Cortical Thickness as a Predictor of Amygdala Reactivity in Healthy Adults

by

Christina Erika Patak

A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
University of Toronto

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2015

Abstract

**Background:** Cortico-limbic affective processing regions undergo structural and functional changes with aging. However, there are no investigations into the relationships between measures of cortical thinning and affective functional reactivity in older adults.

**Methods:** Two groups of Caucasian men (n = 10 each, aged 60 – 85 years, and aged 20 – 40 years) underwent structural and functional magnetic resonance imaging during which they completed affective and sensorimotor (control) tasks administered according to a blocked design.

**Results:** Age groups were comparable in amygdalae response to negative affect. Older men were best distinguished from young by thinning of the gray matter in bilateral frontal, parietal and temporal lobes. Greater mean right amygdala activation was best predicted by a pattern of left orbito- and middle frontal cortical thickness/thinning in older men.
**Conclusion:** Even in the absence of age differences in amygdalae activation, prefrontal structure alterations uniquely influence emotional amygdala response in healthy older adults.
Acknowledgments

I would like to extend my sincerest appreciation to all the individuals that have provided me with their support and encouragement. I owe my deepest gratitude to my supervisor, Dr. Bruce Pollock, who has been my most staunch supporter throughout this process. You are an incredible mentor and have nurtured my passion for geriatric neuropsychiatric research. Thank you for your continued guidance and encouragement, and all that you do to assist me in my scientific career path.

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My sister, Monica Pataky, has been an inspiration to me. You are so brave and pursue your goals wherever they take you; you are perseverant, self-assured, and kind-spirited. You have truly become my best friend and confidant, and I cherish you so much. The laughter we have shared, even from across the pond, has been invaluable to me.
I would like to thank my parents-in-law, Alastair and Sandra Forsyth, for providing much needed humour during some stressful times. I treasure the friendship that we have developed and love you both very much.

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I dedicate this thesis to our precious daughter, Zoe Olivia Forsyth. You are already a bright, independent, curious, and determined individual. I hope that I can instill in you that whatever it is you dream to do you are able to achieve it. You are my greatest accomplishment and you have truly enriched my life.

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Contributions

Christina Pataky Forsyth (Author): the author performed the planning, execution, analysis, and writing of all original research contained in this dissertation, in whole or in part. The following contributions by other individuals are formally acknowledged:

Drs. Bruce Pollock (Supervisor), Cheryl Grady and Randy McIntosh: provided mentorship, guidance and assistance in the planning and analysis of the experiment, as well as input into, and editing of, the resulting thesis.

Dr. Mallar Chakravarty: provided expertise in the analysis of structural data; technical assistance was provided by Raihaan Patel.

Ricky Tong: provided expertise and guidance in conducting the functional data analysis.

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Annette Weeks-Holder and Fred Tam: provided technical expertise in creating the neuroimaging protocol; additionally, Annette Weeks-Holder completed the technical requirements of scanner operations and monitoring of volunteer safety during the imaging procedures.
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<tbody>
<tr>
<td>5HT</td>
<td>Serotonergic</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>AFNI</td>
<td>Analysis of Functional NeuroImages</td>
</tr>
<tr>
<td>ANIMAL</td>
<td>Automatic Nonlinear Image Matching and Anatomical Labeling</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BA</td>
<td>Brodmann area</td>
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<tr>
<td>BAI</td>
<td>Beck Anxiety Inventory</td>
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<tr>
<td>BOLD</td>
<td>Blood-oxygen-level dependent</td>
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<tr>
<td>CAMH</td>
<td>Centre for Addiction and Mental Health</td>
</tr>
<tr>
<td>CEN</td>
<td>Central Executive Network</td>
</tr>
<tr>
<td>CIVET</td>
<td>Corticometric Iterative Vertex-based Estimation of Thickness</td>
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<tr>
<td>dACC</td>
<td>Dorsal anterior cingulate cortex</td>
</tr>
<tr>
<td>dlPFC</td>
<td>Dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DMN</td>
<td>Default Mode Network</td>
</tr>
<tr>
<td>dmPFC</td>
<td>Dorsomedial prefrontal cortex</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo planar imaging</td>
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<tr>
<td>FDR</td>
<td>False Discovery Rate</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
</tr>
<tr>
<td>FPS</td>
<td>Fear-potentiated startle</td>
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<tr>
<td>FWHM</td>
<td>Full width at half-maximum</td>
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<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
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LLD  Late-life depression
IOFC  Lateral orbitofrontal cortex
MADRS  Montgomery-Asberg Depression Rating Scale
MAGeT  Multiple Automatically Generated Templates
MANOVA  Multivariate analysis of variance
MMSE  Mini-Mental Status Exam
MNI  Montreal Neurological Institute
mOFC  Medial orbitofrontal cortex
MPRAGE  Magnetization-prepared rapid gradient echo
MRI  Magnetic resonance imaging
OFC  Orbitofrontal cortex
PANAS  Positive and Negative Affect Schedule
PASA  Posterior-to-Anterior-Shift in Aging
PCC  Posterior cingulate cortex
PET  Positron emission tomography
PFC  Prefrontal cortex
ROI  Region of interest
RRI  Rotman Research Institute
SCID-I  Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Research Version
SCR  Skin conductance response
SSI  Beck Scale for Suicidal Ideation
SSRI  Selective serotonin reuptake inhibitor
SST  Socioemotional Selectivity Theory
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>TAS-20</td>
<td>Twenty-Item Toronto Alexithymia Scale</td>
</tr>
<tr>
<td>TE</td>
<td>Echo time</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition time</td>
</tr>
<tr>
<td>vlPFC</td>
<td>Ventrolateral prefrontal cortex</td>
</tr>
<tr>
<td>vmPFC</td>
<td>Ventromedial prefrontal cortex</td>
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Chapter 1
Introduction

