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Evidence for a cerebral cortical thickness network anti-correlated with amygdalar volume in healthy youths: implications for the neural substrates of emotion regulation

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Abstract

Recent functional connectivity studies have demonstrated that, in resting humans, activity in a dorsally-situated neocortical network is inversely associated with activity in the amygdalae. Similarly, in human neuroimaging studies, aspects of emotion regulation have been associated with increased activity in dorsolateral, dorsomedial, orbital and ventromedial prefrontal regions, as well as concomitant decreases in amygdalar activity. These findings indicate the presence of two countervailing systems in the human brain that are reciprocally related: a dorsally-situated cognitive control network, and a ventrally-situated limbic network. We investigated the extent to which this functional reciprocity between limbic and dorsal neocortical regions is recapitulated from a purely structural standpoint. Specifically, we hypothesized that amygdalar volume would be related to cerebral cortical thickness in cortical regions implicated in aspects of emotion regulation. In 297 typically developing youths (162 females, 135 males; 572 MRIs), the relationship between cortical thickness and amygdalar volume was characterized. Amygdalar volume was found to be inversely associated with thickness in bilateral dorsolateral and dorsomedial prefrontal, inferior parietal, as well as bilateral orbital and ventromedial prefrontal

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cortices. Our findings are in line with previous work demonstrating that a predominantly dorsally-centered neocortical network is reciprocally related to core limbic structures such as the amygdalae. Future research may benefit from investigating the extent to which such cortical-limbic morphometric relations are qualified by the presence of mood and anxiety psychopathology.

Keywords

amygdala; cortical thickness; MRI; normal development

1. Introduction

Given dense anatomical connections between the amygdalae and prefrontal areas (particularly orbital and ventromedial regions), prefrontal cortices are posited to play an integral role in the regulation of amygdalar activity (Carmichael and Price, 1995; Ghashghaei and Barbas, 2002; Ghashghaei et al., 2007; Ray and Zald, 2012). In humans, interactions between the amygdalae and cerebral cortex have been traditionally studied using functional neuroimaging paradigms. In particular, functional magnetic resonance imaging (fMRI) studies of emotion regulation implicate a number of cerebral cortical regions in the top-down modulation of amygdalar activity (Banks et al., 2007; Drabant et al., 2009; Kanske et al., 2011; Mayberg et al., 1999; McRae et al., 2010; Ochsner and Gross, 2005; Ochsner et al., 2004). In such studies, increasing activity in prefrontal areas, including dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex (DMPFC), has been associated with concomitant decreases in amygdalar activity.

Interestingly, several recent resting state functional connectivity MRI studies of the amygdala indicate that, while at rest, amygdalar activity is inversely related to activity in DLPFC, DMPFC, and inferior parietal cortices (Kim et al., 2011; Luking et al., 2011; Roy et al., 2009). Specifically, Roy et al. (2009) reported that activity in superior frontal gyrus, middle frontal gyrus, inferior parietal, as well as posterior cingulate and precuneus cortices, was negatively predicted by amygdalar activity. Conversely, Roy et al. (2009) found that activity in regions of the anterior cingulate, insula, and medial prefrontal cortex was positively predicted by amygdala activity. Of note, these findings by Roy et al. (2009) were replicated in a subsequent study by Kim et al. (2011). Further, these resting state functional connectivity studies seemingly converge with a model of reciprocal limbic-cortical functioning proposed by Mayberg et al. (1999). Despite a growing number of studies investigating functional relations between the amygdalae and cerebral cortex, a dearth of research exists regarding morphological relations between these two brain structures.

Members of our group have previously studied the extent to which morphology in one area of the brain correlates with morphology across other brain regions. When studying across individuals, for example, cortical thickness measures in anterior and posterior language areas (i.e., Broca's and Wernike's areas) are significantly correlated (Lerch et al., 2006). Such cortical thickness correlations are posited to reflect, at least in part, underlying anatomical connectivity via white matter pathways (Lerch et al., 2006). Indeed, cortical thickness correlations across individuals show convergence with diffusion MR-based connectivity (Gong et al., 2012). It has also been suggested that cortical thickness correlations—particularly negative thickness correlations—reflect patterns of functional connectivity between antagonistic brain areas (Gong et al., 2012). What is more, previous work demonstrates that a number of discrete anatomical networks in the human brain can be identified by studying structural covariance in the cerebral cortex (He et al., 2007; Zielinski et al., 2010). Intriguingly, the topographies of such structurally-based networks largely

overlap with functionally-defined brain networks (He et al., 2007; Zielinski et al., 2010). Despite these findings, it remains unclear the degree to which morphological variation in subcortical structures such as the amygdala is associated with cerebral cortical thickness. Critically, studying structural covariance between the cerebral cortex and amygdalae may provide further insight with regard to functional relations between these brain regions.

