LOCALIZED OR DIFFUSE: A VOLUMETRIC INVESTIGATION OF THE RELATION BETWEEN PREFRONTAL CORTICAL REGIONS AND THE HABITUAL ENGAGEMENT OF COGNITIVE REAPPRAISAL

BY

MATTHEW MOORE

THESIS

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Advisers:

Assistant Professor Florin Dolcos, Chair
Professor Monica Fabiani

ABSTRACT

Despite extensive functional brain imaging research pointing to the role of the prefrontal cortex (PFC) in cognitive reappraisal, the structural correlates of habitual engagement of reappraisal are unclear. Functional brain imaging studies of reappraisal have shown broad engagement of bilateral middle frontal cortex (MFC) and left superior frontal cortex (SFC), and specific engagement of the right SFC. However, previous volumetric studies have not identified clear associations between reappraisal and these regions. This discrepancy between functional and structural studies suggests that the broad functional engagement associated with reappraisal might not be detectable at a structural level using highly localized volumetric measures. The present study addressed this issue by assessing the relation between reappraisal and grey matter volume in the MFC and SFC, using methods that allow both broad/diffuse and specific/localized measures. As predicted, results were consistent with diffuse volumetric associations with reappraisal in the right MFC and left SFC, and a localized volumetric association in the right SFC, thus resolving the seeming discrepancy between functional and structural studies of reappraisal. Overall, the present study provides novel evidence supporting the idea that functional engagement related to transient manipulations of reappraisal can be linked to structural associations related to the habitual engagement of similar operations, within the same brain regions.

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CHAPTER 1

INTRODUCTION

The way a person controls his or her emotions, or *emotion regulation*, is often studied in two complementary dimensions, cognitive reappraisal and expressive suppression (Gross & John, 2003). *Reappraisal* refers to the ability to change one's view of a particular situation in order to see it in a different light, whereas *suppression* refers to the tendency to inhibit one's emotional responses to keep them inside (Gross & John, 2003). Although these dimensions of emotion regulation have been extensively studied in functional brain imaging studies (e.g., Buhle et al., 2013; Goldin, McRae, Ramel, & Gross, 2008; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004), relatively little is known about the relation between the habitual engagement of emotion regulation and structural neural markers, such as cortical grey matter volume. Given evidence that reappraisal is a particularly effective emotion regulation strategy (Augustine & Hemenover, 2009; Webb, Miles, & Sheeran, 2012), associated with positive indicators of mental health (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Gross & John, 2003; Hu et al., 2014; John & Gross, 2004; Llewellyn, Dolcos, Iordan, Rudolph, & Dolcos, 2013), understanding its neural associations is a critical step in the development of clinical interventions and educational practices to support emotional well-being. The goal of the present investigation was to clarify the relation between the habitual engagement of emotion regulation through reappraisal and structural associations in the brain, using a volumetric approach.

Reappraisal has been shown to have both functional (Buhle et al., 2013; Ochsner & Gross, 2008; Ochsner, Silvers, & Buhle, 2012) and structural correlates in the brain (Giuliani, Drabant, & Gross, 2011; Hermann, Bieber, Keck, Vaitl, & Stark, 2014; Welborn et al., 2009). However, functional imaging and volumetric studies of the brain have yielded seemingly

inconsistent results regarding the association between reappraisal and key regions involved in emotion regulation and emotion-cognition integration in the prefrontal cortex (PFC; Hermann et al., 2014; Kuhn, Gallinat, & Brass, 2011). Hence, the link between brain function and structure with respect to reappraisal remains unclear. Functional brain imaging literature has systematically associated reappraisal with PFC engagement (Buhle et al., 2013; Ochsner & Gross, 2008; Ochsner et al., 2012), and available evidence suggests a possible distinction between regions showing a relatively broad engagement and regions showing relatively localized effects. Overall, these studies emphasize the role of both the MFC and SFC in emotion regulation through reappraisal, but point to more broad engagement identified in bilateral MFC and left SFC, with peak voxel activations in Brodmann areas (BAs) 6, 9, 10, and 46 (Buhle et al., 2013; Goldin et al., 2008; Mcrae, Ochsner, Mauss, Gabrieli, & Gross, 2008; Ochsner et al., 2002; Phan et al., 2005) and more localized engagement identified in the right SFC, with peak voxel activations primarily restricted to BAs 6 and 8 (Grecucci, Giorgetta, Van't Wout, Bonini, & Sanfey, 2013; Silvers, Weber, Wager, & Ochsner, 2014).

