedial prefrontal (**vmPFC**)	Representing the + or - motivational salience of S-R contingencies in context/goal-dependent way
Dorsolateral prefrontal (**dlPFC**)	Generating or holding re-appraisal strategies in mind to bias processing in other brain regions
Lateral orbitofrontal (**latOFC**)	Reward value/prediction representation
Dorsal anterior cingulate (**dACC**)	Performance and conflict monitoring
Dorsomedial prefrontal (**dmPFC**)	Interpreting one's own emotional states
Ventrolateral prefrontal (**vlPFC**)	Goal-appropriate response selection
Posterior intraparietal cortex (**PPC**)	Attention to reappraisal-relevant stimulus features

Over the past decade, nearly 4 dozen functional neuroimaging studies have been conducted to identify the brain regions that are engaged to accomplish various forms of ER. As a result, the brain regions engaged for cognitive re-appraisal ER are well-known. They have been reviewed numerous times [4, 15-19] including several fMRI [20] meta-analyses. (*See Fig. 1 for our fMRI replication of re-appraisal ER activation. See [21, 22] for all reappraisal fMRI studies, and [23] for fear-specific reappraisal.)* Several prefrontal cortex (PFC) regions, including vmPFC, dmPFC, dlPFC, dACC, vlPFC, and latOFC, are recruited during re-appraisal-based ER. (*See Table 1 to match abbreviations to anatomical regions and a brief summary of their specific theorized cognitive/emotional processing contributions to ER.*). The findings from these studies have prompted a reasonable working theory that prefrontal cortex regions exert control over the amygdala to

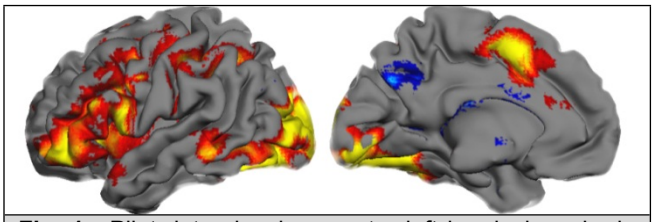

Fig. 1: Pilot data showing greater left hemisphere brain activation during "re-appraisal" ER in *n*=24 healthy young adults compared to simple viewing of negative emotional stimuli (p<.05 FDR). Note, though not depicted, vmPFC ER activity was found at p<.001 uncorrected significance.

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reduce emotional reactions. Strong circumstantial evidence for a possible *PFC→amygdala* control relationship comes from the frequent observation of ↑ PFC with ↓ amygdala activity during ER (see [23]). Many studies also report inverse "functional connectivity" (i.e., correlation between activation decreases/increases in distal brain regions [24]) between amygdala and various PFC regions [25-37] (particularly vmPFC and dmPFC [25-27, 30-33, 37]). This supports a tentative model that successful ER involves prefrontal activation that orchestrates or inhibits amygdala/limbic reactivity.

A current NIMH-funded project in the CNDLAB at the Olin Neuropsychiatry Research Center (R01 MH102854) uses fMRI to better describe the neural architecture of ER. The goals of that project are to provide a validated model of how the causal influences among ER brain regions and to identify any abnormalities in how brain regions interact in adolescents diagnosed with Major Depressive Disorder (MDD). The ultimate objective of that project is to identify neural targets for new ER treatment development. Several major psychotherapies have been formulated upon ER core concepts. Re-appraisal techniques are used in a variety of therapies, including new CBT variants still undergoing validation ([38-40]; see review [41]). Numerous therapies also incorporate mindfulness interventions, including Mindfulness-Based Stress Reduction (MBSR), which was originally designed to help patients with chronic pain [42, 43], but has since been shown efficacy for various clinical groups [14, 44-46]. Mindfulness-Based Cognitive Therapy (MBCT) was developed as a group-format therapy intended to prevent depression relapse (Segal et al 2002) by focusing on awareness of and relationship to thoughts and emotions instead of changing dysfunctional thoughts [47, 48]. MBCT is validated as useful for preventing relapse in treatment-resistant depression [48-52] as well as reducing active symptoms of depression [53, 54] and other disorders ([55-57];see reviews; [14, 44, 45, 58]). More recently-developed therapies combine the strengths of re-appraisal and mindfulness into core intervention features (e.g., Adaptive Coping with Emotions), were these traits and the capacity to improve these skills predict patient outcome [59-61] and symptom severity [59, 62-64]. Perhaps more well-known are the transdiagnostic, ER-focused therapies – such as the Unified Protocol for the Treatment of Emotional Disorders in adults [65] and youth [66].

