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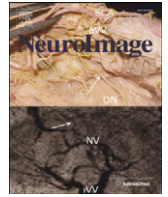
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## Emotion regulation and brain plasticity: Expressive suppression use predicts anterior insula volume

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### ABSTRACT

Expressive suppression is an emotion regulation strategy that requires interoceptive and emotional awareness. These processes both recruit the anterior insula. It is not known, however, whether increased use of expressive suppression is associated with increased anterior insula volume. In the present study, high-resolution anatomical MRI images were used to calculate insula volumes in a set of 50 healthy female subjects (mean 21.9 years) using both region of interest (ROI) and voxel-based morphometry (VBM) approaches. Participants also completed trait measures of expressive suppression usage, cognitive reappraisal usage, and negative emotional reactivity (the latter two served as control measures). As predicted, both ROI and VBM methods found that expressive suppression usage, but not negative affect and cognitive reappraisal, was positively related to anterior insula volume. These findings are consistent with the idea that trait patterns of emotion processing are related to brain structure.

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### Introduction

Throughout their lives, individuals manifest idiosyncratic ways of regulating their emotions. These characteristic patterns of habitual emotion regulation usage have been shown to be related to consistent patterns of affective responding, social relationships, and even overall life satisfaction (Gross & John, 2003). Recent work suggests that individual differences in emotion regulation usage have neural correlates that are evident in the way individuals automatically process emotional stimuli (Drabant et al., 2009). These findings suggest that the way individuals regulate their emotions day in and day out meaningfully impacts neural processing, and might, over the longer term, influence the structure of these underlying brain regions.

#### Use-dependent brain plasticity

A growing literature supports the notion of use-dependent brain plasticity, which holds that the size of a brain region is influenced by its use (Kleim et al., 1998, 2002). This work has focused on the repetition of physical actions or sensory and auditory processing (Kleim & Jones, 2008), and has demonstrated that the repeated practice of a behavior is crucial for brain growth; merely learning a behavior will not cause a significant change in neuroanatomy (Monfils et al., 2005; Monfils & Teskey, 2004). The mechanisms underlying this

effect may involve Hebbian learning, which refers to the notion that neurons that regularly “fire together, wire together” (Hebb, 1949). Such increased synaptic connectivity and dendritic arborization may then lead to increased gray matter volume (May, 2008; Trachtenberg et al., 2002).

Recently, this work has been extended to cognitive behaviors. For example, longitudinal studies have found that acquiring large amounts of knowledge (Draganski et al., 2006), learning a complex motor skill (Draganski & May, 2008), or engaging in aerobic exercise (Colcombe et al., 2006) cause an increase in local gray matter volume. Although prior studies of use-dependent brain plasticity have largely focused on changes in cognition and behaviors, recent cross-sectional work has shown that individual differences in personality traits, emotional expression, temperament, and emotional intelligence also relate meaningfully to regional brain volume (DeYoung et al., 2010; Koven et al., 2010; van Schuerbeek et al., 2011; Welborn et al., 2008). In addition, it has recently been demonstrated that an eight week mindfulness-based stress reduction intervention also affects regional gray matter volume (Holzel et al., 2011).

#### Expressive suppression

One particularly consequential psychological function that is known to show considerable inter-individual variation is emotion regulation (Gross & John, 2003). Emotion regulation refers to the processes by which people seek to influence which emotions they have, when they have them, and how they experience and express these emotions (Gross, 1998). One commonly used form of emotion

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regulation is expressive suppression, a response-focused form of emotion regulation that seeks to prevent the outward expression of emotion after the emotional response has already been generated.

#### *The anterior insula*

Work implicating the anterior insula in interoception suggests that it could play a crucial role in expressive suppression. Activation in the anterior insula represents physical sensations like the viscosity of oral stimuli (De Araujo & Rolls, 2004), and is correlated with individual differences in interoceptive abilities like heart rate detection (Wiens, 2005). These and other related findings have implicated the anterior insula in awareness and consciousness (Craig, 2009). The anterior insula is integral to the subjective awareness of emotion through interoception (Coen et al., 2009), and the subjective idea of the self as a feeling entity (Craig, 2003).