Functional imaging evidence identifying the neural correlates associated with individual differences in the tendency to use reappraisal (Drabant, McRae, Manuck, Hariri, & Gross, 2009) suggests that the habitual ways in which individuals regulate their emotions impacts neural processing and might, over time, influence the structure of the underlying brain regions. Although there is no clear indication of the direction of the relationship between the grey matter volume and individual differences in personality traits, a growing body of evidence suggests that there is a relation between the volume of a brain region and its level of use (Boyke, Driemeyer, Gaser, Buchel, & May, 2008; Draganski et al., 2004). This account, called *use-dependent plasticity* (Butefisch et al., 2000), may describe a result of Hebbian learning, which posits that

repeated patterns of neuronal firing lead to increased synaptic connectivity (Hebb, 1949), and suggests that these structural changes might lead to increases in grey matter volume (Draganski et al., 2006). This would suggest that individual differences in the habitual engagement of reappraisal would be associated with differences in grey matter volume in the underlying brain structures.

In contrast to functional studies, previous anatomical studies (Hermann et al., 2014; Kuhn et al., 2011) have not identified clear associations between reappraisal and MFC and SFC volumes, despite identifying structural associations with other brain regions, such as the ventromedial prefrontal cortex, the dorsal anterior cingulate, and the amygdala (Giuliani, Drabant, & Gross, 2011; Hermann et al., 2014; Welborn et al., 2009). One possible explanation for the discrepancy between functional and structural studies is that the latter used highly localized, voxel-based methods (Hermann et al., 2014; Kuhn et al., 2011; but see Giuliani, Drabant, Bhatnagar, & Gross, 2011; Giuliani, Drabant, & Gross, 2011), which might have prevented the identification of the broader prefrontal areas shown to support reappraisal in functional studies. Thus, it remains unclear how the MFC and SFC regions are related to the habitual engagement of reappraisal at a structural level.

The present study addressed this issue using a comprehensive methodological investigation based on two complementary volumetric methods: surface-based morphometry (SBM), which allows for testing more diffuse associations, and voxel-based morphometry (VBM), which allows for testing more localized associations. Specifically, diffuse associations were expected to be reflected in relatively larger extent, more easily identified by whole-region analyses (SBM) and likely only at lower significance thresholds by voxel-level analyses (VBM). On the other hand, localized associations were expected to be reflected in relatively smaller

extent, less likely to be identified by SBM, but surviving higher significance thresholds in VBM analyses. Based on the functional literature and the theory of association between brain function and structural plasticity, it was expected that habitual engagement of reappraisal would be positively associated with brain volume in the MFC and SFC, and that this association would be (i) more diffuse in the bilateral MFC and left SFC, regions most consistently reported as having broad increased activation for reappraisal and (ii) more localized in the right SFC, the region reported in more specific/localized engagement of reappraisal.

CHAPTER 2

MATERIALS AND METHODS

Subjects

Data were collected from a sample of 85 healthy young participants (18-34 years old; *M* = 23.25 years old, *SD* = 3.95, 48 females), who had undergone MRI scanning. No participants had previously been diagnosed with any neurological, psychiatric, or personality disorders. Two participants were excluded from all analyses, one because of incomplete neuropsychological measures and the other because of outlier reappraisal score. Participants with outlier anatomical measures were removed analysis-wise (see below and Results section). Outlier values were determined using a criterion of 3 standard deviations (Osborne & Overbay, 2004) for trait scores and for SBM/VBM measures. The experimental protocol was approved for ethical treatment of human participants by the institutional Health Research Ethics Board. Participants provided written consent and were compensated with either course credit or money.