SYNTHESIS AND FORMULATION

Despite the intense neuroscientific and translational interest, these lines of research do not converge. At present, there is little understanding how any ER-based therapies influence ER brain function. The goal of this pilot study is to collect preliminary data that will allow us to formulate theories about ER-related brain function change during intervention-like training that will be tested in larger, externally-funded grant proposals submitted to the National Institutes of Health. We are not especially interested in any existing specific, manualized therapeutic technique. Existing ER-based psychotherapies typically incorporate a variety of related interventions, not all of which focus on the ER component itself. Instead, we focus on the "building blocks" of such therapies, i.e., the ER interventions themselves and their effect on negative emotional reactions. Here, we ask a specific question – How does ER-elicited brain function change with repeated sessions of guided practice of various ER techniques? In other words, does increasing familiarity or mastery of ER skills through practice change brain function, and how? There are logical hypotheses about the likely nature of brain function changes that can be gleaned from prior neuroimaging research. For instance, if prefrontal cortex activation is important to ER, perhaps practice simply increases such activation. However, our pilot work for the current NIMH R01 suggests instead that ER practice might work by enhancing the functional integration among key frontolimbic regions. Complicating such hypotheses is the recognition that different ER tactics engage many distinct brain regions depending on which approach is employed. So a person's individual brain function differences prior to ER training might be a potent determinant for what sorts of neural changes result from repeated practice. Because all these issues must be evaluated through the lens of a preliminary study before any coherent theoretical model can be formulated, we propose a pilot study here. Not only will this provide empirical data upon which to base future research, conducting such a pilot will showcase any methodological hurdles or challenges that need to be overcome in order to successfully conduct a larger-scale study.

APPROACH

N=40 adults (ages 18-50, approximately equal numbers of males and females) who are pre-screened to have mild-to-moderate levels of depression or who will serve as non-depressed/anxious controls will be recruited from community resources. Inclusion criteria are described in detail in the Human Subjects section. In brief, we will operationalize inclusion for the depressed group as any participant who scores >1.5 SD from normative levels on the Beck-Depression Inventory-II. Elevated trait anxiety on the Spielberger's State/Trait Anxiety Inventory (STAI) will not disqualify inclusion (as depression and anxiety commonly co-occur). Any depression

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symptoms will not have to reach diagnosable levels of Major Depressive Disorder to qualify for the study. The non-clinical control group will have minimal symptoms on the BDI-II and State/Trait scales. Participants in each of these study groups then will be randomized into two conditions (*n*=10), each of which will receive 2 assessment/MRI appointments along with 6 sessions of guided practice/training in either 1) Re-interpretation or 2) Mindfulness ER techniques. If randomized into the CBT-based regulation training, subjects will be trained to use a cognitive strategy that instructs them to reappraise situations in positive or less negative ways. If randomized into the MBT-based regulation training, subjects will be trained to use a mindfulness strategy that instructs them to notice and accept their feelings without judgment or intent to act upon them. In both conditions subjects will be shown pictures of negative-affective stimuli and asked to use the strategy over and over again. These appointments will take place 'virtually' using a laptop computer that is set up at the participants house and is controlled remotely by Olin NRC staff. The training sessions will then be monitored by the research assistant via Skype, so that the participant can be given instructions and supervised while completing each session. "Training" in this context is conceptualized as the cumulative amount of practice, with the expectation that greater practice leads to greater mastery. Immediately after the first and sixth practice sessions, participants also will undergo fMRI so that brain function relative to that stage of practice can be assessed. In brief, training will be guided-practice sessions where examples of ER tactics are explained, modeled, then practiced with interactive discussion and feedback. To clarify, the primary outcomes for this pilot study will be fMRI-assessed brain function data, examined either to detect any changes in activation amplitude ("level of activity") in *a priori* ER-linked brain regions-of-interest (ROIs) (Table 1) or changes in the degree of functional connectivity among them. Secondary outcomes will be the BDI-II and STAI. Because we have a well-established infrastructure that includes many other datatypes useful for emotion-related neuroscience, we also will collect a variety of other individual-level data for exploratory analyses. By design, we propose to cast a wide net to collect information on the most relevant factors suggested by prior research to be explored. All data collection methods are described next, followed by a brief data analysis plan.

The ~15 minute cognitive evaluation (Table 2) will exclude subjects with less than an eighth grade-normal educational achievement estimate using the Wide Range Achievement Test-4 [243].

Table 2. Neurocognitive Test

Task Name	Domain	Min
WRAT-4 Reading	Achievement	15

Clinical Assessment Information will be collected on participants' age, race/ethnicity, years of education, handedness [67], and family socioeconomic status [68]. DSM 5 psychiatric diagnoses will be assessed using the Structured Clinical Interview for DSM-5 (SCID-5 [69]) by a trained MA-educated research assistant supervised in a weekly diagnosis consensus meeting by PI Stevens (a licensed clinical psychologist with over 15 years of experience supervising clinical assessment and SCID interviewing for several large-scale NIH-funded clinical neuroscience projects). To ensure evaluation standardization and reliability, all assessments will be videoed and stored digitally. A thorough use history for major drugs of abuse (including nicotine dependence; i.e., Fagerstrom test [70]), onset of substance use, quantity and frequency of alcohol/drug use, and number/type of treatment episodes (if any) will be obtained using the Olin NRC Healthcare Questionnaire, which includes a modified Timeline Follow-Back interview method [71]. This measure also assesses major medical conditions and any psychotropic medication use. Familial psychiatric status will be assessed using the Family History Screen for Axis I disorders [72]. Table 3 lists other psychological test measures that will be used to characterize the sample. They will be used in exploratory sub-group analysis of fMRI and other data.

Table 3. Other Psychological Test Measures

Task Name	Domain	Min
Spielberger State/Trait Anxiety Inventory	Self-report of characteristic anxiety	5
Beck Depression Inventory-II [315]	Depression: a 21-item self-report measure assessing existence and severity of depressive symptoms	5
Columbia Suicide Severity Rating Scale[318]	Scale measuring suicidal ideation, intensity and behavior	10
Structured Trauma-Related Experience & Symptoms Screener[319]	Assesses lifetime history of exposure to traumatic events and symptoms of PTSD	10

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Emotion Assessment (Table 4) This 30 minute assessment will quantify habitual use of re-appraisal ER strategies, assess emotional reactivity and evaluate mood state before and after fMRI (to confirm there are no changes that impact study data interpretation).