Suppression of emotional responses involves both interoception and emotional awareness: monitoring of the exterior bodily state (“Am I showing my emotions outwardly?”) as well as the interior emotional state (“What is my emotion now? Do I need to keep suppressing?”). Compared to passively viewing negative emotional stimuli, suppressing emotional expressions was found to increase activation in the left anterior insula, but an alternative form of emotion regulation – cognitive reappraisal – did not (Goldin et al., 2008). Therefore, it may be that regularly activating the anterior insula in the pursuit of the suppression of the outward expression of emotion may increase the volume of the anterior insula. However, this possibility has never been experimentally tested.

#### *The present study*

To date, the only studies that have examined the relationship between use of expressive suppression and regional brain volume have focused on the frontal cortex (Kuhn et al., 2011; Welborn et al., 2008). To explore the relationship between trait usage of expressive suppression and anterior insula volume, we recruited a sample of healthy adult women who underwent high-resolution brain imaging and completed measures of expressive suppression, as well as two control measures, trait negative affect and usage of another emotion regulation strategy, cognitive reappraisal.

Although voxel-based morphometry (VBM) is rapidly becoming the most popular method for testing volumetric hypotheses in humans, past studies directly comparing it with the more traditional region of interest (ROI) methods suggest that VBM and ROI methods produce similar but not identical results (Asami et al., 2008; Bergouignan et al., 2009; Giuliani et al., 2005). For this reason, we used both ROI and VBM methods to test the hypothesis that use of expressive suppression should be positively correlated with the volume of the anterior insula. Importantly, we predicted that this relationship would be specific to suppression and the anterior insula; we did not expect that trait negative affect or cognitive reappraisal usage would be related to anterior insula volume.

## **Materials and methods**

#### *Participants*

Fifty right-handed healthy female volunteers between the ages of 18 and 25 (mean: 21.9 years, SD: 2.4) participated after providing informed consent according to the guidelines of the Stanford University Institutional Review Board. All participants were recruited as part of a larger parent study, and this sample was limited to only females in order to control for known differences in regional brain volume and emotional responding (Bradley et al., 2001; Chen et al., 2007). The Structured Clinical Interview for the DSM-IV was used to rule out past or current Axis I and II disorders (First et al., 1995), and

participants were screened for health conditions that affect cerebral blood flow. They were paid for their participation.

#### *Individual difference measures*

Trait expressive suppression was assessed using an 8-item suppression scale based on the Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003). A matching 8-item scale, also based on the ERQ, was used to measure trait cognitive reappraisal. These items were answered on a 1-to-7 Likert scale, and had satisfactory internal consistency (reappraisal: Cronbach's alpha = .93; suppression: Cronbach's alpha = .92). Both reappraisal (mean 4.82, SD 1.16) and suppression (mean 3.73, SD 1.26) were normally distributed (Shapiro-Wilk:  $p > .75$ ), and there were no outliers.

Trait negative affect was assessed using the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988). For each of 10 items, participants indicated their general frequency of negative mood states on a 5-point Likert scale (1 = not at all, 5 = extremely). Negative Affect (NA; mean 14.09, SD 3.67) was not normally distributed (Shapiro-Wilk:  $p < .001$ ), but a natural log transformation improved the distribution. Two outliers were removed from the NA data.

Reappraisal and suppression were uncorrelated ( $r = -.046$ ,  $p = .744$ ), and neither correlated with NA ( $p > .15$ ). Total brain volume (TBV) was also uncorrelated with reactivity and regulation variables ( $p > .15$ ).