In the present study, we investigate the extent to which the reciprocal functional relation between core limbic areas and prefrontal cortical regions is recapitulated from a purely structural standpoint in a large cohort of healthy, typically developing youths. We predict that amygdalar volume will be related to cortical thickness in regions that have been previously implicated in the modulation of amygdalar functioning. Based on the functional imaging research outlined above, *a priori* regions include bilateral DLPFC and DMPFC, bilateral inferior parietal cortices, as well as bilateral caudal orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC).

2. Materials and Methods

2.1 Sampling and Recruitment

The NIH MRI Study of Normal Brain Development is a large, multi-site project that establishes a normative database to study relations between healthy brain maturation and behavior (Evans, 2006). Subjects were recruited throughout the United States utilizing a population-based sampling method aimed at minimizing selection bias (Waber et al., 2007). Using available U.S. Census 2000 data, a representative, typically developing sample was recruited at 6 pediatric study centers. The 6 pediatric centers consisted of: Children's Hospital (Boston), Children's Hospital Medical Center (Cincinnati), University of Texas Houston Medical School (Houston), UCLA Neuropsychiatric Institute and Hospital (Los Angeles), Children's Hospital of Philadelphia (Philadelphia) and Washington University (St. Louis). Recruitment was monitored throughout the study, ensuring that enrollment across all pediatric centers was demographically representative with regards to age, gender, ethnicity and socioeconomic status (full demographic features of subjects are provided in Evans, 2006). The study was approved by an institutional review board, and informed consent was obtained from parents, as well as child assent. The Objective 1 database (release 4.0) used in this study included 431 healthy youths, and upon enrollment (i.e., first study visit), ages ranged from 4 years and 6 months to 18 years and 3 months. The study followed a longitudinal design such that participants underwent MRI brain scanning and behavioral testing on three separate visits, occurring at roughly 2-year intervals. With regard to subjects utilized in the present study, the age range at Visit 1 was 4.8 to 18.3 years; 6.4 to 20.2 years at Visit 2; and 8.4 to 22.3 years at Visit 3. Given that the aim of the NIH MRI Study of Normal Brain Development was to study healthy, typically developing children, stringent exclusion criteria were utilized including: meeting criteria for a current or past Axis I disorder on structured parent or child interview (Diagnostic Interview for Children and Adolescents) (exceptions, however, included simple phobia, social phobia, adjustment disorder, oppositional defiant disorder, enuresis, encopresis, nicotine dependency), family history of major Axis I disorder, family history of inherited neurological disorder or mental retardation due to non-traumatic events, abnormality on neurological examination, gestational age at birth less than 37 weeks or greater than 42 weeks, and intra-uterine exposure to substances known or highly suspected to alter brain structure or function (for further information, see Evans, 2006). In the present study, it should be noted that none of the subjects met current or past diagnostic criteria for specific phobia, or social phobia (assessed using the Diagnostic Interview Schedule for Children, C-DISC-4). Structural MRI and behavioral data were stored and analyzed within a database at the Data Coordinating Center of the Montreal Neurological Institute (MNI), McGill University.

2.2 MRI protocol

In order to collect data that would permit automated morphometric analysis, as well as accommodate time constraints associated with the participant age range, 30–45 minutes of data acquisition were provided. Both General Electric (GE) and Siemens Medical Systems (Siemens) scanners were used in the NIH Normal Brain Development study. A 3D T1-weighted spoiled gradient recalled (SPGR) echo sequence was selected. Voxel dimensions on Siemens scanners were 1mm isotropic, whereas slice thickness of 1.5mm was allowed for GE scanners because of the scanners' limit of 124 slices. Inter-site reliability was monitored with the American College of Radiology phantom, as well as a living phantom, that were both scanned at regular intervals at each site (Evans, 2006). All MRI scanners used in the NIH Normal Brain Development study were 1.5 T systems. For further details regarding MRI sequence parameters, the reader is directed to Evans (2006). Information on the scanning parameters can also be found in Supplemental Material 1.