Table 4. Emotion Test Battery

Task Name	Domain	Min
Cognitive ER Questionnaire [73]	Typical ER following negative events	5
Emotion Regulation Questionnaire [74]	Habitual use of cognitive re-appraisal or suppression for + and - emotions	3
Beliefs of Self-Control Assessment [75]	39-item self-report measure of emotion sensitivity, intensity, and persistence	5
Five Facets of Mindfullness Questionnaire [76]	21-item self-report measure of the key elements of mindfulness	5
Emotional Reactivity Scale [77]	21-item self-report measure of emotion sensitivity, intensity, and persistence	5
Profile of Mood States 2 [78] Short Form	Mood before and after ER training	5-10
Beliefs About Will Power Scale	Self-reported traits relating to willpower	3
Emotion Impulsivity Questionnaire	Newly created scale that measures a tendency to respond impulsively when emotionally aroused	2

fMRI Assessment Overview There will be 2 MRI sessions, within 5 days of the first and last ER training practice sessions. MR images will be collected using the Olin NRC's Siemens 3T Skyra, requiring ~2 hours in total, with ~1 hour in-scanner. All participants will wear hospital "scrubs" to minimize the chance of introducing metal into the MRI. Participants will provide a urine sample before MRI to be tested for the presence of drugs metabolites, and for pregnancy in females. Drug testing results may be used as the basis to defer MR data collection and will be noted for *post hoc* analyses. Caffeine/nicotine intake will be as normal for each individual to prevent any acute withdrawal effects on brain activity, restricted to $\geq$1 hour prior to MRI.

fMRI Stimulus Delivery/Response Recording The ER fMRI task will be implemented using E-Prime software (Psychology Software Tools, Inc.), which records behavioral ratings for offline analysis. Visual stimuli will be projected via a 5000 ANSI lumens system onto a screen located behind the patients head. Participants view this screen using a mirror attached to the head coil. An MR-compatible 5-button fiber optic response device (Current Designs, Inc.) will acquire behavioral responses. Participants communicate with staff during MRI using an MR-compatible auditory sound system delivered by 30 dB sound-attenuating headphones.

ER fMRI Task Participants are shown pictures of negative-affective or neutral stimuli, and instructed to focus on each picture in one of three ways: (a) Reappraise the emotional image in a positive light ('Reappraise' instruction); (b) Notice any feelings that arise in the present moment and attend to it with an attitude of acceptance ('Accept' instruction); or (c) Simply look at the image ('Look' instruction). At the beginning of each trial, one of the 3 instruction words is presented in the middle of the screen, followed by a picture (negative-affective picture if instruction was reappraise or accept; negative or neutral picture if instruction was look; 8s). After the picture presentation, participants are asked to provide a self-report rating of the magnitude of negative affective on a visual-analogue scale from 1 to 5, where 1 is labeled as 'not at all' and 5 is labeled as 'a lot'. Participants make responses by pressing on a button using a hand-held, MR-safe button-box. In sum, there are four trial types: (1) reappraise-negative image (CBT-based regulation); (2) accept-negative image (Mindfulness-based regulation); (3) look-negative image (no regulation); and (4) look-neutral image (non-affective).

ER Practice Sessions During each of the 6 practice sessions, participants will undergo guided instruction with research staff. They will focus only on decreasing emotion to negative stimuli, using whichever of the two emotion regulation strategies they are assigned to learn. In each section, 25% of the stimuli will serve as a control similar to the fMRI task when they are simply asked to view the picture and let their emotional reaction unroll naturally. On the other 75%, they will be guided in how to use their re-appraisal or mindfulness strategy. Practice will consist of guided instruction, question/answer about their attempted techniques, and use of examples for each stimulus if necessary. An important component of practice is continual reminders and examples for how to use the strategy in real-life situations outside the experimental setting with the exact stimulus they are practicing with. Prior research has shown that implementation instructions enhance generalization and rapid acquisition of emotion regulation skill. Each practice session will last between 45-60 minutes over the three-week practice period. Importantly, the stimuli used for practice are carefully controlled in a way that exposes some pictures repeatedly, while others remain relatively novel. At the end of the final appointment, participants will be tested on each category to tease out any effects of exposure to pictures

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versus a generalized effect of improvement in their assigned emotion regulation tactic.