1.1 Age-Related Change in Affect

Although cognitive functioning declines with aging (for a review see Salthouse 2010), affective perception, well-being, and emotional regulation appear to persist or improve with increasing age (for reviews see Mather and Carstensen 2005; Scheibe and Carstensen 2010). Older adults are able to detect the emotional content of images, showing rapid identification of the presence of threatening schematic faces in complex arrays of neutral faces comparable to young adults (Hahn, Carlson et al. 2006; Mather and Knight 2006), as well as maintained detection of positive information (Leclerc and Kensinger 2008). Older individuals show an attentional and mnemonic benefit for positive material (Charles, Mather et al. 2003; Isaacowitz, Wadlinger et al. 2006; Spaniol, Voss et al. 2008; Sasse, Gamer et al. 2014). Older adults engage in the regulation of emotion more so than young adults (Urry and Gross 2010), successfully moderate their emotional reactivity (Gross, Carstensen et al. 1997; Kessler and Staudinger 2009), and have been shown to preferentially use mood regulation strategies to maintain positive and reduce negative affective states (Riediger, Schmiedek et al. 2009). For example, in an eye-tracking study evaluating participant gaze when viewing faces expressing a neutral emotion paired with either a positive or negative emotion, young adults in a negative mood were more likely to direct their gaze towards negative stimuli and when in a positive mood towards positive or neutral stimuli; however, older adult’s gaze was directed towards positive stimuli when in a negative mood, which is suggested to reflect a regulatory attempt to improve mood (Isaacowitz, Toner et al. 2008). In fact, older adults with good executive control were able to resist diminishing mood by displaying these positive gaze preferences (Isaacowitz, Toner et al. 2009).
Age-related affective differences are often conceptualized within the framework of Socioemotional Selectivity Theory (SST). SST proposes that goals are influenced by the perception of time, whereby a limited sense of time, such as perceiving one’s own mortality in old age, leads to a motivated shift in allocating cognitive resources from knowledge base expansion, which is more relevant for younger individuals, to maximizing positive emotional experience in later life (Carstensen, Isaacowitz et al. 1999; Carstensen 2006). Thus older adults are hypothesized to show a positivity effect, whereby attention is directed away from negative and towards positively valenced information (Carstensen and Mikels 2005; Isaacowitz, Wadlinger et al. 2006; Reed, Chan et al. 2014). Lending support to the notion that the positivity effect is a motivational phenomenon are studies showing that disruptions to emotion regulation strategies result in an elimination of the positivity effect (Reed, Chan et al. 2014). For example, Knight et al. (2007) utilized an eye-tracking paradigm and found that older compared to younger adults attended more to positively valenced images (both scenes and facial expressions) when cognitive resources were not challenged. However, under conditions of divided attention, older adults no longer displayed positive gaze preferences, but rather attended more to negative images, while younger volunteers no longer showed a negativity bias but attended similarly to all affective material (Knight, Seymour et al. 2007). Furthermore, Lockenhoff et al. (2007) found that older adults were more likely to select positive aspects of health care choices (compared to negative or neutral information), and recall their choices more positively, than younger adults, when permitted to evaluate the material undirected. Yet when asked to adjust their motivational goals to a more fact-based gathering of information, older adults no longer showed a positivity preference, and were able to evaluate all information similar to younger adults (Lockenhoff and Carstensen 2007). These results suggest that it is not the processing of
negative information that is inherently dysfunctional in aging, but rather that there is a change in the default approach towards negative information.

Alternate explanations for age-related differences in emotional processing emphasize compensatory mechanisms as related to cognitive or neurologic decline. The theory of Dynamic Integration proposes that decreasing cognitive capacity in aging makes it more challenging to process complex information, such as negative stimuli, that is more demanding, and thus, positive information becomes more salient for older adults (Labouvie-Vief 2003). However, evidence suggests that individuals with greater cognitive control are more likely to show a positivity effect (Mather and Carstensen 2005; Isaacowitz, Toner et al. 2009), and that this effect disappears when cognitive resources are strained (Mather and Carstensen 2005). For instance, Fleming et al. (2003) found that cognitively impaired Alzheimer’s patients recalled more negative than positive words during an affective memory task, as compared to healthy young and older adults (Fleming, Kim et al. 2003). The Aging-Brain Model posits that a degradation in the function of the amygdalae associated with increasing age results in an attenuation of response and arousal to negatively, but not positively, valenced material (Cacioppo, Berntson et al. 2011). Extending SST, older adults are suggested to use cognitive control mechanisms to regulate emotional goals towards positive information (Mather and Knight 2005). Consistent with this notion of cognitive control over affective goals, greater prefrontal cortical (PFC) activations are reported in older adults, which may be reflective of a shift from recruiting posterior visual processing regions to more anterior cognitive areas, similar to the compensatory response that has been reported during cognitive task performance (Grady, Maisog et al. 1994). This change has come to be known as the Posterior-to-Anterior Shift in Aging (PASA; Dennis and Cabeza 2008). Older adults have been found to exhibit greater PFC activation coupled with decreased activation in visual areas during the processing of emotional
stimuli, congruent with the PASA hypothesis, and this pattern is suggested to reflect an affective regulatory strategy (St Jacques, Dolcos et al. 2010). The following sections will consider brain regions involved in emotion and affect-related neuronal changes with age.