Emotion Regulation Measures

Habitual engagement of cognitive reappraisal was assessed using the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). This questionnaire assesses the habitual engagement of two emotion regulation strategies, reappraisal and suppression, using a 7-point Likert scale that ranges from "Strongly agree" to "Strongly disagree". Examples of statements from the reappraisal dimension include "I control my emotions by changing the way I think about the situation I'm in", and statements from the suppression dimension include "I keep my emotions to myself" (Gross & John, 2003). Reappraisal score was measured by 6 items (Cronbach's alpha = 0.735, $n = 83$) and suppression score was measured by 4 items (Cronbach's alpha = 0.787, $n = 83$). Reappraisal was not correlated with control variables of age ($r = -0.186$, $p = 0.092$, $n = 83$),

or total intracranial volume (TIV; r = -0.069, p = 0.542, n = 81), but was negatively correlated with suppression score (r = -0.229, p = 0.037, n = 83). TIV was not correlated with age (r = -0.025, p = 0.823, n = 81). Also, independent sample t-tests did not reveal any significant difference between sex in reappraisal score (t = 0.301, p = 0.764, n = 83), age (t = -0.132, p = 0.896, n = 83), or TIV (t = -1.537, p = 0.129, n = 81). The lack of significant correlation between reappraisal and the control variables indicated that these would be appropriate for inclusion in the multiple regression analyses.

Brain Imaging and Processing Procedures

Anatomical images (3D MPRAGE, TR = 1,600 ms; TE = 3.82 ms; FOV = 256 x 256 mm; volume size = 112 slices; voxel size = 1 x 1 x 1 mm^3) were obtained using a 1.5-T Siemens Sonata scanner. To test predicted diffuse vs. localized volumetric associations, brain imaging data were processed using two procedures, a surface-based segmentation procedure (SBM) and a voxel-based morphometric (VBM) procedure. SBM output included whole-region ROI definitions in order to test diffuseness of associations at a more global level. Surface-based cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite (Freesurfer Version 5.3; Fischl, 2012), which is freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Raw DICOM images were imported directly into Freesurfer, where a semi-automatic workflow was adopted to ensure quality control at the stages of Talairach registration, skull stripping, white matter surface reconstruction, and pial surface reconstruction. Output from each of these stages was visually examined for quality assurance, and major errors were corrected using standard adjustment parameters or manual intervention before re-running the necessary processing steps again until results were of good quality. The Desikan-Killiany (Desikan et al., 2006) atlas in Freesurfer was used to define anatomical ROIs

for the MFC (to approximate lateral regions within BAs 10, 9, 6, 46) and SFC (to approximate superior regions within BAs 10, 9, 8, 6). The combined anatomical ROIs of the rostral middle frontal cortex (rMFC) and the caudal middle frontal cortex (cMFC) from the Desikan-Killiany atlas were used to test the general hypothesis of association in the MFC, as both rostral and caudal regions of the MFC have been shown to be associated with reappraisal in the functional literature (Ochsner & Gross, 2005). Together, the rMFC and cMFC ROIs describe the region bordered by the medial and rostral extent of the superior frontal sulcus, and the inferior frontal sulcus (Desikan et al., 2006). The SFC ROI is described as the region bordered by the rostral and lateral extents of the superior frontal sulcus, the paracentral sulcus, and the medial extent of the frontal lobe (Desikan et al., 2006).

To address sensitivity at a more localized level than whole-region SBM, VBM was performed in addition to the SBM processing, providing complementary analysis at a voxel level. VBM typically uses the grey matter volume (GMV), segmented from white matter volume (WMV) and cerebral spinal fluid (CSF), as the dependent variable that is analyzed (Ashburner, 2009). VBM was performed in SPM8 (Ashburner et al., 2008) with the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/; Gaser, 2009; Kurth, Luders, & Gaser, 2010) using MATLAB 7.4 (Mathworks, Released 2007). Processing included importing raw DICOM images directly into SPM8 (Ashburner et al., 2008), converting the raw images into NIFTI, then aligning the image origins with the anterior commissure and image orientations to be parallel with the anterior-posterior commissural plane, followed by normalizing to a standard template in MNI space using DARTEL via VBM8 (Ashburner, 2009; Gaser, 2009; Kurth et al., 2010). VBM8 default settings are documented elsewhere (Gaser, 2009; Kurth et al., 2010) and were used in processing unless otherwise noted. Grey matter segmentations were modulated using the