Emotional Intensity/Arousal Measurements Consistent with recommendations to measure ER success with convergent measures [83], we use self-ratings, electrodermal response and pupilometry from eye-tracking to obtain measures of emotional experience. ***Self-Ratings*** 10 sec after each trial onset, participants will use the MR response device to rate on a Likert-scale (Fig. 5) how negative (or positive) each image made them feel. Following each fMRI/practice session, participants will indicate the confidence in their successful use of the strategy on a Likert-scale of 1-9. They also will be asked to narratively describe how they approached 5 sample negative stimuli from the fMRI task, along with confidence ratings of their accurate recall. These responses will be digitally recorded, transcribed into text, then examined via word-frequency decomposition for the representativeness of emotion-laden words in their recounting (i.e., an indirect, supplemental means of assessing success or failure of ER for the reappraisal-based tasks). During post-MRI image evaluation (~20 min), subjects also will rate each stimuli's valence, arousal, and dominance, using IAPS recommended 9-point Likert scales [84]. ***Skin Conductance Response (SCR)*** Electrodermal SCR is an index of peripheral sympathetic autonomic arousal whose phasic activity has been linked to fMRI-measured activity in ER-related brain regions such as dlPFC, dmPFC, vmPFC, OFC, insula/vlPFC and amygdala [85-89], or amygdala as measured by invasive techniques [90], making it a valuable (if indirect) index of emotional arousal. Although physiological measures recorded during ER generally track self-reports [6, 7, 25, 91-96]. they do not always change in characteristic ways corresponding to simple dimensions of strong negative or positive emotion (see review [97]), or change at the same magnitude [6], suggesting they could provide unique information in ways that will be valuable to our hypothesis-testing. Our recording system (www.biopac.com) is designed specifically for MRI acquisition use, incorporating signal processing circuitry to remove spurious MRI-induced artifacts in the electrical recording at the source and is integrated with MR paradigm delivery system for task-related data analysis. The EDA100C-MRI amplifier will measure SCR during task trials using a 0.5 constant voltage signal across a pair of single-use dry electrodes, to which we will apply Biopac's biocompatible, isotonic gel (GEL101) to ensure maximum electrical conductivity. After electrode application, we wait $\geq$10 minutes while MR localizer/structural scans are being done to allow skin conductance level to stabilize. Acqknowledge software will convert digital event pulses from E-Prime to data event markers. SCRalyze (vb.2.1.7) [98] will parameterize phasic changes in SCR amplitude evoked by each event class, using a canonical SCR response function [99]. Available secondary measures include SCR response latency/rise time, and spontaneous SC fluctuations indexing tonic arousal [100], as measured by psychophysiological DCM [101-103]. Exploratory analyses will see if they add value to study hypothesis-testing. ***fMRI Eye Tracking*** Participant gaze fixation will be monitored during the fMRI assessment to quantify what stimulus features are being preferentially processed on each trial. Although pupil constriction and dilation are more neurobiologically complex than SCR (i.e., are mediated by both sympathetic and parasympathetic influences) pupil size has been used as a measure of emotional arousal/attention (e.g., [104]) and will be used as a secondary dependent variable. Eye position and pupilometry will be monitored throughout fMRI using the Eyelink® 1000 Fiber Optic Core System, integrated with the MR paradigm delivery systems via 16-bit digital I/O for TTL-based triggering to synchronize data acquisition for offline analysis. The system includes a non-ferromagnetic optimized infrared camera (1000 Hz) with long range mount. The Eyelink 1000 emits infrared (IR) below the internationally accepted standards for safety (1mW per square cm). The IR illuminator and camera are mounted on a non-ferromagnetic stand outside of the MRI bore and makes use of the head coil mirror to view the participant's eye position (the device does not touch the participant). Therefore, the distance between the eye and the camera is about 3 ft, far less than the distance known to be safe (IR intensity dissipates with distance). Exposure at these levels has been found safe for up to 8 hours, as the level of IR used is less than what is found in normal sunlight. In this project, IR exposure will be ~ 45 minutes. Setup requires ~5 minutes as each participant's head is positioned in the MR coil so staff can acquire pupil position, refocus camera if needed, manually set pupil and corneal reflection thresholds, adjust search field, and perform/validate the nine-point HV9 calibration for tracking. Only project staff who are specifically trained in Eyelink 1000 setup data collection will use the device. Our analysis approach will follow that described in [105], where we will define Emotional Areas-of-Interest based upon the entire sample's composite fixation map using Eyelink Data Viewer software combined with participants' post-MR ratings of where the positive or negative features lie in each image. Useful dependent measures will be fixation frequency/dwell and pupil size (trial - calibration baseline), segmented into early (1-3 sec), middle (4-6 sec), and late (7-9 sec) trial phases.

fMRI Task Length and Head Motion Although task run length prompts concern over head motion-related experimental confounds/data loss, we routinely collect artifact-free data using similar task/scanning lengths.

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Subjects practice in a mock-scanner, which simulates MRI experience and acclimates participants to the need to remain still. During MRI, heads are secured in a custom-built cushion that reduces movement. Motion is monitored in real time and unacceptably large head movements will prompt MR staff to restart acquisition. Data are examined within 12 hours and retained only if translation and rotation estimates are <1 voxel length and 3˚, and if minor head motion is not significantly correlated with fMRI task conditions.

MRI Sequences *fMRI* gradient EPI (TR/TE 900/35 msec, flip 60°, multi-band AF=7). *Fieldmaps* (TR/TE 8400/62 msec, flip 80°, AF=1, 0:25 min, run twice with reversed A>>P phase encoding) (EPI/fieldmap sequences have 2.1 mm isotropic voxels, 70 interleaved slices, 228 mm FOV). *T1-weighted* (3D MPRAGE, TR/TE/TI=2400/2.07/1000 msec, flip 8°, FOV=256×256mm, 0.8 mm isotropic vox; 7:02 min). *T2-weighted* (TR/TE=3200/565, FOV=256x256, 0.8 mm isotropic vox; 6:45 min). Structural images will be Radiologist-assessed to be free of macroscopic pathology. Daily MR stability and QA measurements will ensure scans are of equal quality throughout the entire project.