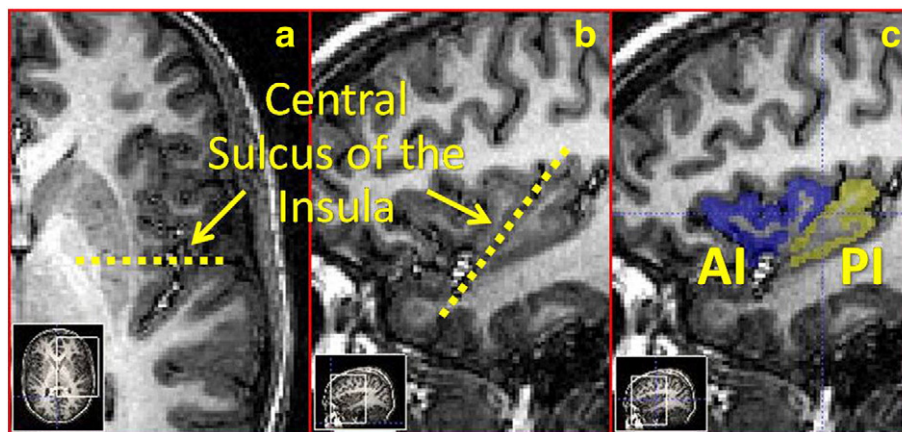
#### *Image acquisition*

Subjects were scanned with a General Electric Signa 3.0T magnet (General Electric Medical Systems, Milwaukee, WI) with a quadrature head coil at Stanford University's Lucas Center. Head movement was minimized using a bite bar and foam padding. A whole brain, high-resolution three-dimensional spoiled gradient recalled (SPGR) T1-weighted anatomical scan ( $0.859 \times 1.2$  mm, field of view = 22 cm, frequency encoding = 256) was acquired for each subject. The total anatomical scan time was about 10 min. Functional scans were also obtained, but are not reported here. Preprocessing was conducted using MATLAB (2008a, The MathWorks, Natick, MA), and consisted of reslicing images to  $1 \text{ mm}^3$  voxels and aligning them into AC-PC space. The AC-PC alignment creates a coordinate system in which individual brains can be placed in a standard orientation. Images were then converted to Analyze format for VBM, and NIFTI format for ROI drawing.

#### *Image analysis*

The relationship between regional brain volume and trait emotion regulation strategy usage was tested using two methods: ROI and VBM. For ROI analyses, independent raters were trained on the following drawing protocol. Insula borders were determined in the coronal view (Naidich et al., 2004). The superior boundary was the circular sulcus of the insula, and the inferior boundary was the Sylvian Fissure. These two sulci were also the posterior and superior boundaries in the lateral portion of the insula. More medially, the vertical ramus became the anterior border. The posterior border of insula was the central sulcus of the insula, which serves to separate the anterior and posterior insula cortices (Naidich et al., 2004), and was located by raters in the sagittal view (Fig. 1). Drawing was performed in the sagittal view, such that both the left and the right insula were drawn in the same location on the computer screen to minimize perceptual biases. To determine inter-rater reliability, 20% of the total number of subjects ( $N = 10$ ) were chosen from the whole study sample, and ROIs were independently traced by two different raters. Inter-rater reliabilities for each rater and region were sufficiently high, with both Cronbach's alphas above .85, and the inter-rater reliability for total anterior insula volume was .92. These





**Fig. 1.** Insula borders: a) axial view indicating location of the central sulcus of the insula, b) sagittal view indicating the location of the central sulcus of the insula, and c) same slice as in Fig. 1b, but with anterior and posterior insula ROIs drawn. AI = Anterior Insula, PI = Posterior Insula.

inter-rater reliabilities are within the acceptable range in this field (see, for example, Cohen et al., 2010; Duggal et al., 2005; Wible et al., 1997).

VBM was used for two different purposes in this study. First, T1 images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and summed to calculate TBV, which was used in ROI analyses as to control for individual variations in global brain volume (Barnes et al., 2010). Each raw ROI volume was divided by that subject's TBV to create a proportion, which was then entered into statistical analyses in SPSS. Second, VBM was used to measure how GM volume varied as a function of emotion reactivity and regulation on a voxel-by-voxel basis. For both purposes, VBM was performed using the following methodology: FSL-VBM was used to perform brain extraction and to create a study-specific template, and SPM-VBM was used for the rest of the processing and statistics.

In FSL-VBM (S. M. Smith et al., 2004), structural images are brain-extracted using the Brain Extraction Toolbox (BET) (S. Smith, 2002). Next, tissue-type segmentation is carried out using FAST4 (Zhang et al., 2001). The resulting gray-matter partial volume images are then aligned to MNI152 standard space using nonlinear registration using FNIRT (Andersson et al., 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The resulting images are averaged to create a study-specific template. The brain-extracted images from FSL were ported into SPM5, where they were segmented into GM, WM, and CSF components using the standardized unified segmentation model in SPM5 (Ashburner & Friston, 2005). Next, the GM and WM segmented images were normalized to the customized template created using FSL-VBM using the diffeomorphic anatomic registration using exponentiated lie algebra (DARTEL) registration method (Ashburner, 2007). This nonlinear warping technique minimizes between-subject structural variations. Finally, spatially normalized images were modulated to ensure that the overall amount of each tissue class was not altered by the spatial normalization procedure, and smoothed with an 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel.

