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Principal component analysis and brain-based predictors of emotion regulation in anxiety and depression

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Abstract

Background. Reappraisal, an adaptive emotion regulation strategy, is associated with frontal engagement. In internalizing psychopathologies (IPs) such as anxiety and depression frontal activity is atypically reduced suggesting impaired regulation capacity. Yet, successful reappraisal is often demonstrated at the behavioral level. A data-driven approach was used to clarify brain and behavioral relationships in IPs.

Methods. During functional magnetic resonance imaging, anxious [general anxiety disorder ($n = 43$), social anxiety disorder ($n = 72$)] and depressed ($n = 47$) patients reappraised negative images to reduce negative affect ('ReappNeg') and viewed negative images ('LookNeg'). After each trial, the affective state was reported. A cut-point (i.e. values <0 based on ΔReappNeg-LookNeg) demarcated successful reappraisers. Neural activity for ReappNeg-LookNeg, derived from 37 regions of interest, was submitted to Principal Component Analysis (PCA) to identify unique components of reappraisal-related brain response. PCA factors, symptom severity, and self-reported habitual reappraisal were submitted to discriminant function analysis and linear regression to examine whether these data predicted successful reappraisal (yes/no) and variance in reappraisal ability.

Results. Most patients (63%) were successful reappraisers according to the behavioral criterion (values<0; ΔReappNeg-LookNeg). Discriminant function analysis was not significant for PCA factors, symptoms, or habitual reappraisal. For regression, more activation in a factor with high loadings for frontal regions predicted better reappraisal facility. Results were not significant for other variables.

Conclusions. At the individual level, more activation in a 'frontal' factor corresponded with better reappraisal facility. However, neither brain nor behavioral variables classified successful reappraisal (yes/no). Findings suggest individual differences in regions strongly implicated in reappraisal play a role in on-line reappraisal capability.

Introduction

Prevalent internalizing psychopathologies (IPs) such as anxiety and depressive disorders are characterized by excessive and/or inappropriate negative emotions suggesting difficulty managing emotions. Therefore, much work has focused on delineating relationships between psychopathology and cognitive reappraisal, a complex adaptive emotion regulation strategy that modifies the emotional response to a salient stimulus or situation by changing its meaning (Gross and John, 2003). Effectual reappraisal impedes the genesis of negative emotion (Gross and John, 2003) and in healthy individuals frequency of reappraisal is positively associated with mental health (e.g. higher self-esteem, more positive mood) (Gross and John, 2003).

Accordingly, individuals with IPs would be expected to engage in reappraisal less frequently and/or be ineffectual when implementing reappraisal 'on-line' relative to non-psychiatrically ill individuals, yet findings have been inconsistent. For example, while self-reported habitual use of reappraisal (i.e. trait reappraisal) in IPs tends to be lower than healthy individuals, the effect size is moderate and generally less robust than links between maladaptive strategies (e.g. avoidance, rumination, suppression) and psychopathology (Aldao *et al.*, 2010; Werner *et al.*, 2011; Liu and Thompson, 2017; Visted *et al.*, 2018). Moreover, when experimentally induced, reappraisal in IPs is largely intact. That is, studies that instruct participants on reappraisal for negative stimuli show subjective real-time reappraisal ability is comparable between IPs (e.g. social anxiety disorder, depressive disorders, posttraumatic stress disorder) and healthy controls (Goldin *et al.*, 2009; Quigley and Dobson, 2014; Rabinak *et al.*, 2014; Liu and Thompson, 2017; Kivity and Huppert, 2018), though see Fitzgerald *et al.* (2017*b*). Motivational factors and other possible differences between laboratory and real-life settings, such as the self-relevance of negative information to be regulated, instruction on reappraisal

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in the laboratory, and the limitations of self-report (e.g. retrospective bias) may contribute to discordance between trait reappraisal and on-line reappraisal performance.

Evidence individuals with IPs are able to implement reappraisal when instructed indicates certain regions that support reappraisal may be intact or play a compensatory role in regulation facility. However, little is known about the relationship between on-line reappraisal in IPs and neurofunctional activity. Meta-analytic studies involving healthy participants show reappraisal of negative stimuli to inhibit or downregulate negative affective state consistently engages frontal, parietal, and temporal regions (Buhle *et al.*, 2014; Messina *et al.*, 2015) signifying involvement in cognitive control, attention, working memory, and semantic processes (Ochsner *et al.*, 2002). In addition to widespread cortical recruitment, reduced activity in emotion structures such as the amygdala (Ochsner and Gross, 2005), a core emotion generating/processing region (LeDoux, 2000), is considered an index of effectual reappraisal as is an inverse relationship between amygdala activity and activity in the dorsolateral prefrontal cortex (PFC), dorsomedial PFC, orbitofrontal cortex (Banks *et al.*, 2007), or ventrolateral PFC (Wager *et al.*, 2008). Nonetheless, amygdala recruitment during reappraisal has also been observed (McRae *et al.*, 2012; Nelson *et al.*, 2015). Mixed amygdala findings may reflect sub-processes that underlie regulation, one of which involves establishing and elaborating on the emotional meaning(s) of a stimulus so that it can be subsequently re-interpreted (McRae *et al.*, 2012) or an incomplete understanding of amygdala function as it pertains to conscious response to threat (LeDoux, 2014). Together, reappraisal relies on greater frontal, parietal, and temporal region engagement and is associated with either increased or decreased amygdala recruitment.