Methods Used To Prepare MRI Data for Study Hypothesis Testing

HCP Pipeline MRI Processing Our MR sequences were chosen for compatibility with Human Connectome Project [106] pre-processing pipelines [107], which provide highly accurate, structural image-guided brain atlas normalization for fMRI. T1/T2 images will be ACPC-oriented, brain extracted, B_0 inhomogeneity-corrected, mutually co-registered, distortion fieldmap-corrected, and finally MNI152 atlas-registered using FSL FLIRT+nonlinear FNIRT algorithms [108]. FreeSurfer-based [109] registration, skull-stripping, and pial extraction on 1mm downsampled T1/T2 data will create structural volume/cortical ribbon files. After fMRI EPI data is slice timing- and, motion-corrected, it will be registered to FS output, resampled to atlas space, intensity normalized, smoothed (volume data @4mm; cortical ribbon surface mapping data @2mm FWHM), and written as timeseries. Both volume and surface-based fMRI data will be compared for hypothesis testing.

Conventional fMRI Analyses FSL FEAT analyses will estimate activation with FMRIB's Improved Linear Model (FILM), using geodesic Gaussian algorithms to estimate autocorrelation and smooth fMRI data. Explanatory Variables (EVs) will use a double-gamma HRF convolution to translate event onsets in conditions of interest into regressors to be fit to the BOLD timeseries. EV contrasts (against other conditions or implicit "rest") will isolate task-induced activation, creating activation maps. The sample data then will be evaluated using FSL's FLAME random-effects models to confirm activation, compare group profiles, etc. Random-effects models for hypothesis-testing will employ PALM [110], a relatively new FSL- and CIFTI-compatible analysis tool. Although we will focus on brain ROIs (Table 1), PALM offers both threshold-free cluster enhancement and corrections for multiple comparisons following permutation-based statistical inference to explore the possible effects of treatment on other brain regions with confidence.

ROI Localization Using Independent Component Analyses (ICA) Accurate ROI identification will utilize ICA, in part to reduce the data into a small handful of datapoints. ICA was developed to solve the "cocktail party" problem in which many people are speaking at once [111]. ICA separates mixed signals into individual sources (e.g., "voices") based on unique temporal characteristics of each signal. When applied to fMRI data, spatial ICA assumes there is a set of non-systematically overlapping (temporally independent) brain regions (or small networks) with unique time courses. When ICA fits a high model order to the data (i.e., asking for >80-130 components) (e.g., [112-115]), components typically depict activity in just 1 or 2 brain regions (e.g., Fig 6), or isolate anatomical sub-regions (e.g., basolateral vs. centromedial nuclei). Localization is quantitatively facilitated by correlation with *a priori* templates (e.g., MNI or cytoarchtectonic [116] atlases). Our whole brain group fMRI ICA methods [117] include a reconstruction step that projects the group-derived ICA solution back onto each participant in a way that preserves individual variability in each spatial map and timecourse for further analysis. We have used these ICA methods in many dozens of previous fMRI studies (e.g., [115, 118-130]), and successfully applied ICA individual timecourses to DCM and other effective connectivity applications [119, 121]. Alternatively, semi-blind ICA methods we developed [131] balance atlas-based ROI selection (e.g., from ER meta-analysis [5, 23]) with subject-specific data-driven influences. Finally, ICA is a widely-appreciated "denoising" technique, in fact originally designed to isolate meaningful signals from background noise. Not only does it isolate signal corresponding to head motion artifacts from ROI activity, metrics can confirm ROI signals are free from motion-related noise (e.g., comparison of low-frequency / high-frequency BOLD signal oscillations [115]).

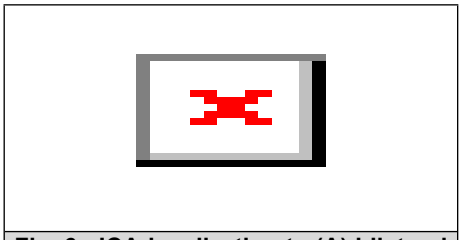

Fig. 6: ICA-localization to (A) bilateral dlPFC and (B) right BL amygdala (*t=15* min threshold) from pilot data.

Analysis Plan The core analyses will employ a 4 (ER group) × 2 (training timepoint) mixed-effects ANOVA to

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test a general hypothesis that brain function or functional connectivity will change for the ROIs being studied. Because there will be 8 ROIs, we will consider results when using a Bonferroni-corrected α of .00625. However, because this is a pilot study, that correction will not be strictly imposed; rather, its use primarily will help us to decide whether any preliminary data might be publication-capable. *Supplemental Analyses*: Because this is a pilot study, we plan to assess the relationship of fMRI-measured ER brain function change throughout training to numerous other factors. Foremost, we need to evaluate whether non-neural measures of emotional function are altered by the ER training. We will use repeated-measures ANOVA to assess whether or not self-ratings of emotional intensity, SCR, pupil size/fixation time to emotional stimuli change across the fMRI sessions. We also will assess if POMS-2, BDI-II or STAI scores collected at baseline and in the final session differ, as these are clinically-relevant indicators of change that is independent of the ER training itself. Typically in this sort of fMRI experimentation, the degree of change in these measures also is correlated with the degree of change in any brain regions found in the primary analysis to bolster the case of the potential clinical relevance of the findings in *post hoc* analyses.