1.2 The Amygdalae and Emotion

The amygdalae are key structures implicated in emotional information processing and encoding of both negative and positive valences (for reviews see Davis and Whalen 2001; Phelps and LeDoux 2005; Hermans, Battaglia et al. 2014). These regions have long been identified as central structures involved in fear processing (Maren 2001). For example, animal models evaluating the effects of amygdalae lesions (chiefly in the basolateral regions) show impaired acquisition of a conditioned fear-potentiated startle (FPS) reflex to auditory and visual stimuli in rodents (Campeau and Davis 1995) and auditory stimuli in nonhuman primates (Antoniadis, Winslow et al. 2007). Furthermore, both young and adult macaques with amygdalae lesions interact with dangerous objects that produce significant fearful and avoidant behaviours in non-lesioned animals, or those with lesions in hippocampal or orbitofrontal cortex (OFC) regions (Machado, Kazama et al. 2009; Bliss-Moreau, Toscano et al. 2011). Recent studies including patients with congenital Urbach-Wiethe disease, which results in bilateral amygdalae calcification, have demonstrated that the FPS reflex is impaired in these patients (Klumpers, Morgan et al. 2014). Using functional magnetic resonance imaging (fMRI) and measurement of skin conductance response (SCR), a physiological index of conditioned fear, greater bilateral amygdalae activation has been demonstrated to correlate with increased SCR during fear conditioning in healthy adults (MacNamara, Rabinak et al. 2015).
While there has been a great deal of focus on the amygdalae’s role in fear, it has been revealed that these regions are also engaged in processing positive affect. A study of rhesus macaques with bilateral amygdalae lesions evaluated expressive response to affective video clips and found these animals to be less expressive to both negative and positive socially-engaging videos compared to non-lesioned and hippocampal-lesioned monkeys, whereas the neurologically intact animals were robustly engaged by the affective social content (Bliss-Moreau, Bauman et al. 2011). Neuroimaging research in human volunteers also implicates the amygdalae in the processing of positive material. In healthy young adults, amygdalae blood-oxygen-level dependent (BOLD) activity has been found in response to facial expressions including negative (fear, anger, disgust, sadness) and positive (happiness) affect (Fitzgerald, Angstadt et al. 2006; Fusar-Poli, Placentino et al. 2009), and to scenes of high-arousing negative and high and low-arousing positive valences (Garavan, Pendergrass et al. 2001). The involvement of the amygdalae across valence categories implies that these regions may be more broadly involved in attention (Davis and Whalen 2001) and the detection of relevance (Sander, Grafman et al. 2003).

The amygdalae are suggested to have localized specializations. Wright et al. (2001) demonstrated hemispheric lateralization of the amygdalae, finding that although affective facial expressions activate the bilateral amygdalae, the right region habituated in response over time and the left amygdala remained responsive to negative faces. The author’s hypothesized that the right amygdala is involved in the automatic detection of emotional material, whereas the left maintains activation specifically to negative valence (Wright, Fischer et al. 2001). The right amygdala is also postulated to act as a relevance detector, for instance, activating more to social versus non-social scenes (Vrticka, Sander et al. 2012). Meta-analysis has confirmed that the left amygdala is particularly responsive during the processing of negative compared to positive
facial expressions (Fusar-Poli, Placentino et al. 2009). Sex-effects may also be lateralized, with men showing greater right (Fusar-Poli, Placentino et al. 2009), and women demonstrating increased left (Stevens and Hamann 2012), amygdala activations. Furthermore, it has been observed that woman demonstrate persistent left amygdala reactivity to familiar negative scenes as compared to men (Andreano, Dickerson et al. 2014).

Dorsal and ventral areas of the amygdalae are thought to be differentially activated in response to arousal, attention and relevance (dorsal) and negative valence (ventral; Whalen, Rauch et al. 1998; Whalen, Shin et al. 2001; Wright, Wedig et al. 2006; Mende-Siedlecki, Said et al. 2013). A recent study found dorsal amygdalae activations to more intense positive scenes (versus low intensity scenes) that was correlated with greater SCR (Bonnet, Comte et al. 2015). Another study investigating affective contextual cuing of surprised facial expressions revealed the left ventral amygdala to be more activated when faces were primed with negative compared to positive sentences (Kim, Somerville et al. 2004). These regional distinctions generally correspond to differences in the positions of the subnuclei of the amygdaloid complex, with the central nuclei located more dorsally and basolateral nuclei being more ventrally situated (Saygin, Osher et al. 2011; Mishra, Rogers et al. 2014). Using a reversal-learning paradigm, Boll et al. (2013) demonstrated an association between greater activities in the central nuclei of the amygdalae and a measure of surprise used to direct attention, consistent with the theory that this area of the amygdalae makes arousal based responses. In this study, the basolateral regions were more activated when aversive stimuli became more predictable, providing support for the notion that the ventral amygdalae regions persist in activation to negative stimuli (Boll, Gamer et al. 2013). The effects of aging on the amygdalae are the focus of the following sections.
1.3 Age-Related Structural Changes in the Amygdalae

Global reduction in total brain volume occurs with healthy aging, and may begin as early as aged 35 years with a decline of 0.2% per year accelerating to a decrease of 0.5% per year at aged 60 years (Hedman, van Haren et al. 2012). Regional alterations, however, are vastly heterogeneous. Using a cross-sectional design, Grieve et al. (2011) stratified volunteers into three age groups and found non-linear trends in volumetric change for structures including the amygdalae. This group found slight increases in amygdalae volume for young volunteers (aged 0 – 30 years, +0.07% annually), with declining volume evident at 30 – 60 years of age (-0.23% annually), and more rapid loss between ages 60 – 90 years (-0.53% annually; Grieve, Korgaonkar et al. 2011). Other cross-sectional studies have indicated a rate of decline in the amygdalae from 4.24% per decade past aged 60 years (also with minimal reductions observed at younger and middle ages; Goodro, Sameti et al. 2012), to a longitudinal rate of shrinkage of 0.81% annually between 60 – 90 years of age (Fjell, Westlye et al. 2013). Differences in findings related to volumetric changes have been attributed to methodological variations, such as the segmentation procedures used or adjustments made for total gray matter (Peelle, Cusack et al. 2012). Walhovd et al. (2011) attempted to mitigate some of the discrepancies by using a uniform methodology across six cross-sectional datasets (total sample size, n = 883).