### Statistics

Statistical analyses of the questionnaire and ROI data were conducted in SPSS 18.0 (SPSS Inc., Chicago, IL). Data were checked for normality using histograms and the Shapiro-Wilk test. If variables were non-normal, log and square root transformations were performed in order to improve normality. The transformation that was the most successful was then chosen. Outliers that were determined to be greater than 1.5 times the interquartile range from the upper and lower quartiles were removed from analyses. Of the original 52 subjects run through the study, two subjects' insula ROI volume data

were determined to be outliers. To ensure that we ran the same subjects through VBM analyses, these two subjects were completely removed from all analyses.

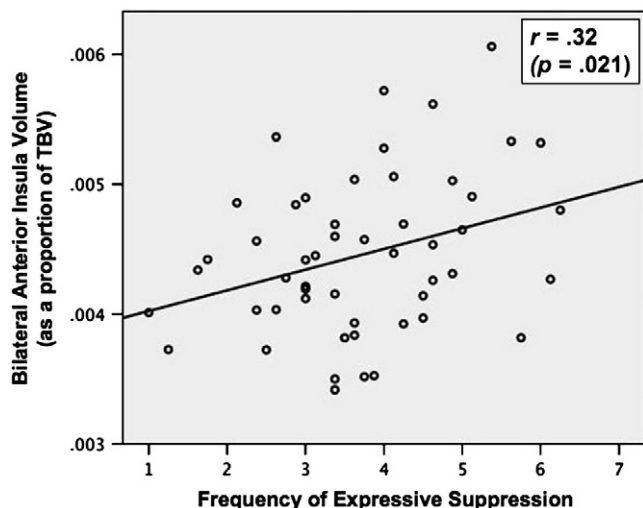
Hypotheses were tested using Pearson's correlations. Significant results were then tested with multiple regression to ensure that the effects of interest held while controlling for others. Lastly, multiple comparison corrections were performed using the false discovery rate (FDR), which assumes positive dependence or independence among variables, and was performed independently for each hypothesis. The FDR is based on the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995), which, according to Benjamini and Yekutieli (2001), is sufficient to use on data that are predominantly independent or positively correlated (Benjamini & Yekutieli, 2001), which holds for this data set.

Statistics on VBM-processed GM images were conducted using the General Linear Model (GLM) in SPM5. This tests the null hypothesis that all estimates are zero using the F-statistic, and tests whether a particular linear combination (contrast) of the estimates is zero at every voxel (Friston et al., 1995). The multiple dependent comparisons inherent in this method are corrected for using FDR, and VBM statistics assume linearity and normality of data (Friston et al., 1995). The GLM included variables of non-interest (age, TBV, NA, reappraisal frequency), as well as the variable of interest (suppression frequency). The set of voxels that results from each study-specific contrast represents a statistical parametric map of the *t*-statistic (SPM-*t*), which are comprised of results of statistical tests on each voxel. As our hypotheses were region-specific, we then applied a small volume correction using the 3D insula region as defined in the Wake Forest University (WFU) PickAtlas to the SPM-*t* maps ( $p < .05$ , FDR corrected) (Maldjian et al., 2003). The contrast was then limited to clusters of more than 50 contiguous voxels.

## Results

### ROI

As shown in Fig. 2, trait usage of expressive suppression positively correlated with bilateral anterior insula volume ( $r = .32$ ,  $p = .021$ ). Using FDR to correct for multiple comparisons, this relationship remained significant. In secondary analyses, we examined left and right anterior insula volume separately. Findings indicated that expressive suppression usage was positively correlated with left anterior insula volume ( $r = .29$ ,  $p = .036$ ) and, at trend levels, with right anterior insula volume ( $r = .26$ ,  $p = .067$ ). As expected, the control variables of negative affect and cognitive reappraisal frequency were not related to bilateral anterior insula volume ( $ps > .3$ ). When included in a linear regression analysis with TBV, negative affect, and