Power Analysis Because this is a pilot study, one of its goals is to allow us to assess the size of any effects. Therefore, our sample size must be adequate so that the effort of data collection is worthwhile. A hypothetical power analysis for a repeated-measures ANOVA for just one of the 3 experimental conditions can control Type II error (1-β=.80) effectively to detect "large" effect size differences (*d*=0.94) across the 2 fMRI sessions in any single brain region (including Greenhouse-Geiser corrections). If that hypothetical model is expanded to include all three ER training groups simultaneously as planned, the total N=40 sample can detect large group difference effect sizes. Changes in brain activity over time common to all groups can be detected if their effect size is as small as *d*=0.48 (or "medium"). Finally, the planned analyses can detect *d*=0.56 effect sizes for the interaction of group × training timepoint. This makes us confident that the proposed sample size will be adequate for both identifying scientifically-notable effects in the data and allow us to empirically-support their magnitude for future study design planning.

HUMAN SUBJECTS

General Comments The investigators are well-informed regarding proper guidelines for ethical human research, and they will insure that all research activities are in full compliance. Furthermore, the investigators participate in ongoing training, including continuing education courses, seminars and online education dealing with topics specifically of interest to clinical researchers, offered by Yale and Hartford Hospital reflecting a commitment to the highest ethical standards in research. All research participants will be competent adults who willingly provide their written consent to participate during a formal informed consent interview prior to research participation. Careful attention is paid to screening of volunteers prior to participation and to monitoring them during participation to insure their protection. All research volunteers with psychiatric or behavioral disorders are encouraged to engage in treatment for those conditions and are provided assistance in doing so (e.g., referrals). If danger to self or others is discovered through psychiatric interview, steps will be taken to immediately ensure participant safety, e.g., by making appropriate treatment referrals, or involving authorities as per Connecticut state law in extreme cases of clear, imminent danger that cannot be addressed in other means. All volunteers will understand that research participation is voluntary, and that after enrollment they are free to discontinue at any time without prejudice whenever they so choose. The investigators have extensive experience in neuroimaging research and have had no instances of significant research-related adverse events. Volunteers generally report that they feel respected and well cared for by research staff. We credit this safe and positive experience to careful attention to ensuring volunteer safety and to following proper guidelines for ethical human research.

RISKS TO THE SUBJECTS

Human Subjects Involvement and Characteristics All potential participants will undergo initial telephone screening to ensure they meet general inclusion/exclusion criteria. Qualified participants will then meet with study staff for informed consent. Following consent, they will undergo psychiatric interview and complete a battery of questionnaires to ensure none of the study exclusion criteria are met. At this point, participants will be randomized to one of the two ER training conditions (Reinterpretation or Mindfulness). The protocol requires 6 visits over three consecutive weeks at a time that is convenient for participants, and that they agree they can accommodate. We will attempt to structure an ideal schedule of appointments each week that follows a Mon/Wed, Tue/Thu, or Wed/Fri format. At each appointment, participants will undergo guided training in a specific ER tactic. Also, at the first and last MRI appointments, participants will complete a 60-minute fMRI

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session. Prior to fMRI, participants will be tested for the presence of drugs and pregnancy (if female) through urinalysis.

Inclusion/Exclusion Criteria Inclusion: Ages 18-50, right-handed, a high-school level of education (11th grade attainment for 18 year-olds is acceptable if they haven't completed their final year yet), and ≥8th grade English reading level to complete self-report evaluations (most are only available in English). Exclusion: Medical history that will exclude any potential participant includes head injury sufficient to have caused >30 minutes lost consciousness; past or current CNS disease (e.g., MS, epilepsy, tumor, etc.) or brain lesion identified by MR (structural MR scans will be reviewed by a radiologist for the presence of clinical neuropathology that may affect cognitive task performance); hypertension or juvenile-onset diabetes (current treatment with antihypertensives or insulin); current pregnancy (menstruating females will be tested). Psychiatric exclusion criteria include DSM-IV Axis I lifetime history of Bipolar disorder, PTSD, OCD, psychotic disorder, Tourette's disorder, or any Pervasive Developmental Disorder (e.g., Autistic disorder, PDD NOS, etc.); current DSM-IV substance dependence, ADHD, Conduct Disorder. Any participant who currently takes psychotropic medications will be excluded, even if psychiatric diagnostic criteria are not met.

Sources of Materials Participants will be recruited from the community via public notices at community centers (i.e., YMCA, rec centers, libraries, etc.), local newspapers, internet-based resources (e.g., Craig's List or Facebook), or through community support groups for families coping with mental illness. We plan to balance our sample by gender and ensure that it will reflect the demographic characteristics of the Hartford region. Research information includes psychiatric interview results, ratings made by participants on self-report questionnaires, medical history, family psychiatric history, MRI measures of brain structure and function collected during different neurocognitive tasks, electrodermal and eye-tracking responses during fMRI task completion, and identifying information such as name, DOB and contact information.

Potential Risks and Protection Against Risks The risks in this study involve procedures performed solely for the purposes of research. These risks include: psychological ratings, fMRI involving exposure to emotion-eliciting images, skin conductance recordings, eye-tracking, discomfort from interviewing, urinalysis, risks related to privacy/confidentiality of records, and unanticipated risks.