Compared with healthy participants, individuals with IPs generally exhibit reduced activation in frontal (e.g. dorsolateral PFC, ventrolateral PFC), dorsal anterior cingulate cortex, and parietal areas (e.g. angular gyrus) during reappraisal (Picó-Pérez *et al.*, 2017; Zilverstand *et al.*, 2017). Yet, similar to healthy cohorts, evidence of amygdala effects has been inconsistent (Picó-Pérez *et al.*, 2017; Zilverstand *et al.*, 2017). Even so, cumulative findings based on case-control studies indicate atypical activity during reappraisal cuts across diagnostic boundaries, supporting a transdiagnostic model of regulation (Fernandez *et al.*, 2016). Thus, an important next step in identifying a reappraisal 'biosignature' in IPs is to examine links between reappraisal-related neural activity and behavior.

There is a growing interest in data-driven approaches to elucidate brain-behavior relationships in IPs and efforts are underway to develop a neuroscience-based taxonomy given limitations of the current categorical psychiatric classification system (e.g. extensive comorbidity, symptomatic heterogeneity) and neurobiological discoveries demonstrating psychiatric disorders are 'brain disorders' (Insel *et al.*, 2010; Downar *et al.*, 2016; Kozak and Cuthbert, 2016; Williams *et al.*, 2016). Rather than a disorder-specific approach, the objective is to identify transdiagnostic, psychobiological constructs that play a role in the onset and/or maintenance of psychiatric illnesses and classify phenotypes (Insel *et al.*, 2010; Kozak and Cuthbert, 2016).

An essential aspect of classification is the development of a criterion to reduce varied interpretation as to what constitutes a 'real' outcome regarding a construct and to establish the sensitivity and specificity of classifier performance based on the criterion. In the laboratory setting, a Likert-type scale (e.g. 1 = not at all negative, 5 = extremely negative) is commonly used to assess the effectiveness of reappraisal (e.g. Ochsner *et al.*, 2002, 2012; Banks *et al.*, 2007; Eippert *et al.*, 2007; Frank *et al.*, 2014; Rabinak *et al.*, 2014; MacNamara *et al.*, 2015; Gorka *et al.*, 2016; Fitzgerald *et al.*, 2017*a*; Klumpp *et al.*, 2017). In line with the development of a criterion, we recently used a cut-point to denote successful reappraisal based on subjective ratings (see Methods) in our prior functional magnetic resonance imaging (fMRI) study comprising healthy individuals (Klumpp *et al.*, 2018). Specifically, participants completed a regulation task during fMRI and online behavioral results revealed the majority of participants met the benchmark for successful reappraisal (i.e. 63%). In the same study, Principal Component Analysis (PCA), a data-driven approach that decreases the redundancy of information while maximizing explanatory variance across measures to improve classification accuracy (e.g. reduce over-fitting; Clementz *et al.*, 2016; Drysdale *et al.*, 2016) was performed to identify unique components of brain response during reappraisal.

PCA results showed reappraisal-related factors largely mapped onto the functional properties of brain regions. Regarding classification, successful reappraisal (yes/no) was predicted by more activation in a factor linked with frontal regions (e.g. dorsomedial PFC, inferior orbitofrontal gyrus) and less activation in a factor with high loadings for limbic structures (e.g. amygdala, parahippocampal gyrus) (Klumpp *et al.*, 2018). Findings are consonant with previous correlational and regression studies showing reappraisal is positively associated with frontal engagement and inversely related with amygdala activity (Banks *et al.*, 2007; Eippert *et al.*, 2007; Ochsner *et al.*, 2012; Frank *et al.*, 2014). However, no relationship between trait reappraisal and on-line reappraisal performance was observed indicating these approaches may pertain to differences between naturalistic and laboratory settings and/or capture different facets of reappraisal. Nonetheless, we demonstrated the neural signature of reappraisal-related brain activity.

The objective of the current study was to extend these findings in IPs. Using the same brain regions and methods as our prior study of healthy individuals (Klumpp *et al.*, 2018), we evaluated which factors predicted successful reappraisal (yes/no) as well as individual differences in reappraisal ability in IPs. Based on a neuroscience model of reappraisal (Ochsner *et al.*, 2002), meta-analytic study findings (Buhle *et al.*, 2014; Messina *et al.*, 2015), and our previous findings, we hypothesized successful reappraisal would be predicted by relatively more activation in a factor with high loadings for frontal regions and less activation in a factor with high loadings for limbic regions. We expected a similar pattern of activity when testing for individual differences in regulation performance. We explored whether anxiety symptoms, depression symptoms, and/or trait reappraisal classified reappraisal groups and explained variance in reappraisal facility.

Method

Participants

As part of an on-going study, treatment-seeking individuals were recruited via advertisement (e.g. flyers) in the Chicago community and referrals from a local psychiatric mood and anxiety clinic. Patients diagnosed with generalized anxiety disorder ($n = 43$), social anxiety disorder ($n = 72$), or major depressive disorder ($n = 47$) participated in the study. Participants completed a consent form approved by the local Institutional Review Board at the University of Illinois at Chicago. A master's-level clinician

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Table 1. Participant characteristics