Jacobian determinant, that is, an index of the nonlinear warping factor used to expand or shrink local grey matter volume for each subject in order to normalize the subject brain to the standard template (Ashburner, 2009), and were saved using the VBM8 default setting (Gaser, 2009; Kurth et al., 2010). Quality of normalization accuracy was assessed using visual inspection of the normalized T1 weighted images for each subject, and through boxplot display of covariance to assess homogeneity of the normalized image data (i.e., modulated smoothed grey matter segmentations), which are both standard steps in VBM8. A Gaussian smoothing kernel of 10 mm full width at half maximum (FWHM) was used on the grey matter maps to correct for registration inaccuracies inherent to the normalization process. ROIs were selected using automatic anatomical labeling (AAL) in the WFU PickAtlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002). ROI masks were created in the PickAtlas toolbox and resliced from atlas space to normalized grey matter space in SPM8. Again, the ROI used for MFC analysis was the middle frontal gyrus ROI, described as the region bordered by the superior frontal sulcus and the inferior frontal sulcus (Tzourio-Mazoyer et al., 2002), and the ROI for SFC analysis encompassed the region bordered by the superior frontal sulcus, the paracentral sulcus, and the medial extent of the frontal lobe (Tzourio-Mazoyer et al., 2002).

Five participants were determined to have outlier anatomical volumes or poor registration, with one participant having outlier values in both, and were removed analysis-wise, as follows: as assessed by SBM, two participants had outlier TIV, one had outlier right MFC volume, one had outlier right SFC volume; as assessed by VBM, two were identified as having possibly anomalous registration quality in VBM (determined by plotting covariance of normalized smoothed grey matter images with a criterion of 3 standard deviations; one of these was also an outlier for SBM TIV).

Statistical Analyses

Statistical analyses for demographic variables and the whole-region ROIs were performed in IBM SPSS Statistics 22 (IBM, Released 2013). For both the SBM and VBM approaches, multiple regression analyses were used to test the hypotheses regarding the relation between emotion regulation and PFC volume. In SBM, the selected ROI volume was used as the dependent variable, with the model including independent variables of sex, age, TIV as nuisance variables, and reappraisal score as the variable of interest. Quality assurance of all SBM regression analyses was assessed by examining the probability of Mahalanobis D^2 and variation inflation factor (VIF). In all cases, no subjects showed probability of Mahalanobis $D^2 < 0.001$, supporting the assumption that no subject had anomalous values of multiple variables. In all cases, VIF was less than 2, supporting the assumption that the emotion regulation scores and the nuisance covariates were measuring unique aspects or relations in the model.

The multiple regression model was also performed at the voxel level using VBM data. The modulated smoothed grey matter segmentation for each subject was used as the dependent variable, with the regression model including the covariates of sex and age as nuisance variables, and reappraisal score as the covariate of interest. An absolute threshold mask of 0.1 was used, along with an implicit mask. For the targeted analyses, contrast maps were created by controlling for effects of sex and age and then examining the relation of emotion regulation through reappraisal within each of the selected ROIs (MFC and SFC). Initial analyses used a height threshold corrected for multiple comparisons for within the extent of the ROI at $p\text{FWE} \leq 0.05$. Follow-up analysis used an uncorrected threshold of $p \leq 0.001$, unless otherwise described. For initial analyses, extent thresholds were determined empirically using the expected voxels per cluster as calculated by SPM8 (Ashburner et al., 2008; Kurth et al., 2010). For VBM, TIV was

corrected for by scaling the grey matter data, which was accomplished by exporting grey matter segmentations normalized with the non-linear normalization component only, which effectively removes the affine normalization accounting for global brain size and allows for analysis to be considered to be on relative volume corrected for overall brain size differences (Kurth et al., 2010). This is a suggested approach for VBM (Kurth et al., 2010) that has been used successfully in previous literature (Hermann et al., 2014) and, in principle, provides a similar correction to controlling for TIV through the use of a statistical covariate.