Psychological Ratings: Patients may find the battery of psychiatric and neuropsychological tests tedious and boring, or intrusive. If the former, brief breaks will be given during assessment. The latter concern is addressed through use of trained interviewers who have experience discussing sensitive material with clinical research subjects. However, if a subject finds a topic too uncomfortable or sensitive, those questions will be skipped, or with severe reactions, subjects will be debriefed and reminded they can discontinue participation without penalty, if necessary.

FMRI: The FDA has approved the MRI system and the scanning protocols to be used. The MRI scanning procedure in a 3 Tesla system is safe in normal healthy humans. However, subjects who could suffer potential risks from the MRI scanning procedure include those with metal implants (pacemaker, metal rods, bone screws, orthodontics, metal flakes from metalworking). Subjects are told during the informed consent process about the need to carefully screen for metal implants or any other exposure to metal in the body. Subjects who could potentially suffer harm will be screened for metal prior to scanning using a HH Radiology Department screening checklist, and on the day of the MRI will change clothes prior to entering the MRI suite, be scanned for metal using a whole-body ferromagnetic scanner, and be verbally checked by the MR technologist performing the scan. Although there is no proven harm to developing fetuses, women will be screened for pregnancy before scanning. Urinalysis for a one-step pregnancy test is conducted on the scan day to ensure that female participants are not pregnant. Participants with claustrophobia may experience some anxiety symptoms, and will be discouraged from participating. Subjects who feel claustrophobic during the experiment will be encouraged to notify experimenters at any time to discontinue scanning. There are no known risks associated with the visual or auditory stimuli presented during recording of event-related fMRI. All structural MR results are reviewed by Hartford Hospital Radiology staff and a brief clinical report prepared if there seems to be a need for more in depth evaluation. Any indication of pathology/abnormality is communicated to Co-PI Dr. Pearlson (a licensed psychiatrist), who then will order a full clinical MR for the participant. If participants cannot assume the cost of the MR, one is provided to them by the Olin NRC. This procedure ensures that any

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risk to health can be identified and proper clinical planning can be done.

Emotional Stimuli During MRI: The IAPS stimuli to be used in this project are well-known to include images of a graphic or sexual nature. We have used such stimuli in previous NIH- and foundation-funded projects (i.e., R01 MH102854, K23 MH070036 and a recent grant from the American Foundation for Suicide Prevention) to probe emotional neural systems. We do not utilize any erotica stimuli at all. The informed consent procedure carefully and explicitly discusses the issue of image content, and offering several examples of stimuli similar to those used in the experimentation. They also are reminded immediately before fMRI that they can discontinue at any time during the experimentation without penalty and still receive compensation for that part of the research. After fMRI, participants are debriefed, which includes initiating a discussion of their overall reaction to the experiment, how the stimuli made them feel, whether they have any questions or problems that they would like to talk about further, etc. Note, our previous experience using tasks that include IAPS stimuli for fMRI assessment in >200 adolescent and young adult participants have never met with any unforeseen, negative reaction after using these procedures.

Skin Conductance Recording During MRI: Risks of physiological recording during MRI include problems related to ferromagnetic equipment being introduced into the MR environment, induced voltages, and radiofrequency (RF) heating [132]. The Biopac electrodermal recording devices we use for MR are classified as MR conditionally safe by the American Society for Testing of Materials [133]. During scanning, time-varying magnetic fields are generated by the gradient coils and RF transmitter, which induce voltages across any conductive loops that can possibly stimulate nerves or heat tissue. These risks are reduced by ensuring that MRI-approved electrodes will be placed between 3-5 cm apart in a configuration that avoids loops, “S” or “U” shapes. Electrode leads will not be twisted and none of the radio-translucent, MRI-compatible wires on SCR-recording electrodes cross on the body. Electrode wires will be run out of the chamber bore in the straightest line possible. After electrode setup with the patient supine in the MR, all SCR wires will be secured with surgical tape at several locations (min 1’ apart) to ensure that casual body movement during the ~1 hour MRI session will not displace them. A blanket will cover each participant to ensure wires do not touch the skin. All electrodes will be checked to ensure close contact with the skin (including use of conductive gel) so that air gaps will not break the electric pathway to build up heat at the electrode center and cause burns. Participants are reminded before and periodically during MRI to report any heating or tingling sensations, which will prompt MR staff safety checks of the SCR recording equipment setup.

Infrared Eyetracking During MRI: The Eyelink® 1000 Fiber Optic eyetracking system is approved for use within an MRI environment. The device conforms to numerous international safety standards (e.g., IEC 60825-1, the Safety of Laser Products standard) which covers laser and LED devices. The Eyelink 1000 is classified as a Class 1 LED device, the highest safety certification, which states that it is “safe under reasonably foreseeable conditions of operation, including the use of optical instruments for intrabeam viewing.” Class 1 classification is similar to that granted for door motion sensors, TV remotes, etc. Therefore any risks of IR exposure to the eye are minimal. Moreover, IR camera use will be limited to <1 hour throughout the entire MRI experiment.

Videotaped Interview: Some participants may be uncomfortable with the idea of being videotaped during interviews or with research staff having access to their medical files. These study procedures are explained in detail during informed consent procedures so that subjects may make an informed decision whether to participate in the study. To assure the confidentiality and protection of participants with respect to videotaping, videos are stored in digital format and are directly uploaded to a secure, HIPAA-compliant database at the Olin NRC immediately following interview; any local copies of the file are destroyed.