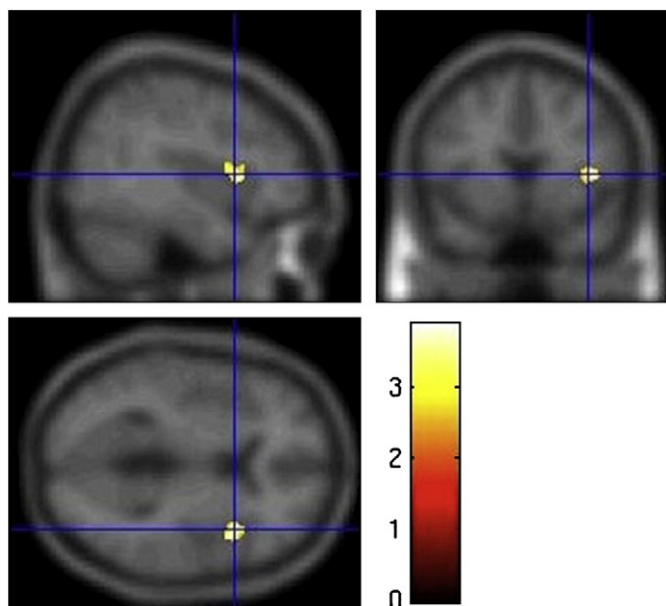


**Fig. 2.** Scatter plot showing the positive relationship between frequency of expressive suppression and bilateral anterior insula volume from ROI results.

reappraisal frequency as covariates of non-interest, the relationship between suppression frequency and bilateral anterior insula volume remained significant ( $\beta = .31$ ,  $p = .029$ ).

#### VBM

Expressive suppression usage was significantly positively correlated with gray matter volume in the right anterior insula (Talairach coordinates: 45, 10, 8;  $k = 904$ ) at a regionally-corrected  $p < .05$ , FDR corrected. As seen in Fig. 3, this effect was limited to the anterior insula. The GLM used to model this effect controlled for age, total brain volume, negative affect, and cognitive reappraisal frequency. In addition, negative affect and cognitive reappraisal alone did not show significant relationships with gray matter volume in the anterior insula.



**Fig. 3.** Statistical parametric map of VBM results, showing the cluster of gray matter voxels in the right anterior insula that positively correlate with frequency of expressive suppression ( $p < .05$ , FDR corrected using small volume correction through WFU PickAtlas). Scale represents the  $F$  score.

#### Discussion

Use-dependent brain plasticity refers to the idea that if a neural circuit is used frequently, its volume will increase (Kleim et al., 1998, 2002). Although prior work on use-dependent plasticity has mostly focused on the repetition of physical actions or cognitive processes, a few studies have shown a relationship between repeated patterns of psychological functioning and the volume of associated brain regions.

One type of psychological functioning that becomes habitual for individuals is emotion regulation. Of the many types of emotion regulation, the present study focused on expressive suppression, in which an individual aims to prevent the outward expression of emotion. This may recruit the anterior insula, which is known to be involved in bodily and emotional awareness (Coen et al., 2009; Craig, 2003, 2009), such that increased usage of expressive suppression may increase connections in, and thus the volume of, the anterior insula. The first step in exploring this hypothesis is determining whether this relationship exists in a cross-sectional sample of healthy individuals.

In this study, we specifically hypothesized that there would be a positive correlation between trait suppression usage frequency and the volume of the anterior insula. Both ROI and VBM analyses found that suppression was indeed positively correlated with the volume of the anterior insula in a sample of healthy adult women.

#### The role of the anterior insula in expressive suppression

In addition to its primary role in supporting interoception and emotional awareness, the insula also serves as a relay point between the brain regions involved in emotional responding, such as the amygdala, and other regions involved in cognitive regulation, such as the prefrontal cortex (Nunn et al., 2008). Thus, in addition to monitoring an individual's outward emotional expression during expressive suppression, the anterior insula would be strongly innervated both by bottom-up signals regarding inward emotional state, and top-down signals indicating regulation goals.

Past fMRI studies examining the neural correlates of instructed expressive suppression have found anterior insula activation (Goldin et al., 2008; Hayes et al., 2010); however, not all neuroimaging studies of expressive suppression have shown anterior insula activation (Vrticka et al., 2011). These inconsistent findings may indicate that instructed use of expressive suppression recruits a more conscious, top-down emotional control network that engages many other frontal regions in addition to the anterior insula. In contrast, the present findings indicate that habitual, bottom-up use of expressive suppression may rely more heavily on the anterior insula, which affects the local gray matter volume of that region.