Primary disorder	GAD ($n = 43$), %	MDD ($n = 47$), %	SAD ($n = 72$), %
Female	69.77	80.85	69.44
Race/Ethnicity			
Caucasian	67.44	63.83	62.50
African-American	9.30	14.89	5.56
Asian	11.63	19.15	19.44
Hispanic/Latino	16.28	25.53	26.39
American Indian or Alaskan Native	2.33	0.0	1.39
More Than One Race	4.65	2.13	8.33
Other or Unknown	4.65	0.0	2.78
	M (*s.d.*)	*M* (*s.d.*)	*M* (*s.d.*)
Age in years	27.07 (6.82)	25.51 (8.36)	24.31 (5.53)
Education in years	16.21 (2.83)	15.23 (2.67)	15.26 (2.47)
Hamilton Anxiety Rating Scale	14.81 (6.04)	18.77 (7.36)	14.04 (7.87)
Hamilton Depression Rating Scale	10.56 (3.92)	15.06 (5.05)	11.21 (5.34)

GAD, Generalized Anxiety Disorder; MDD, Major Depressive Disorder; SAD, Social Anxiety Disorder.

performed the Structured Clinical Interview for DSM-5 (First *et al.*, 2015) and other clinician-administered measures. Comorbidity was permitted and the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) were used to assess symptom severity across disorders. See Table 1 for participant characteristics and Table 2 for comorbidity. None of the participants were receiving treatment (i.e. pharmacotherapy or psychotherapy). All participants tested negative on a urine toxicology screen before the scan.

Participants were free of a major medical or neurological illness as confirmed by a Board Certified physician. Exclusion criteria included <18 or more than 65 years of age, contraindications to magnetic resonance imaging (e.g. pregnancy, ferrous objects), current substance dependence (within 6 months of the study), and current or history of major psychiatric illness (e.g. bipolar disorder, schizophrenia) or cognitive dysfunction (e.g. traumatic brain injury, pervasive developmental disorder). Trait reappraisal was evaluated with the reappraisal subscale of the Emotion Regulation Questionnaire (ERQ), a 10-item questionnaire shown to have good internal consistency and test-retest reliability (Gross and John, 2003). All participants were compensated for their time and all procedures complied with the Helsinki Declaration.

fMRI Task

During fMRI, participants completed a well-validated Emotion Regulation Task (ERT) using reappraisal as the form of regulation (e.g. Rabinak *et al.*, 2014; MacNamara *et al.*, 2015; Gorka *et al.*, 2016; Fitzgerald *et al.*, 2017*a*, 2017*b*; Klumpp *et al.*, 2017). ERT comprised 64 unpleasant and 32 neutral International Affective Picture System images (Lang *et al.*, 2008). Eight 20 second (s) blocks of each condition (four images presented for 5 s each) were interspersed with 20 s baseline blocks (comprising a fixation cross). At the beginning of each block, participants were instructed to (1) use reappraisal to reduce negative affect evoked by an aversive image (ReappNeg); (2) attend to, be aware of, and 'feel what you naturally feel' when looking at an aversive image (LookNeg); or (3) view neutral images (LookNeut). The order of blocks was pseudo-randomized over two separate runs of 5 minutes each.

Consistent with prior studies (Ochsner *et al.*, 2002; Phan *et al.*, 2005; Rabinak *et al.*, 2014; MacNamara *et al.*, 2015; Gorka *et al.*, 2016; Fitzgerald *et al.*, 2017*a*, *b*; Klumpp *et al.*, 2017), participants practiced each condition with images not used in the experiment before the scan to ensure understanding of task instructions and reappraisal strategies. For example, transforming the scenario depicted by an image into positive terms or rationalizing or objectifying the content of the image (Phan *et al.*, 2005).

Behavioral reappraisal

Following each block, participants were asked to rate 'How negative do you feel?' on a 5-point scale (1 = 'not at all' to 5 = 'extremely') via button response. To confirm participants followed task instructions for ReappNeg, LookNeg, and LookNeut conditions, a repeated measures analysis of variance (ANOVA) was performed.

The cut-point for effectual reappraisal (yes/no) was based on a difference value wherein negative values (i.e. < 0; ΔReappNeg-LookNeg) indicated *successful reappraisal* and no difference (i.e. 0), or positive values (i.e. > 0; ΔReappNeg-LookNeg), denoted *unsuccessful reappraisal.*

fMRI data acquisition and preprocessing

Scanning was conducted on a 3 Tesla GE Discovery System (General Electric Healthcare; Waukesha, WI, USA) using a standard radiofrequency coil. Blood-oxygen-level dependent-functional images were acquired using a gradient-echo echo-planar imaging sequence with the following parameters: TR = 2s, TE = 25 ms, flip angle = 90°, field of view = 22 × 22 cm^2, acquisition matrix 64 × 64; 44 axial, 3-mm-thick slices with no gap. For anatomical

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Table 2. Primary and comorbid diagnosis

Primary diagnosis	*N*	%
Social anxiety disorder	72	44.4
Major depressive disorder	47	29.0
Generalized anxiety disorder	43	26.5
Comorbidity	**N**	**%**
Social anxiety disorder	46	28.4
Major depressive disorder	35	21.6
Generalized anxiety disorder	34	21.0
Panic disorder	24	14.8
Persistent depressive disorder	23	14.2
Specific phobia	21	13.0
Posttraumatic stress disorder	13	8.0
Agoraphobia	4	2.5
Eating disorder	4	2.4
Obsessive compulsive disorder	3	1.9
Alcohol abuse	2	1.2
Acute adjustment disorder	1	0.6

localization, a high-resolution, T1-weighted volumetric anatomical scan was acquired.