2.3 Automated Image Processing

Quality controlled native MR images were processed through the CIVET automated pipeline (version 1.1.9, 2006), and included the following steps (Ad-Dab'bagh et al., 2006). To account for gross volumetric differences between subjects, native MR images were linearly registered to a standardized MNI-Talairach space based on the ICBM152 dataset (Collins et al., 1994; Mazziotta et al., 1995; Talairach and Tournoux, 1988). Intensity non-uniformity artifacts introduced by the scanner were corrected for using N3 (Sled et al., 1998). Subsequent classification of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) was performed using the INSECT algorithm (Zijdenbos et al., 2002). The pipeline includes the CLASP algorithm for generating high-resolution hemispheric surfaces with 40,962 vertices per hemisphere (Kabani et al., 2001; Kim et al., 2005; Lyttelton et al., 2007; MacDonald et al., 2000). Hemispheric surfaces were generated for both the WM/GM interface, as well as the GM/CSF (i.e., pial surface). Both surfaces for each hemisphere were non-linearly registered to an average surface created from the ICBM152 dataset to establish correspondence of vertices (i.e., cortical points) between subjects (Grabner et al., 2006; Lyttelton et al., 2007; Mazziotta et al., 1995). Of note, members of our group have previously shown that there is in fact a slight bias when using the adult template to analyze pediatric data (4.5–6.9 age group) compared to using the closer age-appropriate templates for DBM studies (Fonov et al., 2011). In the present study, the ICBM template was used only to bring the MRIs into a standard orientation (with linear registration) before tissue classification and surface extraction. We have not been able to demonstrate an advantage of using a pediatric template for this task (Fonov et al., 2011; Yoon et al., 2009). In addition, use of the ICBM152 standard facilitates comparison with other publications that use this template. A reverse linear transformation was performed on each subject's images, allowing for cortical thickness estimations to be made at each cortical point in the MR image's native space (Ad-Dab'bagh et al., 2005). At each cortical point, cortical thickness was calculated using the *t* link metric (Lerch and Evans, 2005). As has been previously reported by members of our group, blurring along the cortical surface is a critical step in conducting cortical thickness analyses, and serves to increase the sensitivity of cortical thickness analysis (Lerch and Evans, 2005). To increase the signal-to-noise ratio, each subject's cortical thickness map was blurred using a 20-millimeter full width at half maximum surface-based diffusion smoothing kernel (Chung et al., 2001). This kernel size closely approximates previously recommended values, affording optimal sensitivity for cortical thickness analysis (Lerch and Evans, 2005). A visual quality control of the native cortical thickness images of each subject was carried out by members of our group to ensure that there were no significant aberrations in cortical thickness estimates for a given subject (inter-rater reliability was .93) (Karama et al., 2009).

2.4 Amygdala Segmentation

Volumetry measures were obtained using a validated, fully automatic segmentation method for the hippocampus and amygdala in human subjects from MRI data (Collins and Pruessner, 2010). The method utilizes a large, manually labeled MRI dataset (n=80) of young healthy adults that serves as a template library. The segmentation method is characterized by label fusion techniques that combine segmentations from a subset of 'n' most similar templates. Specifically, each template is used to produce an independent segmentation of the subject using the ANIMAL procedure (Collins et al., 1995) followed by a thresholding step to eliminate CSF, which results in 'n' different segmentations. To fuse the segmentations at each voxel, a voting strategy is used; the label with the most votes from the 'n' templates is assigned to the voxel. The rationale for combining multiple segmentations is to minimize errors and maximize consistency between segmentations. When using n=11 templates, the label fusion technique has been shown to yield an optimal median Dice Kappa of 0.826 and Jaccard similarity of 0.703 for amygdala (Collins and Pruessner, 2010) (example segmentations can be viewed in Supplemental Figure 1).

2.5 Current Sample

In the present study, quality controlled cortical thickness measures and amygdala volumetric data were available for 297 subjects (162 females, 135 males) in the Objective 1 dataset. A total of 572 MRI scans were analyzed for these subjects. Subject ages ranged from 4.8 to 22.3 years, with a mean age of 12.7 years (SD = 3.9 years). Of the 297 youths, 104 participants had data available at only one time point (35.0%), 111 had data available at two time points (37.4%), and 82 participants had data for all three time points (27.6%).

2.6 Statistical Analysis

First, simple relations between total amygdalar volume, total brain volume, and age were investigated for males and females separately. This work was carried out in IBM SPSS 19 (SPSS Inc, Chicago, IL), utilizing mixed-effects models with subject ID entered as a random effect. This approach was used given that mixed-effects models allow for the use of subject data from one or more time points (i.e., unbalanced longitudinal data), and can account for correlated error terms (Diggle, 2002; Shaw et al., 2011; Singer and Willett, 2003)

Next, cortical thickness analyses were implemented using SurfStat, a toolbox created for MATLAB 7 (The MathWorks, Inc., Natick, Massachusetts) by Dr. Keith Worsley (http://www.math.mcgill.ca/keith/surfstat/). Contrary to past reports, cortical thickness trajectories across the age range in our total sample have been found to be best described by first-order linear functions in contrast to cubic or quadratic functions (Supplemental Figure 2), and, as a result, the relation between cortical thickness and age was modeled as a first-order linear function.