To quantify the relative diffuseness in MFC and SFC of the reappraisal associations, volumes were extracted from the modulated smoothed grey matter segmentations. Significant clusters were initially identified at a range of uncorrected height thresholds: $p \leq 0.0005$, $p \leq 0.001$, $p \leq 0.0025$, $p \leq 0.005$, $p \leq 0.01$, $p \leq 0.025$, and $p \leq 0.05$ within each ROI mask for a positive association of reappraisal, while controlling for sex and age. No extent thresholds were used for this analysis. The resulting cluster maps were saved as binary masks and where then used for volume extraction using a MATLAB script. Additionally, total volume for each ROI was extracted and used to convert the cluster volumes at each significance level into proportions for comparison. Then, to test for differences between region volumes, proportional volumes were entered into a repeated measures ANOVA with a factor of brain region and repeated measure of proportional volume at each significance level. ANOVA results are reported using Greenhouse-Geisser correction.

CHAPTER 3

RESULTS

Evidence for Diffuse vs. Localized Associations of Cognitive Reappraisal with Right MFC vs. Right SFC Volumes

As expected, reappraisal score showed positive associations with whole-region but not voxel-level volumes in the right MFC and left SFC, and voxel-level but not whole-region volumes in the right SFC. Consistent with a diffuse volumetric association, reappraisal was significantly associated with right MFC whole-region volume ($\beta = 0.208$, $p = 0.035$, $n = 80$), and was marginally associated with left SFC volume ($\beta = 0.199$, $p = 0.056$, $n = 81$); reappraisal was not associated with left MFC volume ($\beta = 0.153$, $p = 0.134$, $n = 81$). At a voxel level, no association was shown in the right MFC, left MFC, or left SFC that survived both the corrected height and empirically-determined extent threshold, suggesting that there were no localized effects detectable within these regions. However, consistent with the prediction of a more diffuse association, there were extended clusters associated with reappraisal in the right and left MFC when the height threshold was lowered. Additionally, when the threshold was lowered to uncorrected $p \leq 0.001$, a cluster was shown in the left SFC (*Tmax* = 3.51, empirically-determined extent threshold of 152 voxels; MNI coordinates: x = -14, y = 11, z = 70; $k = 403$; $n = 81$), suggesting a more diffuse, lower threshold volumetric association. Cluster volumes were extracted and quantified for testing in subsequent analyses with right SFC, as described below. To check for differences due to sex, a sex and reappraisal interaction term was added to the original regression analyses in both SBM and VBM. To avoid variance inflation due to the interaction term, mean-centered reappraisal score was used in these models and in calculating the

interaction terms. The sex and reappraisal interaction analysis did not show any significant effect in MFC or SFC for either approach.

For the right SFC, the voxel-level results were consistent with a localized volumetric association. Specifically, the regression model showed a significant positive association between reappraisal score and right SFC (*Tmax* = 4.62, height threshold of pFWE ≤ 0.05 corrected for within the extent of the right SFC ROI and empirically-determined extent threshold of 82 voxels; MNI coordinates: x = 29, y = 14, z = 61; $k = 95$; $n = 81$). At a whole-region level, reappraisal score did not show a significant association with right SFC volume ($\beta = 0.159$, $p = 0.134$, $n = 80$), suggesting that there was not a diffuse volumetric association with reappraisal in this region. Sex and reappraisal interaction analysis did not show a significant effect in right SFC for VBM or SBM.

Based on the previous results identifying a diffuse association in right MFC and a localized association in right SFC, an additional analysis was performed to assess the gradient of diffuseness of association between reappraisal and proportional region volume using volumes extracted from VBM ($n = 81$). A repeated measures ANOVA showed a significant main effect of brain region, $F(1, 80) = 4180.055$, $p < 0.001$, of significance threshold, $F(1.100, 87.961) = 51237.126$, $p < 0.001$, and a significant interaction between brain region and significance threshold $F(1.282, 102.561) = 4173.756$, $p < 0.001$, indicating that there was a difference in the average percentage of ROI volume associated with reappraisal across significance levels. Results for the ANOVA are shown in Figure 1.