Data from all participants met criteria for quality control with minimal motion correction (movements were <3 mm and <3° rotation in any direction) and the first 4 volumes from each run were discarded to allow for T1 equilibration effects. Conventional preprocessing steps were used in the Statistical Parametric Mapping (SPM8) software package (Wellcome Trust Centre for Neuroimaging, London www.fil.ion.ucl.ac.uk/spm). Briefly, images were temporally corrected to account for differences in slice time collection, spatially realigned to the first image of the first run, normalized to a Montreal Neurological Institute template, resampled to $2 \times 2 \times 2$ mm^3 voxels, and smoothed with an 8 mm isotropic Gaussian kernel.

fMRI analyses

A general linear model was applied to the time series, convolved with the canonical hemodynamic response function and with a 128s high-pass filter. Nuisance regressors comprising six motion parameters were included to correct for motion artifacts. Blocks of ReappNeg, LookNeg, and LookNeut were modeled separately, the effects of which were estimated for each voxel for each participant and taken to the second level for random effects analysis. ReappNeg (*v.* LookNeg) was the contrast of interest as both conditions comprised negative stimuli; therefore, the effects of reappraisal was contrasted with experiencing naturally the emotions elicited by negative images.

Principal component analysis

The Automatic Anatomical Labeling system (Tzourio-Mazoyer *et al.*, 2002) was used to generate regions of interest (ROIs) for regions consistently associated with reappraisal (Buhle *et al.*, 2014; Messina *et al.*, 2015). Occipital areas were included to evaluate the specificity of predictors as visual processes are not strongly implicated in reappraisal (Buhle *et al.*, 2014; Messina *et al.*, 2015). Thus, there were 37 regions in total comprising frontal, parietal, temporal, limbic, and occipital systems (Table 3). Activation (β weights, arbitrary units [a.u.]) derived from these ROIs (Poldrack, 2007) based on ReappNeg (*v.* LookNeg) were submitted to PCA in the Statistical Package for the Social Sciences (SPSS) (Chicago, IL; Version 24). Eigenvalue coefficients >0.60 (Guadagnoli and Velicer, 1988) based on Varimax rotations indicated significant loading of ROIs on a factor.

Classifier analysis

To examine predictors of successful reappraisal (yes/no) based on a behavioral cut-point (i.e. <0 or ⩾0 ΔReappNeg-LookNeg) resulting PCA Bartlett factor scores, each a composite of all ROIs with loadings of varying degrees, were submitted to discriminant function analysis in SPSS, a multivariate method to predict group membership. The discriminate function assumes different classes generate data based on different Gaussian distributions. Here, classes were successful and unsuccessful reappraisers (Model 1). Cross-validation (leave one out) was used to estimate the generalizability of significant results. The same analysis was performed with anxiety (HAM-A), depression (HAM-D), and trait reappraisal (ERQ) total scores (Model 2).

Linear regression analysis

To examine whether brain or behavioral data predicted individual differences in affective state (ΔReappNeg-LookNeg ratings), stepwise regression was performed where the dependent variable was the ΔReappNeg-LookNeg value and the independent variables were all PCA Bartlett factors (Model 1). The same analysis was conducted with anxiety (HAM-A), depression (HAM-D), and trait reappraisal (ERQ) total scores as independent variables (Model 2).

For significant findings, post-hoc regression analysis (enter method) was performed to examine potential moderators. All variables (e.g. behavioral performance, PCA factor scores, symptoms) were mean centered. Effect codes (k-1) were generated for diagnostic status. The dependent variable always comprised affective state (i.e. ΔReappNeg-LookNeg ratings); Blocks 1 and 2 consisted of the independent variable of interest and interaction term, respectively.

Results

Behavioral results (manipulation check)

The ANOVA showed a main effect of Condition [$F(2, 322) = 393.63$, $p < 0.001$]. Follow-up paired t tests revealed that average affective state was less negative in the ReappNeg (2.56 ± 0.72) than LookNeg (2.89 ± 0.75) condition [$t(161) = 5.89$, $p < 0.001$]. When viewing neutral images (i.e. LookNeut), average affective state was less negative (1.33 ± 0.44) compared with either ReappNeg [$t(161) = 21.59$, $p < 0.001$] or LookNeg [$t(161) = 24.91$, $p < 0.001$] conditions.

Reappraisal groups

Across participants the behavioral criterion for reappraisal indicated 102 participants (63%) successfully employed reappraisal

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Table 3. Regions of interest in Principal Component Analysis

Frontal Cortex
L Orbitofrontal inferior gyrus
R Orbitofrontal inferior gyrus
L Frontal inferior triangularis
R Frontal inferior triangularis
L Dorsolateral prefrontal cortex
R Dorsolateral prefrontal cortex
L Superior frontal gyrus
R Superior frontal gyrus
Dorsal anterior cingulate cortex
Dorsomedial prefrontal cortex
Ventromedial prefrontal cortex
Parietal Cortex
L Inferior parietal lobule
R Inferior parietal lobule
L Superior parietal lobule
R Superior parietal lobule
L Angular gyrus
R Angular gyrus
Temporal Cortex
L Inferior temporal gyrus
R Inferior temporal gyrus
L Middle temporal gyrus
R Middle temporal gyrus
L Superior temporal gyrus
R Superior temporal gyrus
L Anterior insula
R Anterior insula
Occipital Cortex
L Inferior occipital gyrus
R Inferior occipital gyrus
L Middle occipital gyrus
R Middle occipital gyrus
L Superior occipital gyrus
R Superior occipital gyrus
Limbic System
L Amygdala
R Amygdala
L Putamen
R Putamen
L Parahippocampal gyrus
R Parahippocampal gyrus

L = left; R = right.