Volumetric loss was demonstrated in the amygdalae across five out of six healthy adult samples, with a linear decline ranging from 1.48 – 7.07% per decade, corrected for total intracranial volume. Across the samples, the greatest volumetric amygdalae reduction was seen during the sixth decade (-8.6%; Walhovd, Westlye et al. 2011).

There is evidence that women have smaller amygdalae volumes compared to men (uncorrected for total volumes; Ruigrok, Salimi-Khorshidi et al. 2014). Using a region of interest (ROI) based
analysis of age and sex interactions for subcortical volumes, Pruessner et al. (2001) found no differences in amygdalae volumes between men and women with advancing age. Although the age range examined in this study did not include any older adults (i.e., ages ranged between 18 – 42 years; Pruessner, Collins et al. 2001). A subsequent ROI analysis including volunteers ranging in age between 19 – 70 years, and correcting for total brain volume, found no age and sex interactions in the volume of the amygdalae, indicating a relative structural preservation of the amygdalae with aging for both men and women (Li, van Tol et al. 2014). When accounting for age and total intracranial volume, Barnes et al. (2010) demonstrated that while men did show a volumetric decline in the amygdalae (reduction of 3.26%), volumes were no longer significantly different from women after corrections (Barnes, Ridgway et al. 2010). Overall, while the amygdalae do consistently show some structural change, which appears to be similar between sexes when correcting for head size, this region remains relatively intact across the lifespan, compared to other limbic, or frontal and parietal areas which show greater rates of decline (Good, Johnsrude et al. 2001; Grieve, Clark et al. 2005; Grieve, Korgaonkar et al. 2011; Goodro, Sameti et al. 2012; Fjell, Westlye et al. 2013).

1.4 The Effect of Aging on Amygdalae Reactivity to Emotional Challenge

The functional changes of the amygdalae are less well understood than the structural alterations that take place with aging. During the processing of positively valenced stimuli there appears to be agreement that amygdalae reactivity is sustained in older adults (Mather, Canli et al. 2004; Leclerc and Kensinger 2008; Leclerc and Kensinger 2011; Moriguchi, Negreira et al. 2011; Roalf, Pruis et al. 2011; although see Williams, Brown et al. 2006). Whereas for negatively valenced material, some research suggests that older individuals show an attenuation of
amygdalae activations compared to their younger counterparts (Iidaka, Okada et al. 2002; Gunning-Dixon, Gur et al. 2003; Mather, Canli et al. 2004; Fischer, Sandblom et al. 2005; Tessitore, Hariri et al. 2005; Williams, Brown et al. 2006; Fischer, Nyberg et al. 2010; Leclerc and Kensinger 2011). However, this is not always the case; there is evidence for preserved amygdalae response to negative stimuli under conditions of sufficient/similar arousal (Leclerc and Kensinger 2008; St Jacques, Dolcos et al. 2010; Roalf, Pruis et al. 2011; Dolcos, Katsumi et al. 2014; also see Mather, Canli et al. 2004), novelty (Wright, Wedig et al. 2006; Wright, Feczko et al. 2007; Moriguchi, Negreira et al. 2011), and successful encoding (Kensinger and Schacter 2008; St Jacques, Dolcos et al. 2009). Furthermore, for sufficiently arousing emotional information (i.e., combining both negative and positively valenced stimuli), amygdalae response has been found to be comparable between older and young adults (Mather, Canli et al. 2004; Kensinger and Schacter 2008; Ritchey, Bessette-Symons et al. 2011).

The first fMRI study to pursue an analysis of age-related amygdalae activation differences during affective facial processing was conducted by Iidaka et al. (2002). This group employed an implicit sex discrimination task where volunteers viewed negative, positive, and neutral facial expression pairs (one man and one woman) and were asked to indicate the left or right location of the target sex. While both healthy young and older adults were found to exhibit activation in the left amygdala to the negative faces, the older group showed significantly less activation when compared to the younger group (Iidaka, Okada et al. 2002). Williams et al. (2006) included healthy volunteers ranging in age from 12 – 79 years in a paradigm where participants were explicitly asked to attend to fearful, happy, and neutral faces in preparation for subsequent recognition accuracy and intensity rating tasks. When viewing facial expressions of fear, healthy older adults (aged 50 – 79 years) showed attenuated activation in the left amygdala compared to adults aged 20 – 49 years (Williams, Brown et al. 2006). Another study found age-
related attenuated activation in the left amygdala during the incidental processing of negative versus positive scenes (Leclerc and Kensinger 2011). Decreased right amygdala activation in older compared to young volunteers has been demonstrated during tasks requiring the passive viewing of angry facial expressions (Fischer, Sandblom et al. 2005), explicit processing of fearful and threatening facial expressions (i.e., matching a probe emotional expression to a target versus a sensorimotor control task; Tessitore, Hariri et al. 2005), valence ratings of predominantly negative expressions (compared to a sex-discrimination task; Gunning-Dixon, Gur et al. 2003) and successful encoding of fearful faces (Fischer, Nyberg et al. 2010).