Post-hoc comparisons showed that, consistent with the expectation of a more diffuse association in right MFC, mean proportional volume of right MFC (13.990% ± 0.080%) was significantly larger than for right SFC (9.459% ± 0.056%, $p < 0.001$, Bonferroni corrected). The

interaction between region and significance threshold provided additional clarification about this effect. Consistent with the expectation of diffuse (relatively larger extent, lower significance) association of reappraisal in right MFC compared to localized (relatively smaller extent, high significance) association of reappraisal in right SFC, right MFC showed a numerically lower proportional volume associated with reappraisal at a significance level of $p \leq 0.0005$ compared to right SFC, and showed a numerically higher proportional volume compared to right SFC at a significance level of $p \leq 0.0025$. This suggests that for this data, the cross-over point between diffuse compared to localized associations was around the typical exploratory significance threshold of $p \leq 0.001$.

To visualize the relative diffuseness of the effects in right MFC and SFC, T-maps from the initial VBM analysis were converted to maximum intensity plots and then projected as surfaces in MATLAB. As can be seen in Figure 2, the MFC association showed more diffuse, lower significance cluster(s), while the SFC showed a more localized, higher significance cluster. Consistent with the ANOVA analysis, this visualization indicated that the significance level around $p = 0.001$ is the point where significance and volume effects interact.

CHAPTER 4

DISCUSSION

In the current report, diffuse and localized volumetric associations of reappraisal were examined in the MFC and SFC using two complementary methods: one allowing whole-region (SBM) and the other allowing voxel-level (VBM) assessments. Results showed novel positive volumetric associations between habitual engagement of reappraisal and these regions, identifying a diffuse volumetric association in the right MFC and left SFC, and a localized association in the right SFC. These findings provide structural evidence consistent with the idea of use-dependent plasticity as a possible mechanism explaining the link between brain function and structure described by Hebbian learning (Hebb, 1949) neurons that "fire together, wire together"). Consistent with this idea, suggesting that systematic differences in function may also be associated with systematic differences in structure, if the bilateral MFC and left SFC are broadly engaged by general reappraisal processing, then the structural association with reappraisal should also be evident across diffuse neuronal populations. Furthermore, if the right SFC is focally engaged by specific reappraisal processing, then the structural association with reappraisal should be evident in a localized neuronal population. The current results support this idea in the right MFC, showing volumetric associations of reappraisal at a whole-region level, and in the right SFC, showing volumetric association of reappraisal at a voxel level. As discussed below, these results reconcile the seeming discrepancy between functional and structural brain imaging studies of reappraisal effects in the PFC.

The right MFC findings support the broad functional role of this region in reappraisal (Ochsner et al., 2012; Silvers et al., 2014), and extend this association to the structural level. These findings provide novel empirical support for interpretations of previous comparisons

between different anatomical methods (Giuliani, Drabant, Bhatnagar, et al., 2011), suggesting that some associations are more diffuse, and therefore may be captured by more holistic ROI methods such as SBM or manual tracing. The SFC results support the idea that the right SFC may be specifically and more focally engaged when particularly intense emotions are being regulated, whereas the left SFC may broadly handle regulation for lower and higher intensity emotions (Silvers et al., 2014). This has implications for future volumetric studies, as it indicates that the context in which a function engages a brain region, and the extent of the region that is engaged by a function, should be taken into account when generating predictions, selecting methodological approaches, or defining ROIs. Together, the SBM and VBM results suggest a possible explanation as to why some volumetric literature has shown seeming discrepancies with functional literature and has failed to detect effects in some regions while successfully detecting them in others. A combined SBM-VBM approach might therefore be useful for the study of other individual differences, where associations might be more distributed, and might be a complementary analysis to methods targeting individual differences across many regions, or at the level of networks. For example, the extant literature which has focused on individual differences within the framework of personality neuroscience has depended largely on voxel-level analyses (DeYoung et al., 2010). Additional clarifications may emerge if a multi-method approach is taken to investigations in these areas.