Cortical thickness analysis was conducted using a mixed-effects model, and each subject's absolute native-space cortical thickness was linearly regressed against total amygdala volume at each cortical point. Mixed-effects models provide a way in which to analyze unbalanced longitudinal data, while maximizing statistical power (i.e., utilizing all available data) (Diggle, 2002; Shaw et al., 2011; Singer and Willett, 2003). In each mixed-effects model, subject ID was entered as a random effect in order to account for within-individual dependence. Age, total brain volume (TBV), gender, and scanner site were statistically controlled for in each model. The regression equation for the mixed-effects model was as follows:

$$Cortical\ Thickness = intercept + d_1 + \beta_1(age) + \beta_2(TBV) + \beta_3(Gender) + \beta_4(Scanner\ Site) + \beta_5(Total\ Amygdala\ Volume) + e$$

where d_1 represents the random effect of subject ID, and e corresponds to residual error. To control for multiple comparisons, false discovery rate (FDR) correction was applied to the entire cortical surface ($q \leq 0.05$).

Lastly, in a series of exploratory analyses, we investigated the extent to which the relation between cerebral cortical thickness and total amygdalar volume was moderated by age and gender. In three separate mixed effects models, we tested for "Age × Total Amygdala Volume," "Gender × Total Amygdala Volume," and, "Gender × Age × Total Amygdala Volume" interactions on cortical thickness. Again, FDR correction was applied to the entire cortical surface ($q \leq 0.05$).

3. Results

Both males and females demonstrated a positive first-order linear relation between total amygdalar volume (adjusted for total brain volume) and age—with both sexes exhibiting amygdala volume increase with age (Supplementary Figure 3). For both males and females, the addition of a quadratic age term did not significantly account for more variance when modeling amygdalar volume change over time. Thus, the relation between amygdalar volume and age was modelled as a first-order linear function in subsequent cortical thickness analyses.

Total amygdalar volume was found to be negatively associated with cortical thickness in a number of cortical regions (Figures 1 and 2). Associations surviving whole-brain FDR correction were found principally in bilateral DLPFC and DMPFC, bilateral OFC and vmPFC, as well as bilateral inferior parietal cortices. Unpredicted negative associations surviving FDR-correction were revealed in bilateral posterior cingulate cortices, as well as bilateral inferior temporal cortices. In order to determine the degree to which including multiple measurements of the same subject influenced our main finding, a follow-up cross-sectional analysis was conducted using only baseline data for each of the 297 subjects. The results of this baseline analysis can be viewed in Supplemental Figure 4. Although the inverse relation between amygdalar volume and cortical thickness did not survive FDR correction ($q \leq 0.05$) in this baseline analysis, trends were revealed in the vmPFC, OFC, DLPFC, and inferior parietal regions. Importantly, the topography of these results largely overlapped with FDR-corrected findings from the mixed-model regression analysis.

Both the "Age × Total Amygdala Volume" and "Gender × Total Amygdala Volume" interactions were not significantly related to cortical thickness (the relation between amygdalar volume and cortical thickness across different ages is depicted in Supplementary Figure 5). However, there was a significant "Gender × Age × Total Amygdala Volume" interaction on cortical thickness in left superior temporal gyrus (including portions of superior temporal sulcus), right temporoparietal cortex, right superior temporal sulcus, and left frontopolar cortex (Supplementary Figure 6). Post hoc probing revealed that the interaction was driven by a positive association between amygdalar volume and thickness among young males (under roughly 13 years of age) that was absent in young females.

4. Discussion

In the present study, we found negative associations between amygdalar volume and cerebral cortical thickness in bilateral DMPFC, DLPFC, inferior parietal cortices, as well as bilateral OFC and vmPFC. To the best our knowledge, this is the first report of an inverse relation between amygdalar volume and cortical thickness among children and adolescents. Intriguingly, our results bear resemblance to recent resting state functional connectivity findings in which amygdalar regions were used as seed points (Kim et al., 2011; Luking et al., 2011; Roy et al., 2009). In such studies, BOLD response in DLPFC, DMPFC, as well as

inferior parietal cortices, was inversely correlated with hemodynamic activity in the amygdala. Importantly, our findings suggest that a network of cortical regions, principally comprised of DLPFC, DMPFC, and inferior parietal cortices, is reciprocally related with the amygdalae at not only a functional level (as has been previously reported by others), but also a structural level.