(negative values based on ΔReappNeg-LookNeg; average = −0.73 ± 0.52) whereas 60 participants (37%) were unsuccessful (average = 0.35 ± 0.42).

Data structure

The Kaiser-Meyer-Olkin value was 0.94 indicating sampling with 37 ROIs was adequate (Kaiser and Rice, 1974; Cerny and Kaiser, 1977). The PCA revealed 4 factors explained 87.5% of the total variance and all ROIs were significantly correlated with each other (all $r's > 0.30$, all $p's < 0.05$); therefore, none of the ROIs were excluded from the model. Loadings of ROIs on Varimax rotations for each factor were as follows: Factor 1 was robustly associated with limbic and temporal structures (e.g. amygdala, parahippocampal gyrus, superior temporal gyrus, anterior insula) ('limbic-temporal' factor); Factor 2 with frontal regions (e.g. frontal superior gyrus, dorsolateral PFC) ('frontal' factor); Factor 3 largely consisted of occipital regions ('occipital' factor); and Factor 4 mostly comprised parietal areas (e.g. inferior and superior parietal gyrus) along with dorsal anterior cingulate cortex ('parietal' factor). See Table 4 and Fig. 1 for details.

Reappraisal classifier performance

Discriminant function analysis was not significant for any factor (Model 1; Wilks $\lambda = 0.97$, $\chi^2(4) = 5.52$, $p = 0.24$)†[1] or anxiety, depression, or trait reappraisal (Model 2; Wilks $\lambda = 0.97$, $\chi^2(3) = 4.40$, $p = 0.22$).

Individual differences and reappraisal

Regression analysis revealed more effectual reappraisal based on ΔReappNeg-LookNeg ratings was predicted by higher activation in the 'frontal' factor [$R^2 = 0.03$, $F(1,160) = 4.85$, $p < 0.029$] ($B = 0.12$, $p < 0.029$) whereas 'limbic-temporal', 'occipital', 'parietal' factors were not significant (all $p's > 0.05$). To aid in the interpretation of significant results, we performed a two-tailed partial correlation analysis for the 'frontal' factor and ΔReappNeg-LookNeg ratings, controlling for diagnostic status. Results were significant ($r = 0.17$, $p < 0.033$), however, a scatter plot pointed to two possible outliers (Fig. 2, left panel). Therefore, regression analysis was performed without these participants and significant results were preserved [$R^2 = 0.03$, $F(1,158) = 4.66$, $p < 0.032$] ($B = 0.15$, $p < 0.032$). See Fig. 2, right panel, illustrating a scatter plot based on partial correlation analysis. The same regression analysis comprising anxiety (HAM-A), depression (HAM-D), and trait reappraisal (ERQ) was not significant (all $p's > 0.05$).

For post-hoc regression analysis, the interaction term involved the 'frontal' factor (e.g. HAM-A × 'frontal' factor). Regarding anxiety (HAM-A), there was no main effect ($p = 0.81$) or moderator ($p = 0.97$). Null findings were also observed for depression (HAM-D), trait reappraisal (ERQ), and diagnostic status (all $p's > 0.05$). See Table 5 for all results.

Discussion

The objective of the present study was to use PCA to identify factors in anxious and/or depressed patients that captured distinctive neurofunctional activity during reappraisal and to examine

†The notes appear after the main text.

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Table 4. Principal Component Analysis Varimax rotated component matrix results for Reappraise Negative (v. Look Negative)

Regions of interest	Factors/Components			
	1	2	3	4
L Parahippocampal gyrus	**0.846**	0.183	0.275	0.136
R Parahippocampal gyrus	**0.823**	0.234	0.346	0.207
R Amygdala	**0.785**	0.390	0.309	0.185
L Amygdala	**0.784**	0.346	0.339	0.184
L Superior temporal gyrus	**0.735**	0.263	0.239	0.413
L Putamen	**0.699**	0.538	0.284	0.223
R Anterior insula	**0.684**	0.535	0.177	0.269
R Putamen	**0.681**	0.558	0.254	0.237
L Anterior insula	**0.681**	0.591	0.217	0.229
L Middle temporal gyrus	**0.649**	0.297	0.423	0.457
L Orbitofrontal inferior gyrus	**0.637**	**0.602**	0.276	0.232
R Superior temporal gyrus	**0.627**	0.248	0.324	0.524
R Orbitofrontal inferior gyrus	0.590	0.531	0.287	0.355
L Inferior temporal gyrus	0.587	0.321	0.531	0.296
L Superior frontal gyrus	0.319	**0.810**	0.323	0.276
R Superior frontal gyrus	0.345	**0.809**	0.293	0.281
Dorsomedial prefrontal cortex	0.350	**0.807**	0.281	0.293
L Dorsolateral prefrontal cortex	0.327	**0.760**	0.317	0.393
L Frontal inferior triangularis	0.409	**0.675**	0.373	0.341
R Dorsolateral prefrontal cortex	0.305	**0.658**	0.268	0.545
Ventromedial prefrontal cortex	0.524	**0.604**	0.319	0.096
R Frontal inferior triangularis	0.400	0.594	0.404	0.457
R Middle occipital gyrus	0.283	0.286	**0.820**	0.331
R Superior occipital gyrus	0.308	0.288	**0.772**	0.358
L Middle occipital gyrus	0.403	0.325	**0.755**	0.316
R Inferior occipital gyrus	0.340	0.265	**0.751**	0.312
L Inferior occipital gyrus	0.400	0.329	**0.727**	0.322
L Superior occipital gyrus	0.363	0.327	**0.707**	0.361
R Inferior temporal gyrus	0.454	0.297	**0.615**	0.407
R Inferior parietal lobule	0.165	0.217	0.234	**0.885**
R Angular gyrus	0.196	0.192	0.276	**0.840**
L Inferior parietal lobule	0.281	0.340	0.387	**0.729**
R Superior parietal lobule	0.162	0.252	0.555	**0.669**
L Angular gyrus	0.327	0.324	0.331	**0.659**
Dorsal anterior cingulate cortex	0.311	0.429	0.343	**0.640**
L Superior parietal lobule	0.223	0.388	0.565	0.567
R Middle temporal gyrus	0.523	0.221	0.517	0.525