Yet, instances of preserved amygdalae function with aging have also been reported for negative material. Two studies using volunteer’s subjective classifications of valence to evaluate implicit processing of negative and positive objects (Leclerc and Kensinger 2008) and explicit processing of negative scenes (St Jacques, Dolcos et al. 2010), found that older and young adults exhibited a similar pattern of amygdalae reactivity to affective stimuli. The latter group subsequently determined that in a subset of older adults who rated a portion of negative scenes as neutral there was a decrease in right amygdala activation compared to young adults, while the correctly rated negative pictures elicited comparable activation in the amygdala for both age groups (possibly because these correctly categorized scenes were normatively rated as slightly, but significantly, more negative and thus potentially more challenging to regulate; St Jacques, Dolcos et al. 2010). This suggests that differences in amygdalae reactivity to negative stimuli may be a result of the volunteer’s subjective experience of valence (St Jacques, Bessette-Symons et al. 2009), which for older adults may be influenced by a tendency to regulate emotion towards less negativity. In other words, if older adults are experiencing negative stimuli as less negative there may be a greater tendency to find attenuated amygdalae activation relative to young adults. For example, Gunning-Dixon et al. (2003) found attenuated right amygdala
activation in their group of older volunteers using an emotion discrimination task of facial expressions. However, in this study, older adults were found to be less accurate in ratings of valence compared to younger adults (i.e., made more mistakes classifying negative and positive stimuli; Gunning-Dixon, Gur et al. 2003), which may account for the observed activation differences. Similar results were obtained by Williams et al. (2006) in a group of older adults where ratings of fearful faces were less accurate and perceived to be less intense compared to younger and middle-aged adults. Furthermore, although this latter study found no age-related differences in recognition accuracy for happy expressions, older adults did rate positive affect less intensely, and reduced amygdalae response was found for those expressions as well (Williams, Brown et al. 2006).

Age-differences in amygdalae response seem to disappear when level of arousal is controlled during both explicit and implicit processing of negative (and positive) imagery (Ritchey, Bessette-Symons et al. 2011). In a study of arousal effects, Roalf et al. (2011) included negative scenes with high standard valence and arousal ratings, confirmed to be comparably rated in their young and older groups, to demonstrate a similar magnitude of bilateral amygdalae response between groups. Additionally, no age-related differences in response were found for equivalently arousing positive scenes (Roalf, Pruis et al. 2011). Mather et al. (2004) found reduced amygdalae response in older compared to young adults for negative scenes where arousal ratings differed (i.e., negative scenes were found to be less arousing by older than young volunteers). However, when equivalent arousal ratings were used to compare age groups for both negative and positive scenes, activation differences were not seen (Mather, Canli et al. 2004). This effect is also observed during facial processing; when valence and arousal are equated between young and older adults, similar patterns of amygdalae activations are detected during the implicit processing of novel fearful faces (Wright, Wedig et al. 2006; Wright, Feczko
et al. 2007), and the explicit processing of own- versus other-age faces expressing anger and happiness (Ebner, Johnson et al. 2013). In the latter study, both young and older volunteers displayed amygdalae reactivity to young affective faces, but older volunteers exhibited greater activations when viewing older emotional faces, suggesting that older adults may find own-age faces particularly salient (Ebner, Johnson et al. 2013). Collectively, these studies tend to contradict the Aging-Brain Model, which implicates dysfunctional amygdalae response to processing deficits for negative stimuli, considering that there is clear evidence for preserved amygdalae activation in older adults for sufficiently stimulating negative imagery. Although a promising explanation for divergent age-related activation results between studies is the difference in the arousal levels of stimuli, it should be noted that limited statistical power may also contribute to the reported disparities (Button, Ioannidis et al. 2013). Examining the sample sizes included in the studies described herein reveals similar mean sample sizes between studies reporting augmented (seven studies, M = 33.86, SE = 11.74) versus analogous (seven studies, M = 37.14, SE = 11.89) amygdalae activations for older compared to young adults. Thus the limited power arising from these small sample sizes may potentially diminish the detection of true effects by some investigations. While there may be some discrepancy in the literature regarding the functional response of the amygdalae to negative stimuli with aging, it is known that these regions are not solely responsible for the processing of all affective material; the PFC also plays a role.

1.5 Emotional Processing and the Prefrontal Cortex

The emotion regulation network includes limbic, prefrontal, and medial structures (e.g., amygdalae, anterior cingulate cortices [ACC], ventromedial [vm] PFC), which are recruited during automatic emotional regulation and cognitive control processes. The amygdalae have
been shown to have reciprocal projections to regions such as the OFC, mPFC, ACC, and insulae (Stefanacci and Amaral 2002; Ghashghaei, Hilgetag et al. 2007). The predominant theory suggests that regions such as the vmPFC exert top-down regulatory inhibition of negative affect via the amygdalae, and where PFC function is disrupted there is a subsequent lack of modulatory effect over limbic regions resulting in hyperactivity towards negative stimuli (Quirk and Gehlert 2003). Several quantitative coordinate-based meta-analyses of fMRI studies have been conducted to examine brain regions that are consistently associated with affect. Frank et al. (2014) focused on emotional modulation (i.e., down- or up-regulation of response to affective material) and found that a tempering of emotional response to negative stimuli resulted in increased activation in the inferior, middle, and superior frontal gyri, and ACC, as well as decreased amygdalae response; whereas intensification of response resulted in greater signal in the left amygdala, superior frontal gyrus, thalamus, and supplementary motor area (Frank, Dewitt et al. 2014). Recognition of affective facial expressions has consistently resulted in bilateral ventrolateral (vl) PFC, dorosmedial (dm) PFC and left amygdala activations (Fusar-Poli, Placentino et al. 2009). In another meta-analysis, both affective face and scene stimuli elicited consistent BOLD activations not only in the amygdalae, but also in regions including the inferior and mPFC (Sabatinelli, Fortune et al. 2011). When evaluating stimuli type separately, Sabatinelli et al. (2011) found that affective facial processing engaged regions such as the amygdalae, medial, inferior, middle, and superior frontal gyri, with emotional scene processing also recruiting the amygdalae, mPFC, OFC, and ACC.