The results of the confirmatory analysis on the relative diffuseness of associations between reappraisal and volume provide further support for the diffuse effect in right MFC and localized effect in right SFC. Consistent with the Hebbian learning model (Hebb, 1949), one possible mechanism that could underlie volumetric effects is changes in synaptic connectivity and dendritic arborization. However, it has also been noted that volumetric effects could

represent differences in cell size (Draganski et al., 2006). In either case, the relative diffuseness of association is informative about what regions are more broadly involved in emotion regulation, and may suggest possible regions where structural changes may occur related to affective disorders. Indeed, the current results are consistent with previous research that has shown decreased MFC and SFC volume in patients with depression (Chang et al., 2011). Although volumetric studies provide partial insight into the underlying anatomy, the present findings are also consistent with postmortem investigations which have shown decreased density and size of neurons and glial cells within the PFC of subjects with depression (Rajkowska et al., 1999), which points to possible changes that might underlie observed volumetric effects. Additionally, several recent lesion studies have examined the prefrontal cortex and reappraisal performance (as compared to habitual emotion regulation), and have shown that reappraisal performance was impaired by PFC lesions (Falquez et al., 2014; Salas, Gross, & Turnbull, 2014). Together, the present results and the extant literature suggest that interventions that involve training for emotion regulation through reappraisal might result in beneficial structural changes.

Reappraisal has also been shown to be a protective emotion regulation factor against other biological risk factors. For example, the influence of genetic polymorphisms associated with risk of depression have been shown to be moderated by reappraisal (Ford, Mauss, Troy, Smolen, & Hankin, 2014), suggesting that the benefits of emotion regulation fit within a larger biological framework of individual differences. This is consistent with extant models positing that individual differences at the level of genotype, experience, and personality influence the neural correlates of emotion processing (Hamann & Canli, 2004). Targeting emotion regulation through reappraisal to improve the health of brain regions at a structural and functional level could improve the contribution of emotion regulation to relevant outcomes, such as resilience

against developing clinical conditions (Aldao et al., 2010; Llewellyn et al., 2013) and academic resilience (Graziano, Reavis, Keane, & Calkins, 2007; Schelble, Franks, & Miller, 2010).

Caveats

One caveat to this study is that although previous literature examining emotion-cognition networks was used to inform the hypotheses, the current study focused only on two key brain regions. Another region that has been indicated in emotion regulation, for example, is the ventrolateral prefrontal cortex (vlPFC; Buhle et al., 2013; Ochsner et al., 2012; Silvers et al., 2014; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). However, the vlPFC has been indicated as a region that overlaps across a number of networks (Corbetta & Shulman, 2002; Dolcos, Iordan, & Dolcos, 2011; Power & Petersen, 2013) and hence it may be functionally more heterogeneous; therefore, it was not targeted in the current study. Another caveat of the present study is the cross-sectional design, which does not allow us to assess the directionality of the associations between habitual reappraisal and the identified brain structures. Future research using longitudinal or intervention designs are needed to clarify this issue.

CHAPTER 5

CONCLUSION

In summary, by using complementary volumetric methods to assess the relation between habitual engagement of reappraisal and grey matter volume in the MFC and SFC, the present study provides novel empirical evidence reconciling the seeming discrepancy between functional and structural brain imaging studies of reappraisal. As predicted, results are consistent with diffuse volumetric associations with reappraisal in the right MFC and left SFC, and a localized volumetric association in the right SFC. These results provide novel evidence supporting the idea that functional engagement related to transient manipulations of emotion regulation is paralleled by structural associations of habitual engagement of similar operations, within the same brain regions.