(*Continued*)

Table 4. (*Continued.*)

L, left; R, right.
Eigenvalue coefficients >0.60 are in bold.

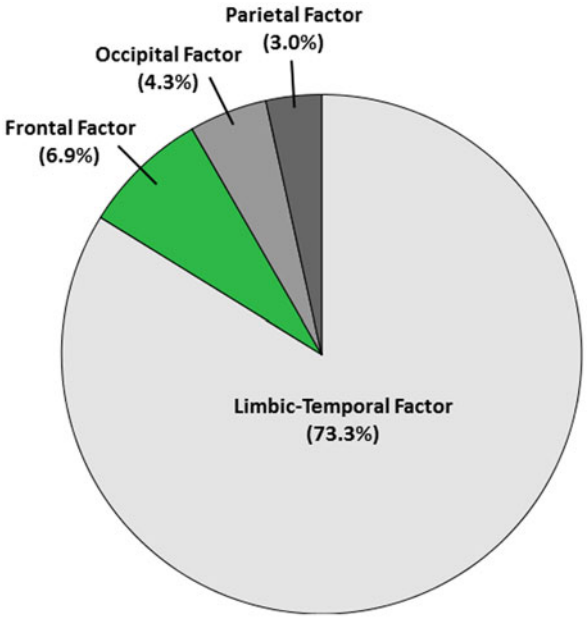

Fig. 1. Pie chart illustrating Principal Component Analysis in terms of the total variance explained; extraction sums of squared loadings percent of variance.

whether the factors classified successful reappraisal (yes/no) based on a behavioral criterion. We also evaluated the extent to which individual differences in on-line reappraisal facility corresponded with brain-based factors, illness severity, and trait reappraisal. PCA results yielded a 4-factor solution and the coherence of regions mostly mapped onto (i.e. had strong loadings according to) their functional properties when reappraising negative images *v.* looking at negative images. Discriminant function analysis failed to show brain response, symptoms, or trait reappraisal classified reappraisal groups. However, regression analysis demonstrated the 'frontal' factor corresponded with better on-line reappraisal ability across participants. There was no relationship between real-time reappraisal capacity and other brain-based factors, symptoms, or trait reappraisal and no moderators were detected.

Findings expand on our previous study and the broader psychopathology literature regarding reappraisal. Hypotheses were partially supported. Though reappraisal-related neural activity

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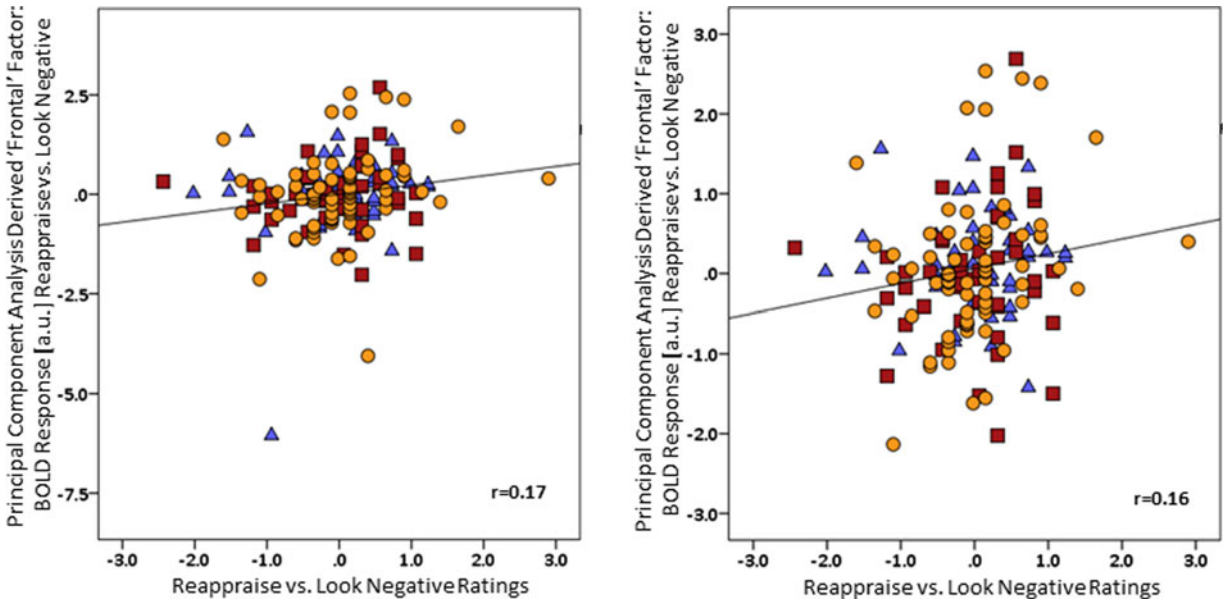