Audiotaped Task Debriefing Responses: All digitally recorded responses collected during the task debriefing procedure will be uploaded onto a computer and saved as an electronic file to be transcribed.. Linguistic transcription will be stored on the same secure, HIPAA-compliant database as the videotaped interviews. All electronic files will be destroyed within 6 years following completion of the study.

Urine Collection: Urine specimens are collected to test menstruating females for pregnancy and to monitor unreported substance use prior to MRI scanning and therefore serve as safeguards to participants. It adds no

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risks other than those normally associated with providing a specimen in a private bathroom.

Psychological status: During the course of the evaluation, it is possible that some participants may express either suicidal or homicidal ideation or intent. During consent, potential participants are advised that these issues will be cause to break confidentiality to ensure the safety of the participant or others. The Olin NRC has established procedures to escort participants to the Hartford Hospital Emergency Department psychiatric intake if necessary, or to Children's Hospital ED (which is contiguous with Hartford Hospital/The Institute of Living campus on the same city block, roughly the same distance from the Olin NRC as Hartford Hospital's ED). If study personnel ascertain that participants have increased risk to self or others, the study PI will contact the participant's treatment provider, if any, or police (if necessary). If an unmet treatment need is discovered during the course of psychiatric assessment, study staff under direction of the Principal Investigator will recommend further treatment to the participant. The Olin NRC maintains an updated list of both IOL and non-IOL community practitioners for most psychiatric or substance disorder treatment services. However, study personnel cannot break confidentiality to ensure that participants seek treatment for unmet treatment needs if there is not an imminent danger to self or others. The final exception is that researchers are mandated reporters of child abuse to the CT Department of Children and Families. This role also is explained to participants during informed consent.

Unanticipated risks: Any experiment may involve risks that we cannot predict or anticipate. Participants will be told of any important new information that might affect their decision to continue in the study. In addition, the IRB at Hartford Hospital will be notified if any new risks are identified.

Confidentiality: Confidentiality risks will be minimized by using coded records and by storing signed consent forms in double-locked file cabinets in a secure area of the Olin NRC. Electronic records are kept in HIPAA-compliant databases, with secure, user account/password-controlled access to specific records. All procedures are fully-HIPPA compliant and approved by HH Research Administration. All information and data concerning volunteers are confidential and never released to anyone outside of the project without the volunteer's written authorization. The identity of participants is never revealed in research reports.

Adequacy of Protection Against Risks

Informed Consent Informed consent is obtained in writing from all volunteers prior to research participation by a trained research staff. Informed consent meetings will always include a trained research staff member and the potential participant. The detailed consent form will be read to and discussed with these persons. They will be given several opportunities to ask questions and will have the option to watch movies of the laboratory procedures before signing the consent. Prior to agreeing to be in study, it is reinforced that participants can discontinue at any time without prejudice and that questions at any time are encouraged. All potential participants are offered an opportunity to review Hartford Hospital's Patient Bill of Rights and given phone numbers of Olin NRC faculty and disinterested third-party Hartford Hospital officials who oversee research activities or advocate patient rights if there are any complaints. Understanding of study procedures is ascertained by the potential participant's ability to repeat back the procedures and the risks involved in their own words. Any doubts about a potential subject's willingness to participate and their understanding, the PI will opt to exclude the subject.

Potential Benefits of the Proposed Research to the Subjects and Others / Importance of the Knowledge to be Gained Although a substantial investment of time and effort will be required of research participants for clinical interviewing, ER training, and MRI scanning, these methods are fairly non-invasive with regard to importance of information obtained. Such information is routinely collected in clinical research. Appropriate safeguards are in place to protect the well-being and confidentiality of subjects who agree to participate in the study. Furthermore, participants will be compensated monetarily for their time to a degree that does not offer an undue incentive for their cooperation. Therefore, we judge the risks and the intrusion to subjects to be minimal. The scientific benefits of the planned study are high, given the scientific importance of understanding the neurobiology of emotion regulation network changed following ER training. With the safeguards in place as described above, we believe the risks of the study are low. The risk-benefit ratio appears, therefore, to be favorable.

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Data Safety and Monitoring Plan Whether or not this study should be considered a clinical trial is debatable. On the one hand, we will randomize participants into conditions and train them in how to regulate their emotions with separate tactics. Moreover, we are specifically recruiting a sample who will range from having mildly-elevated depression/anxiety symptoms to those who might meet DSM 5 diagnostic criteria for MDD or anxiety disorders. However, we purposefully are not employing any standardized treatment protocol in favor of using a "bare-bones" training-based intervention that provides guided practice on specific ways to regulate negative affect. We will not present this study opportunity to potential participants with any expectation that by the end of the study they will have achieved any relief for any mood or anxiety problems. Unless directed by the IRB to construct a more formal DSMP, we plan to follow standard Hartford Hospital adverse event reporting guidelines, which require reporting within 24 hours to the hospital Research Administration and Institutional Review Board any serious adverse event (i.e., serious injury or death related to the investigation) and within 7 days for minor adverse effects. However, if a DSMP typically is deemed appropriate by the IRB, we will formulate one that is appropriate to the perceived low-risk entailed in this experimental protocol.

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