The topography of our findings also overlaps with results from numerous functional imaging studies of cognitive emotion regulation (For example, see Figure 3) (Banks et al., 2007; Drabant et al., 2009; Kanske et al., 2011; Mayberg et al., 1999; McRae et al., 2010; Ochsner and Gross, 2005; Ochsner et al., 2004). Evidence spanning multiple neuroimaging modalities and paradigms indicates that a dorsally-situated cognitive control network, primarily consisting of DLPFC and DMPFC, as well as inferior parietal cortices, is involved in the voluntary regulation of emotions (Ochsner and Gross, 2005). Such voluntary forms of emotion regulation include reinterpreting the meaning of a stimulus or situation (i.e., cognitive reappraisal), as well as actively shifting attention away from emotional stimuli (i.e., attentional distraction) (Ochsner and Gross, 2005). Further, in numerous functional imaging studies, voluntary emotion regulation (e.g., cognitive reappraisal, attentional distraction) has been associated with increased BOLD signal in the DLPFC and DMPFC, as well as concomitant decreases in BOLD activity within the amygdalae (Banks et al., 2007; Drabant et al., 2009; Kanske et al., 2011; McRae et al., 2010; Ochsner and Gross, 2005; Ochsner et al., 2004).

In addition to more dorsally-situated cortical areas, thickness in orbital and ventromedial regions was also found to be inversely related to amygdalar volume. The vmPFC is strongly implicated in more automatic, or involuntary, aspects of emotion regulation such as extinction learning (Milad et al., 2005; Phelps et al., 2004). For example, Milad et al. (2005) reported that cerebral cortical thickness in the vmPFC was positively associated with extinction memory in healthy adults—with thicker cortices predicting an increased ability to extinguish a previously learned fear association. Previous work also indicates that the vmPFC is involved in voluntary aspects of emotion regulation. Delgado et al. (2008) reported that cognitive emotion regulation in humans activated vmPFC regions in addition to more dorsolateral prefrontal areas. Given these findings, Delgado et al. (2008) contend that brain areas involved in cognitive emotion regulation influence amygdalar activity via phylogenetically older portions of the vmPFC that possess robust inhibitory projections to the amygdalae (Delgado et al., 2008). This hypothesis is supported by nonhuman primate findings that neocortical areas comprising the cognitive control network (e.g., DLPFC, DMPFC), in general, do not possess strong connections with the amygdalae (Ghashghaei and Barbas, 2002; Ghashghaei et al., 2007; Ray and Zald, 2012). Other functional imaging studies have also reported that BOLD response in orbital and ventromedial prefrontal cortices is inversely correlated with hemodynamic activity in the amygdalae during voluntary forms of emotion regulation (Banks et al., 2007; Urry et al., 2006). Interestingly, findings in the present study appear in line with orbital and ventromedial prefrontal cortices, in combination with dorsal neocortical regions (e.g., DLPFC, DMPFC), comprising a unified network.

In both human and nonhuman primate imaging studies, heightened amygdala reactivity has been associated with dysregulated emotional behavior and anxious/depressed symptoms (Fox et al., 2008; Rauch et al., 2000; Stein et al., 2002; Stein et al., 2007; Thomas et al., 2001). It remains unclear, however, the extent to which such functional findings relate to potential differences in brain structure. Interestingly, both increased neuronal excitability and structural hypertrophy in the amygdala have been reported in rodents exposed to chronic stress—biological changes that may underpin the emergence of dysregulated emotional behavior and anxiety-like symptoms (Mitra et al., 2005; Rosenkranz et al., 2010; Vyas et al.,

2003). In contrast, heightened amygdalar activity among clinically depressed adults has been associated with reduced amygdalar volume (Siegle et al., 2003). Such discrepant findings underscore the current lack of clarity regarding relations between amygdalar morphology and amygdalar functioning. Similarly, it remains unclear the degree to which anxious/depressed behaviors are related to amygdalar morphology. Although evidence suggests that larger amygdalae are associated with environmental stress, emotion dysregulation, and increased anxiety in human pediatric populations (Barros-Loscertales et al., 2006; Davidson and McEwen, 2012; De Bellis et al., 2000; Lupien et al., 2011; MacMillan et al., 2003; Tottenham et al., 2010; van der Plas et al., 2010), decreased amygdalar volume has also been associated with anxiety in clinical pediatric samples (Milham et al., 2005). As suggested by others, hypertrophy and increased volume in the amygdalae may occur initially in response to early environmental stress and adversity—but may ultimately result in premature volume reductions due to excitotoxic processes (Davidson and McEwen, 2012; Tottenham and Sheridan, 2009).