Damage to the PFC results in emotional processing difficulties. Patients with lesions to the vmPFC are impaired at recognizing and distinguishing basic emotional expressions compared to patients with PFC damage elsewhere (i.e., dorsal, lateral) and healthy neurologically intact volunteers (Heberlein, Padon et al. 2007). In an extension of this work, Tsuchida et al. (2012)
compared three groups of PFC lesioned patients and healthy volunteers to disentangle the effects of lesion location on affective processing. This group confirmed that patients with damage to the OFC/vmPFC (Brodman areas [BAs] 11, 13, 14; 25, subcallosal BAs 24, 32) exhibited detection deficiencies across all six basic emotions (versus neutral expressions) compared to patients with lesions in the dmPFC (dorsal BAs 24, 32; superior BAs 8, 9, anterior BA 6) and vlPFC (BAs 44, 45, 46, 46/9, with some extensions to anterior insula) and healthy volunteers. However, controlling for affective detection impairments, left vlPFC lesioned patients were found to be particularly poor at distinguishing between affective expressions when compared to other lesioned patients and intact volunteers; that is, vlPFC damaged patients had difficulties matching expressions to the correct affective categories (Tsuchida and Fellows 2012). The PFC does undergo structural changes during the aging process, and these variations are the subject of the following section.

1.6 Alterations in the Structural Morphology of Prefrontal Regions with Increasing Age

Volumetric reductions across the cortex, including the frontal lobes, have been seen with advancing age. However, as previously noted, degeneration is not uniform throughout the brain, including the PFC. Sex effects are also apparent, where men show greater whole brain and gray matter volumes compared to women (Sowell, Peterson et al. 2007; Ruigrok, Salimi-Khorshidi et al. 2014). Although after correcting for head size and age, women have been found to have larger whole brain volumes than men (Barnes, Ridgway et al. 2010), and increased gray matter in the frontal lobes (Ruigrok, Salimi-Khorshidi et al. 2014). Studies assessing age and sex interactions report similar rates of total gray matter volumetric decline in older men and women (Lemaitre, Crivello et al. 2005), but greater regional gray matter decline in older men in areas
including the PFC (Curiati, Tamashiro et al. 2009). In a small cross-sectional analysis by Salat et al. (2001), total volume of the PFC has been shown to be reduced in older compared to young adults (controlling for sex); although, when examining each region in relative proportion to all other regions combined, although volumes were smaller in superior, middle and inferior frontal areas these regions were not found to be statistically different between the age groups. Furthermore, a lack of age-related volumetric difference has been exhibited in the OFC in proportion to other PFC areas (Salat, Kaye et al. 2001). However in a prospective 10-year longitudinal analysis (n = 138, age range at baseline 64 – 86 years), accelerated annual rates of volumetric decline were observed in the middle frontal gyrus, with less reduction in the inferior, superior, medial and OFC regions in healthy volunteers, with women showing less age-related decline in frontal regions (Driscoll, Davatzikos et al. 2009). Another large longitudinal evaluation of the annual rate of whole-brain volumetric change in a sample of 381 healthy volunteers (ranging in baseline age from 21 – 80 years) found accelerated volumetric decline with aging (controlling for sex) in regions including the left vIPFC, dorsolateral (dl) PFC, and right insula; whereas preservation was evident in the bilateral OFC, and cingulate cortices (Taki, Thyeau et al. 2013). Thus, medial and OFC regions show relatively modest structural decline while lateral PFC regions appear to show more rapid volumetric loss in aging (Raz, Gunning-Dixon et al. 2004).

While volumetric change has been a significant focus of the structural neuroimaging of aging populations, more research is beginning to include measures of cortical thickness, which in concert with surface area encompass volumetric measures (Panizzon, Fennema-Notestine et al. 2009). The thicknesses of cortical regions appear to be altered during aging, with global thickness declining at a rate of 0.016 mm per decade, and thinning apparent as early as the third decade of life (Salat, Buckner et al. 2004). There is some evidence for sex differences in cortical
thickness, with women having thicker cortex across the brain (van Velsen, Vernooij et al. 2013), which appears to be independent of differences in head size (Sowell, Peterson et al. 2007; Barnes, Ridgway et al. 2010). Women tend to have thicker inferior parietal and posterior temporal cortices as compared to men, though the left vPFC and right lateral frontal cortex have also been found to be thicker in women, with men showing greater right OFC thickness than women (Sowell, Peterson et al. 2007). Age by sex interactions have been observed using lobe-wise analysis for the frontal cortex (van Velsen, Vernooij et al. 2013), and vertex-wise in the bilateral dPFC (Sowell, Peterson et al. 2007), whereby older women show less thinning in this region compared to men. Thinning in lateral superior and inferior prefrontal, precentral, and temporoparietal regions takes place with aging (Salat, Buckner et al. 2004; Fjell, Westlye et al. 2009), but again there is some evidence of either thickening or preservation of mPFC and OFC regions, and these studies did not find age by sex interactions (Salat, Buckner et al. 2004; Fjell, Westlye et al. 2009). A longitudinal investigation of healthy older adults found thinning across the cortex, with frontal and parietal regions exhibiting more rapid loss compared to temporal and occipital areas, and women showing less decline in regions including the middle frontal gyrus (Thambisetty, Wan et al. 2010). A recent investigation by Fjell et al. (2014) utilized both cross-sectional and longitudinal data to evaluate cortical thickness changes with age, controlling for the effects of sex, and confirmed thinning in the superior, middle, and inferior frontal gyri, pre/postcentral gyri, and temporoparietal junction. However, in the cross-sectional sample no age-related differences in ACC and OFC thickness were observed, whereas in the longitudinal sample evidence for thinning was apparent, though at a slower rate than other regions examined (Fjell, Westlye et al. 2014). The authors attributed the discrepancy to sampling bias in cross-sectional studies, which may select for especially healthy older volunteers and thus may not capture more subtle rates of decline. Collectively, results tend to converge in suggesting cortical
thinning across most PFC regions, with relative sparing/lower rates of decline in medial and OFC regions, with advancing age. In addition to the structural changes seen in the PFC, aging alters the functionality of this area.