The insula is one of the most volumetrically stable regions of the brain, thus even a slight alteration in volume implies a profound effect on mental processing (Kennedy et al., 1996; Makris et al., 2006). The current finding of a .3% variation in anterior insula volume (as a proportion of TBV) between individuals as a function of their use of expressive suppression is striking. It may be argued that individuals who engage in frequent usage of expressive suppression do so to manage the high levels of negative affect in their lives, which would then regularly engage the insula (Britton et al., 2006; Critchley et al., 2002; Jabbi et al., 2007). However, insula volume was not related to trait levels of negative affect, and the relationship between suppression use and anterior insula volume held even when controlling for negative affect. Furthermore, these findings were specific to one form of emotion regulation; they are not the result of general regulatory behaviors.

#### ROI versus VBM

Although ROI and VBM analyses produced largely convergent results, there were some inconsistencies. ROI found that suppression

positively correlated with the volume of the bilateral anterior insula, but VBM found this relationship only in the right hemisphere. This inconsistency between ROI and VBM is most likely due to a more diffuse effect in the left hemisphere than the right, which was picked up in the ROI analyses but not VBM. Indeed, when the cluster threshold for VBM was lowered from 50 to 0 voxels, a small 20-voxel cluster of gray matter at the border of the left orbitofrontal cortex and anterior insula emerged. The difference in results between methods could be due to the normalization process that takes place in VBM, wherein each individual brain is warped to a template. Creating a study-specific template and using a newer version of VBM that modulates the results in order to reverse normalization-based warping minimized the effect of this step, but this step still could have affected the results in the most lateral parts of the cortex, including the insula.

In the present study we attempted to control for confounding variables, including age and trait negative affect, in our GLM in order to isolate the relationship between suppression usage and anterior insula volume. However, we may have found very different results had we used different variables in our GLM. *Hu and colleagues (2011)* directly tested how the precise makeup of a GLM affects VBM results, and concluded that different combinations of nuisance covariates produce different results (*Hu et al., 2011*). The current ROI and VBM results are much more similar than past findings directly comparing the two methods (*Asami et al., 2008; Giuliani et al., 2005*), which may be attributed to improved VBM methods, including the usage of DARTEL registration (*Bergouignan et al., 2009*). As most of the newer studies examining the effects of individual differences in cognition, emotion, and behavior on regional gray matter volume employ only VBM methods to test their hypotheses, the present results provide evidence that using only that method may obscure crucial results.

#### Limitations and future directions

The present study has several important limitations. First, our cross-sectional design does not permit us to draw causal inferences, or assess the directionality of the association between regional brain volume and emotion regulation. Future research should employ longitudinal or intervention designs to test the direction of this relationship. Second, we chose to focus our analyses on female subjects because they have been found to have greater hemispheric symmetry compared to males (*Yucel et al., 2001*). It remains to be determined whether these results apply to males, and future research should also examine subjects of different ages, cultures and socioeconomic backgrounds. Third, we limited this study sample to younger adults, to capitalize on the existing literature on the neural correlates of emotion reactivity and regulation on this population (*Gross & John, 2003; Hajcak & Nieuwenhuis, 2006; Mauss et al., 2005; Ochsner et al., 2004*). In future work it will be important to examine whether these results apply to individuals encompassing a broader age range. Fourth, we prioritized the assessment of two control measures, cognitive reappraisal and trait negative affect, in order to capitalize on the known behavioral and neuroimaging literature on these forms of individual differences (*Goldin et al., 2008; Gross & John, 2003*). In future work it will be important to assess a broader range of control measures using both behavioral and self-report methods in order to conclude that the present results are indeed specific to expressive suppression. Lastly, we did not incorporate functional imaging in order to focus on the hypothesized relationship between everyday emotional behavior and brain structure. Although past studies have found inconsistent relationships between structural and functional MRI changes (see, for example, *Drevets et al., 1997; Pezawas et al., 2005; Pizzagalli et al., 2004, 2009*), it will be important to understand how these experience-related changes in local brain volume affect the functioning of those regions in future work.

#### Conclusion

The findings from the present study demonstrate that individual differences in usage of expressive suppression positively correlate with the volume of the anterior insula. The anterior insula is thought to support emotional and bodily awareness, both of which are engaged during the suppression of emotional responses. This is the first study to demonstrate that habitual engagement of expressive suppression relates meaningfully to anterior insula volume. Further work is needed to explore the longitudinal relationship between long-term usage of expressive suppression and gray matter volume change.

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