Cortical structure in top-down modulatory regions has been linked to amygdalar reactivity (Foland-Ross et al., 2010). In particular, studying healthy human adults, Foland-Ross et al. (2010) found that thinner vmPFC was associated with greater amygdalar activity during an emotionally valenced cognitive task (affect labelling task). Although speculative, it is possible that reduced thickness in top-down regulatory regions, and a resultant lack of modulation over amygdalar functioning, may contribute to both hyperexcitability and structural hypertrophy in amygdalar regions. Alternatively, concomitant excitability and hypertrophy in the amygdalae may lead to structural compromise within regulatory cortices through heightened activation of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol release (Dedovic et al., 2009; Kremen et al., 2010; Shansky et al., 2009; Wellman, 2001). Although such processes could potentially account for an inverse relation between amygdalar volume and cortical thickness, further research is needed to test these hypotheses.

In the only other study that has investigated relations between cortical morphology and amygdala volume, Blackmon et al. (2011) found that self-reported anxiety was negatively associated with left amygdalar volume (as a percentage of intracranial volume), and positively associated with thickness in left lateral orbitofrontal (lOFC) and temporoparietal cortices (including portions of inferior parietal cortex). Further, decreased amygdalar volume was associated with increased thickness in lOFC—the same area in which a positive association between cortical thickness and self-reported anxiety was found (Blackmon et al., 2011). Interestingly, these findings appear at odds with the notion of larger amygdalae and thinner regulatory cortices underpinning dysregulated emotional behavior. Critically, participants in the Blackmon et al. (2011) study ranged from 21 to 62 years of age. It is possible that the relation between amygdalar morphology and internalizing problems may be qualified by age—particularly when considering age-related changes in cerebral cortical structure, and intermediary white matter pathways (Asato et al., 2010; Shaw et al., 2008; Tottenham and Sheridan, 2009).

Previous work by other groups has demonstrated significant overlap between structural covariance networks and resting state functional connectivity networks. Using structural MRI data from the NIH Normal Brain Development study, Zielinski and colleagues (2010) reported eight structural covariance networks that recapitulated the topologies of previously reported resting state functional connectivity networks (e.g., “salience,” “executive control,” and “default mode” networks). Furthermore, large-scale structural connectivity patterns based on cortical thickness measurements have been defined using graph theoretical approaches. Chen et al. (2008) segregated the cerebral cortex into six modules, each with apparent functional significance (e.g., strategic/executive functions, auditory/language functions, sensorimotor/spatial functions, etc.). Interestingly, cortical regions that were

inversely related to amygdalar volume in the present study appear to overlap with what has been labeled as an executive control network, both in studies of structural covariance (Chen et al., 2008; Zielinski et al., 2010) as well as resting state functional connectivity studies (Seeley et al., 2007).

In the present study, negative associations between cortical thickness and amygdalar volume were revealed in areas possessing weak anatomical connections with the amygdalae (e.g., DLPFC, DMPFC, inferior parietal cortex) (Ghashghaei et al., 2007). However, negative associations were also revealed in several areas sharing robust connections with the amygdalae (e.g., caudal OFC, vmPFC) (Ghashghaei et al., 2007). This observation seemingly lends support to speculation by others that negative morphometric correlations reflect underlying functional connectivity between antagonistic areas rather than direct anatomical connections (Gong et al., 2012). Specifically, Gong et al. (2012) found that positive cortical thickness correlations showed the greatest degree of convergence with diffusion MR-based connectivity, whereas the majority of negative thickness correlations (>90%) diverged with diffusion data (Gong et al., 2012). Similar to negative cortical thickness correlations, the inverse relation between cortical thickness and amygdala volume may primarily reflect functional connectivity patterns. Although positive associations between amygdalar volume and cortical thickness failed to reach statistical significance, trend-level positive associations were found in cortical regions possessing direct anatomical connections with the amygdalae (e.g., superior temporal gyrus, insular cortices) (Amaral and Price, 1984).

Analysis did reveal a significant “Gender × Age × Total Amygdala Volume” interaction on cortical thickness, most notably in left STG and right temporoparietal cortex. This interaction was largely driven by a strong positive association between amygdalar volume and cortical thickness in younger male subjects that was absent in similarly aged female subjects. Notably, cortical regions associated with this three-way interaction did not overlap with areas in which thickness was inversely related to amygdalar volume. The functional implications of this exploratory finding are unclear; however, De Bellis et al. (2000) have reported not only increased amygdalar volume among child and adolescents with generalized anxiety disorder (GAD), but also increased STG volumes (De Bellis et al., 2002). It is somewhat surprising that this positive association was found in younger males given epidemiological data indicating that young males are not more vulnerable to anxious/depressed problems (Bongers et al., 2003). We emphasize, however, that this is an exploratory finding that should be subsequently tested in healthy as well as clinical populations.