### 1.7 Prefrontal Cortical Involvement in Age-Related Affective Processing

Aging may shift affective information management from automated processing in subcortical regions (such as the amygdalae) to higher-order, controlled regulatory and attentional processing in neocortical regions (such as the PFC and ACC), and this has been suggested to correspond to the positivity shift, whereby PFC regions exert top-down regulatory control over negative stimuli (St Jacques, Dolcos et al. 2010). For example, an analysis of event related potentials revealed an early decrease of response in the dmPFC for the processing of happy facial expressions (40 – 150 ms) and a later increase of this region’s response during the processing of fearful faces (180 – 450 ms) for older compared to younger adults, supporting an involvement of the PFC during more controlled stages of processing for negative information and a maintenance of automated response to positive information (Williams, Brown et al. 2006). This PFC response was found to be predictive of a reduced level of neuroticism in aging, suggesting that more cognitive control over negative affect promotes emotional stability (Williams, Brown et al. 2006). Older adults show increased vmPFC and ACC signal coupled with decreased amygdalae signal to negative stimuli that elicit low levels of arousal, and the vmPFC/ACC activity is related to lower arousal ratings in this age group (Dolcos, Katsumi et al. 2014). Both young and older adults exhibit greater PFC/ACC activation and amygdalae attenuation when asked to reappraise or regulate negative and positive affective scenes (Urry, van Reekum et al. 2006; Winecoff, Labar et al. 2011). Functional connectivity analysis allows for the evaluation of
how the activation of one region correlates with the activation of another region. The functional connectivity between PFC/ACC and the amygdalae has been shown to be stronger in older versus young adults (Murty, Sambataro et al. 2009; St Jacques, Dolcos et al. 2009; St Jacques, Dolcos et al. 2010; Sakaki, Nga et al. 2013), suggesting that older adults are effective at engaging these regions for emotion regulation, particularly for low arousing, extraneous, negative stimuli.

Studies showing attenuated amygdalae activations in older compared to young adults are consistent in showing an accompanied increase in prefrontal activations. Using an emotional matching paradigm requiring the explicit processing of fearful and threatening facial expressions, healthy older compared to young adults have demonstrated increased activation in the bilateral vlPFC and left dmPFC (Tessitore, Hariri et al. 2005). During an affective facial expression valence-rating task, older adults demonstrated increased ACC and left vlPFC activation relative to younger adults (Gunning-Dixon, Gur et al. 2003), and indicating the fearfulness or neutrality of facial expressions elicited greater activations in the left insula and right dlPFC for older versus young volunteers (Fischer, Nyberg et al. 2010). Similar increases in activation are observed in the right vlPFC/insula (Fischer, Sandblom et al. 2005) and bilateral dmPFC (Williams, Brown et al. 2006) during the passive viewing of angry and fearful facial expressions, respectively, with aging.

Increased PFC recruitment in aging is also evident in studies showing preserved amygdalae response. Older compared to young adults have been shown to activate more in the vmPFC to successfully encoded (Kensinger and Schacter 2008) and subjectively experienced (Leclerc and Kensinger 2008) positive objects. Negative scenes categorized based on volunteer’s subjective ratings have also elicited greater activations in older adults in the bilateral vmPFC (Leclerc and
Kensinger 2011), right dmPFC and dIPFC (St Jacques, Dolcos et al. 2010). Greater response of the left dIPFC was found to the successful encoding of negative scenes and increased activation in the bilateral vlPFC was functionally connected to the right amygdala in this study for older adults (St Jacques, Dolcos et al. 2009). One study found activation in the bilateral vmPFC and right vlPFC to be specific to an elaborative processing task that asked volunteers to fully attend to the content of positive scenes, as opposed to a task that divided attention by shifting focus to perceptual details of the images, suggesting these regions are involved in more effortful or controlled processes (Ritchey, Bessette-Symons et al. 2011). Processing of facial affect (negative, positive and neutral expressions) has revealed augmented dmPFC activation to same-age faces (versus younger age faces) in a group of older volunteers, suggesting this region may be particularly important to self-referential processing in aging (Ebner, Johnson et al. 2013). It is noteworthy that these studies have used stimuli that elicit comparable arousal between age groups, which might suggest that, although older adults are making regulatory attempts as seen by the over-recruitment of PFC regions, when stimuli are highly arousing, the amygdalae may persist in response regardless, and age-related differences in these region’s activations abate. This notion appear to be in line with behavioural evidence which shows that arousal based processing of negative stimuli is preserved with aging. For example, Kensinger (2008) evaluated the recall and recognition of affective words that were either highly arousing or non-arousing in a group of healthy young and older adults, where both valence and arousal levels were comparable between the age groups. Young and older volunteers were found to remember highly arousing negative and positive words equally well; while age differences emerged for the low arousing words, in that older adults showed a mnemonic benefit for positive words and young adults had an advantage for negative words (Kensinger 2008). Another study assessing emotional reactivity to negative scenes, which were varied according to arousal level (and
matched for arousal between age-groups), found that under conditions of high arousal both young and older adults reported similar unpleasant responses to highly arousing negative scenes; whereas low arousing negative scenes elicited less self-reported unpleasant arousal in older compared to young adults (Streubel and Kunzmann 2011). In light of the age-related structural alterations taking place within the PFC it would be interesting to determine how these changes influence the functional response of the amygdalae; however, to date, such an analysis has not been undertaken in an older population.