FIGURES

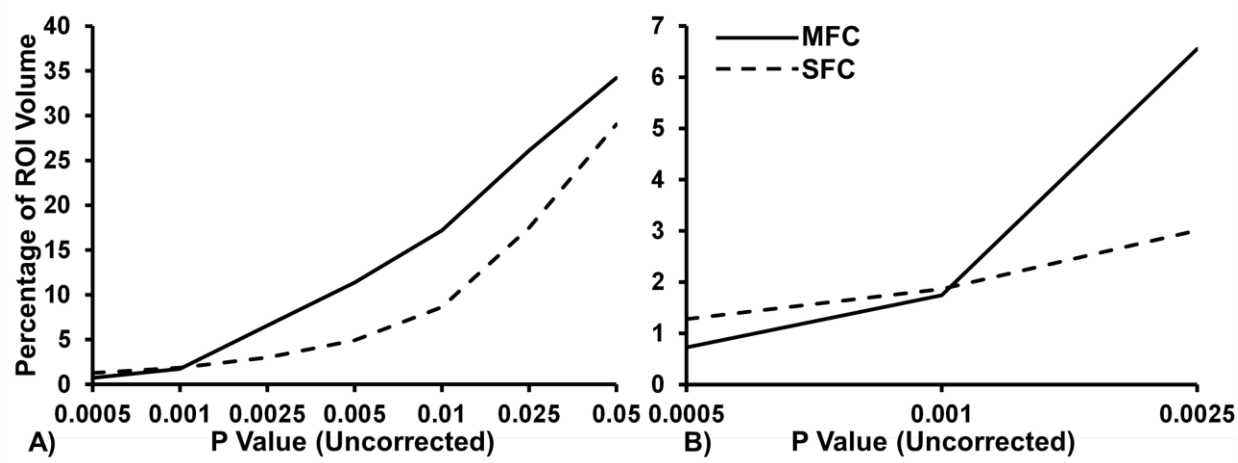

Figure 1. More diffuse volumetric association with reappraisal in the right MFC than right SFC. A) The estimated marginal means plot for significance threshold and percentage of ROI volumes. The right MFC shows a smaller percentage of ROI volume associated with reappraisal at higher significance levels compared to right SFC, but larger increase in volume associated with reappraisal compared to right SFC. B) The cross-over interaction between the right MFC and right SFC occurs around the significance threshold of $p = 0.001$. ROI = Region of Interest; MFC = Middle Frontal Cortex; SFC = Superior Frontal Cortex.

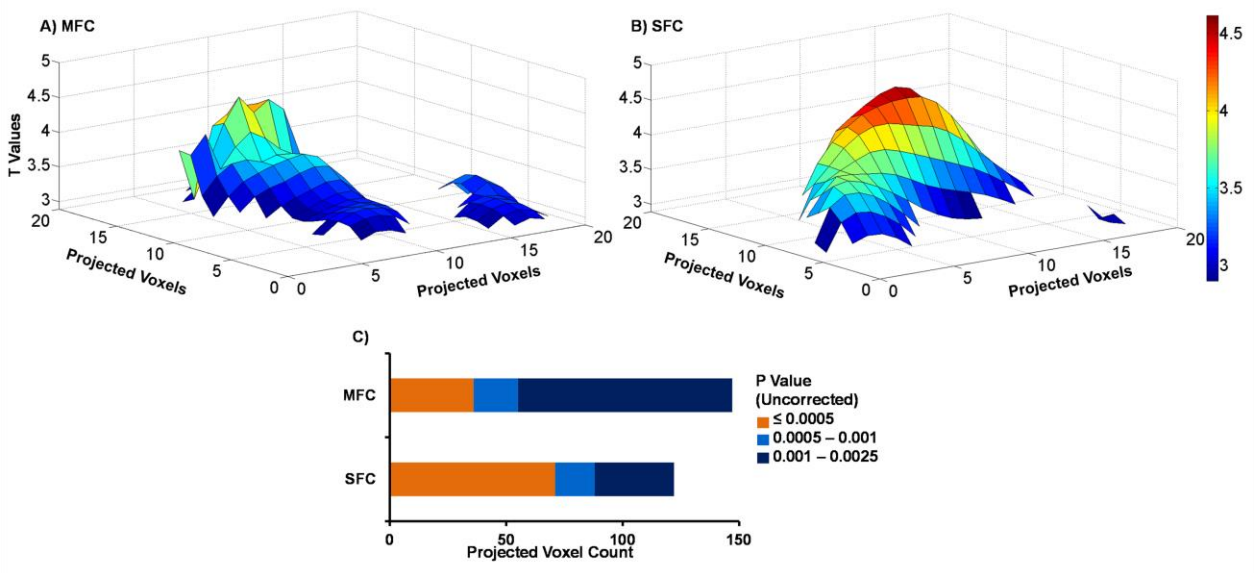

Figure 2. Differential intensity distribution of volumetric association with reappraisal in the right MFC (A) compared to in the right SFC (B). T-maps for the right MFC and SFC were converted to maximum intensity plots and mapped as surfaces in MATLAB. The matrix values have been thresholded at the critical T-value associated with a contrast at $p \leq 0.0025$. The X and Y axes show projected voxel dimensions, the Z axis shows T values. C) Projected voxel counts for MFC and SFC. MFC = Middle Frontal Cortex; SFC = Superior Frontal Cortex.

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