Several additional factors should be considered when interpreting results of the present study. Similar to resting state functional imaging studies of the amygdalae (with the exception of Roy et al., 2009), analyses in the present study have treated the amygdala as a single functional unit. The amygdala, however, is comprised of many discrete subnuclei, each with distinct patterns of connectivity. Future methods of reliably segmenting the amygdala into separate functional units (e.g., basolateral and central nuclei) may illuminate potential differences with regard to the relation between amygdala volume and cortical thickness. Further, when comparing results from the mixed-model regression analysis (utilizing repeated measurements of the same subject) and the follow-up baseline analysis, it is worth noting that the relation between amygdalar volume and cortical thickness was significant only when repeated measurements were included in the analysis. Thus, it would appear that a large degree of statistical power is needed to detect this morphometric relation, and that the accompanying effect size of this relation is relatively low.

Offsetting strengths of the present study include the use of a large longitudinal cohort of healthy, typically developing youths with cortical thickness measures and amygdalar volumetric data. Importantly, this study is the first to investigate the relation between amygdalar volume and cortical thickness in a large sample of typically developing youths. Future research may benefit from investigating the degree to which the presence of mood and anxiety psychopathology qualifies the morphometric relation between amygdalar volume and cerebral cortical thickness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We study relation between cortical thickness and amygdala volume in healthy youths.
- Amygdala volume is inversely associated with thickness in emotion regulatory areas.
- Topography of relation dovetails with fMRI voluntary emotion regulation reports.
- Findings overlap with resting state functional connectivity studies of amygdalae.

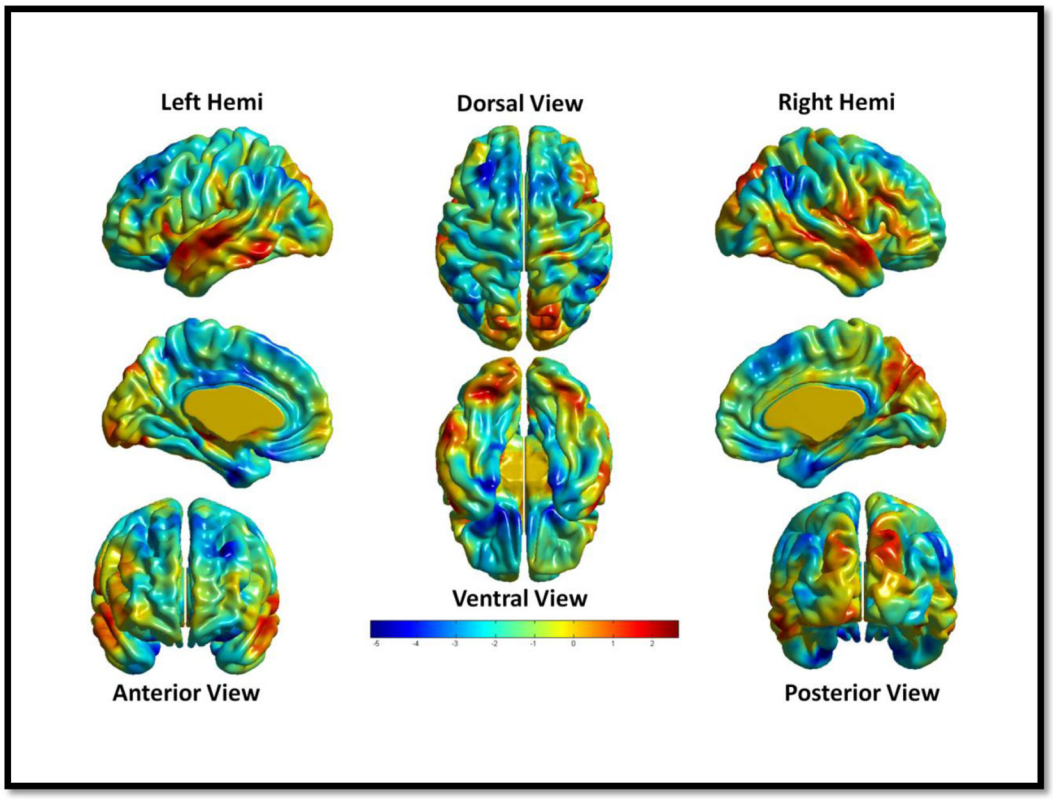

Figure 1.
Brain areas where local cortical thickness is associated with total amygdala volume (n=297; 572 MRIs). Colors correspond to t-statistic values, with cold shades depicting negative associations and warm shades representing positive associations. Controlled for age, gender, total brain volume, and scanner.