Fig. 2. Post-hoc scatter plot showing more activation in a 'frontal factor' derived from Principal Component Analysis (PCA) is positively associated with greater reduction in affective state during reappraisal (v. looking at negative images) across all participants controlling for diagnostic status (left panel). After the removal of two potential outliers, post-hoc scatter plot depicting more activation in a 'frontal factor' derived from PCA corresponds with greater reduction in affective state during reappraisal (v. looking at negative images) across remaining participants controlling for diagnostic status (right panel).
Note: For Fig. 2, triangles = Generalized Anxiety Disorder, squares = Major Depressive Disorder, and circles = Social Anxiety Disorder.

did not classify successful reappraisers, variance in reappraisal performance was predicted by a factor with high loadings for frontal regions (e.g. superior frontal gyrus, dorsolateral PFC). The failure of PCA derived factors to classify reappraisal groups may be due in part to the data structure. In our prior study of healthy participants, the same regions comprising reappraisal-related activation produced a 5-factor PCA solution, each factor having high loadings for regions with similar functions. Specifically, latent factors represented occipital, frontal, parietal, temporal, and limbic systems with the factor strongly linked to occipital regions explaining the majority of variance (Klumpp *et al.*, 2018). Yet, in the current study, a 4-factor solution was observed as certain factors were more diffuse than others with regard to their functional properties. For example, the factor that explained the majority of variance had high loadings for limbic and temporal regions thus a clear underlying limbic dimension was lacking. Furthermore, the orbitofrontal gyrus had high loadings across 'limbic-temporal' and 'frontal' factors and the factor largely associated with parietal structures also had a high loading for dorsal anterior cingulate cortex. Even so, while the more diffuse neural-based dimensions of reappraisal may have reduced its power to serve as a classifier, average non-PCA-related activity in occipital, frontal, parietal, temporal, and limbic systems also failed to classify successful reappraisers. Potentially, combining activity across multiple *a priori* regions is not optimal in predicting reappraisal ability (yes/no) in IPs and/or reappraisal in IPs extends beyond regions consistently observed in healthy individuals (Buhle *et al.*, 2014; Messina *et al.*, 2015). Future work may benefit from data-driven methods encompassing all brain regions.

Regarding data structure, the qualitative difference between our prior study and the current study highlights features of reappraisal, which includes the visual processing of images (e.g. perceptual and attentional resource allocation) and cognitive-linguistic strategies to manage response to negative information. Namely, healthy participants may vary more in the visual processing substrate of reappraisal as indicated by the 'occipital' factor accounting for the majority of variance (68.0%) whereas individual differences in IPs may pertain more to emotion processing and semantic systems. Here, the 'limbic-temporal' factor explained the majority of variance (73.3%) possibly reflecting differences in the semantic content used to reappraise negative images, which interacted with emotion processing circuitry. Put another way, in our healthy cohort, the 'temporal' and 'limbic' factors only accounted for 4.4% and 3.0% of total variance, respectively. Thus, healthy participants may have been more comparable in their semantic approach thereby reducing variance in the limbic-related factor. Further study is necessary to understand reappraisal-related data structure differences and the characterization of component-associated variance.

As hypothesized, a positive relationship between a factor with high loadings for frontal regions and reappraisal performance was shown suggesting a greater reduction in negative affective state due to reappraisal corresponded with more engagement of regions strongly implicated in reappraisal (Buhle *et al.*, 2014; Messina *et al.*, 2015). However, findings were limited to the 'frontal' factor; the lack of an expected correspondence between variance in on-line reappraisal facility and limbic activity may again pertain to the lack of a clear underlying limbic dimension. Moreover, evidence of limbic (e.g. amygdala) activity in reappraisal for negative stimuli in IPs has been mixed (Picó-Pérez *et al.*, 2017; Zilverstand *et al.*, 2017), therefore, further study is needed to understand the contribution of the limbic system in reappraisal. In addition to this null finding, variance in reappraisal did not correspond with factors that had high loadings for occipital or parietal regions indicating activity in such areas did not play an important role in foretelling reappraisal performance.

At the behavioral level, the majority of participants met the cut-point for successful reappraisal (63%) adding to accumulating evidence that clinically anxious or depressed individuals are able to implement reappraisal when instructed (Goldin *et al.*, 2009;

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Table 5. Linear regression results for ΔReappraise Negative-Look Negative as the dependent variable

Planned analysis (stepwise method)	*R*	Adjusted R^2	*B*	*p*
Model 1				
'Frontal' factor	0.17	0.03	0.12	0.03
Excluded variables				
'Limbic' factor	–	–	−0.02	0.84
'Occipital' factor	–	–	−0.08	0.32
'Parietal' factor	–	–	0.01	0.93
Model 2				
Excluded variables				
HAM-A	–	–	0.002	0.77
HAM-D	–	–	−0.002	0.88
ERQ	–	–	−0.002	0.84
Post Hoc Analysis (enter method)				
Anxiety symptoms				
Block 1				
HAM-A	0.02	−0.01	0.01	0.81
Block 2				
HAM-A	0.02	−0.01	0.01	0.97
HAM-A × 'Frontal' factor			−0.004	
Depression symptoms				
Block 1				
HAM-D	0.01	−0.01	−0.01	0.95
Block 2				
HAM-D	0.02	−0.01	−0.004	0.98
HAM-D × 'Frontal' factor			0.01	
Trait reappraisal				
Block 1				
ERQ	0.02	−0.01	−0.01	0.84
Block 2				
ERQ	0.09	−0.01	−0.02	0.55
ERQ × 'Frontal' factor			−0.06	
Diagnostic status; MDD as reference group				
Block 1				
GAD	0.06	−0.003	0.05	0.48
Block 2				
GAD	0.07	−0.01	0.05	0.70
GAD × 'Frontal' factor			0.04	
Block 1				
SAD	0.05	−0.004	−0.04	0.56
Block 2				
SAD	0.09	−0.01	−0.04	0.53
SAD × 'Frontal' factor			0.07	

HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; ERQ, Emotion Regulation Questionnaire (reappraisal subscale); MDD, Major Depressive Disorder; GAD, Generalized Anxiety Disorder; SAD, Social Anxiety Disorder.

Quigley and Dobson, 2014; Rabinak *et al.*, 2014; Liu and Thompson, 2017; Kivity and Huppert, 2018). However, in contrast to our earlier study, brain response did not predict successful reappraisers, therefore, more work is necessary to delineate a reappraisal 'biosignature' in IPs based on a criterion.

Future studies may benefit from employing multiple measures to define successful reappraisal. For example, our participants may have been subject to social desirability bias or fears of being perceived as incompetent thereby reducing the ability to detect a classifier based on self-report. Hence, the inclusion of less face valid measures of effectual reappraisal such as (neuro) physiological measures (e.g. reduced skin conductance response, decreased late-positive potential; Hajcak and Nieuwenhuis, 2006; Gruber *et al.*, 2014; Fitzgerald *et al.*, 2016) will aid in the development of reliable and construct valid classifiers. Measures that impact emotion are also important to consider. Deficits in emotional clarity, namely, difficulty in identifying which emotions one feels (Salovey *et al.*, 2002) is associated with depression and social anxiety symptoms and mediated by self-reported regulation difficulties (Vine and Aldao, 2014). Therefore, an important direction for future research is the examination of emotional clarity and other emotion-related factors that may interact with regulation (e.g. alexithymia, emotional tolerance; Visted *et al.*, 2018).

We explored whether symptoms or trait reappraisal predicted successful reappraisal (yes/no), individual differences in on-line reappraisal facility, or moderated the link between 'frontal' activation and variance in reappraisal ability. Results were not significantly adding to accruing reports of discrepancy between trait reappraisal and its associations with symptoms and real-time reappraisal performance in IPs (Goldin *et al.*, 2009; Rabinak *et al.*, 2014; Liu and Thompson, 2017; Kivity and Huppert, 2018). Reasons for the incongruence may depend on the way reappraisal was defined in either setting. For instance, as is conventional, participants were provided examples of reappraisal strategies prior to the ERT. In contrast, reappraisal, as assessed with the ERQ (Gross and John, 2003), is relatively vague (e.g. 'When I want to feel less negative emotion, I change the way I'm thinking about the situation'). Consequently, the cognitive approaches used on a day-to-day basis may be more diverse than the reappraisal strategies used in the experiment. Furthermore, the frequency of reappraisal as measured with the ERQ does not necessarily imply effectiveness (Ford *et al.*, 2017), and the stimuli used in the laboratory (i.e. images of general negative content) may not be as salient as events in real-world settings.

More broadly, evidence that neurofunctional activity was superior to non-fMRI data in predicting on-line reappraisal facility suggests proximal measures of brain function may be more

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sensitive than distal measures (e.g. symptoms) in identifying emotion regulation phenotypes. In studies that use neuroimaging to predict treatment outcome, brain response has also been shown to outperform clinical measures in foretelling which patient is likely to benefit from treatment (Mayberg *et al.*, 1997; Doehrmann *et al.*, 2013; Ball *et al.*, 2014; Thompson *et al.*, 2015; Klumpp *et al.*, 2017). Collectively, findings are in keeping with the proposal that a brain-based taxonomy will improve psychiatric nosology.

This study is not without limitations. First, there were more patients with a primary anxiety disorder than depression; it will be important to replicate these results in a sample matched on primary diagnosis. Second, the sample was heterogeneous and comorbidity extensive, therefore, results may not replicate in a more homogeneous cohort with few or no concurrent psychiatric illness. Third, the sample was relatively small for a data-driven analytic approach to identify predictors of reappraisal ability. Fourth, when using PCA, factors encompass a composite of all measures. Consequently, interpretations based on regions with high loadings does not imply that results are exclusive of other regions that were entered into the model. Fifth, the regions submitted to PCA were those implicated in reappraisal, thus, results may not replicate when all regions based on a conventional atlas are used. Sixth, participants were given examples of cognitive approaches that provided alternative paths to cognitive change. Though the examples were used to aid in clarifying what was meant by 'reappraisal', the lack of a standard cognitive strategy could have introduced confounds.

Despite limitations, a brain-based factor with prominent loadings for frontal regions uniquely predicted individual differences in reappraisal ability across anxious and depressed patients. Findings suggest that when instructed to reappraise negative images, the recruitment of regions involved in cognitive control plays a role in reappraisal facility in a transdiagnostic patient population.

Note

[1] Due to null results, we explored whether average neural activity across regions that underlie each frontal, parietal, temporal, limbic, and occipital system predicted successful reappraisal; results were not significant (Wilks $\lambda = 0.98$, $\chi^2(5) = 3.55$, $p = 0.62$).

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