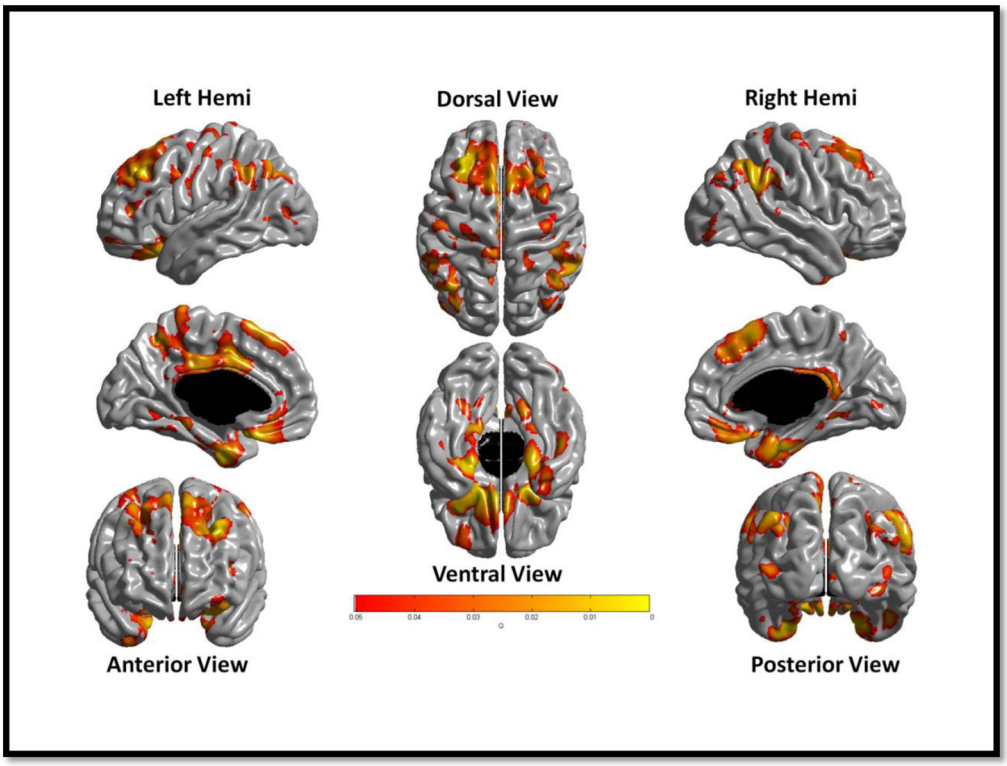

Figure 2.
Brain areas where local cortical thickness is negatively associated with total amygdala volume (n=297; 572 MRIs). The figure is shown at $q \leq 0.05$ with a false discovery rate correction. Controlled for age, gender, total brain volume, and scanner.

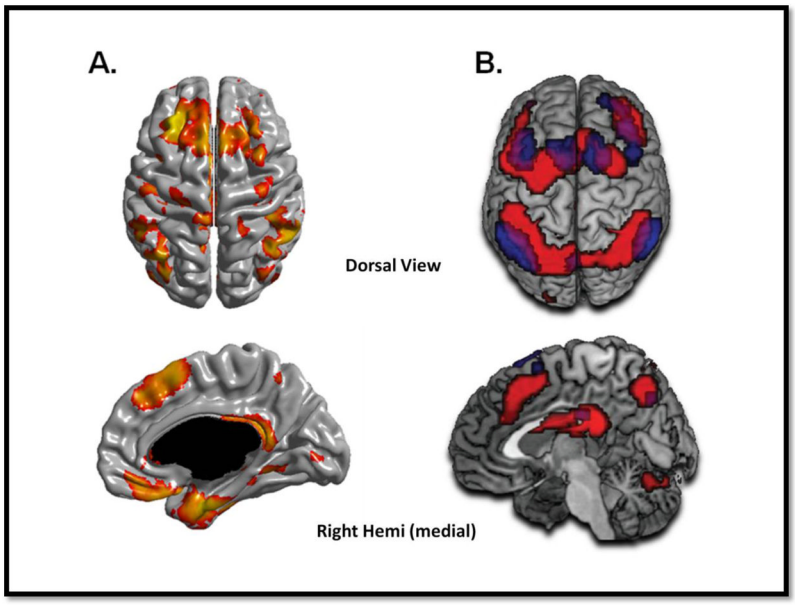

Figure 3.

Comparison of cortical thickness-amygdalar volume relation (A.) and fMRI study of cognitive emotion regulation (B.) (from Kanske et al., 2011). In column B., blue shades correspond to activation during cognitive reappraisal, whereas red shades correspond to activation during attentional distraction. Column A. is displayed at $q \leq 0.05$ with a false discovery rate correction (FDR), and column B. is shown at whole-brain FDR-corrected $p \leq 0.01$ with an extent threshold of 20 voxels.