1.8 Sex Differences in Functional Activations During the Processing of Affect and Interactions with Age

Affective-task related activation patterns have been reported to be divergent between the sexes. In a sub-analysis of a larger meta-analysis including 105 fMRI studies evaluating the processing of affective facial expressions, Fusar-Poli et al. (2009) demonstrated that, compared to women, men exhibited greater activations in regions including the right amygdala/parahippocampal gyrus, right mPFC (BA6), and left fusiform gyrus. Women were found to activate more in the subcallosal gyrus compared to men in response to emotionally expressive faces (Fusar-Poli, Placentino et al. 2009). A more recent coordinate based meta-analysis by Stevens et al. (2012) explicitly tested sex effects on the processing of a broader range of affective stimuli (e.g., faces, scenes, words) to reveal that women (compared to men) exhibited increased response to negative stimuli in regions including the left amygdala/hippocampus, right mPFC/ACC (BAs 10, 32, 9), hypothalamus/thalamus, middle/inferior temporal gyri and middle occipital gyrus. Whereas, negative valence elicited greater activations in regions including the right inferior frontal gyrus/insula, superior temporal gyrus/putamen, posterior cingulate cortex (PCC), and left middle temporal/fusiform gyri in men versus women (Stevens and Hamann 2012). These
analyses do provide support for a differential activation pattern in emotional processing between the sexes (with regional discrepancies potentially attributable to the type of stimuli included in analyses); however, these analyses did not evaluate age and sex interactions.

While studies examining age-related structural alterations have either included age by sex interaction effects, or controlled for sex, there are limited reports of these effects as related to functional brain response. Of the studies reviewed in the previous sections, only a few indicate accounting for sex. For example, Tessitore et al. (2005) included separate sex analyses within their young and older age groups and found that regional activation patterns to an affective facial matching paradigm were unaltered by sex. Furthermore, sex effects were not apparent in the direct comparisons of young and older adults revealing PFC, amygdala, and fusiform activation differences (Tessitore, Hariri et al. 2005). Other studies evaluating age-related amygdalae and PFC response differences to affective scene processing have included only women to mitigate any potential sex confounds (St Jacques, Dolcos et al. 2009; St Jacques, Dolcos et al. 2010). However, the majority of studies not reporting sex confounds may be overlooking important age and sex interactions relevant to affective processing and functional response, for example with respect to hormonal changes.

The amygdalae contain receptors for estrogen (Osterlund, Gustafsson et al. 2000), and reactivity in these regions in response to emotional stimuli has been shown to be modulated by low and high estrogen phases of the menstrual cycle (Goldstein, Jerram et al. 2005). Pruis et al. (2009) evaluated the differences between older women taking hormone replacement therapy (HRT), and older and young women not using HRT on self-reported arousal to affective material (scenes and stories). Older women taking HRT reported greater subjective arousal to all negative stimuli as compared to both young and older women without HRT, indicating that
estrogen may modify reactivity to emotional stimuli differentially with aging (Pruis, Neiss et al. 2009). In a randomized, double blind, placebo-controlled, crossover pilot trial, a group of older women were evaluated on the short-term effects of HRT during affective scene processing using fMRI (Love, Smith et al. 2010). Love et al. (2010) found that HRT resulted in significantly increased activations in the OFC, precentral gyrus, PCC, and occipital cortex during the processing of negative scenes compared to the placebo condition, with deactivations relative to placebo localized to the dLPFC, postcentral gyrus, and dorsal (d) ACC. While most studies included in the current review of the literature did report excluding volunteers taking medications with central nervous system effects, only a single study explicitly mentioned hormonal contraceptives and HRT, indicating that the use of these medications by volunteers was permitted (Tessitore, Hariri et al. 2005). Considering the potential for age and sex interactions on functional brain response, it is important at minimum to take into account, or control for, the potential effects of sex in studies of aging.

1.9 Impact of Cortical Structure Alterations on Functional Reactivity

The relationship between brain structure and functional activations has been evaluated by some studies including older volunteers with a primary focus on memory. A longitudinal analysis by Persson et al. (2006) examined cognitive decline in older adults and found greater right vPFC (BA47) activation to a working memory task in a cognitively impaired compared to a stable memory group, as well as smaller bilateral hippocampal volume and decreased structural white matter integrity in the anterior corpus callosum. Although no significant correlation between volume and activation was found, the white matter tract change was correlated with functional activation in the vPFC region for older individuals with memory decline (Persson, Nyberg et al. 2006).
Using a verbal episodic memory task, Brassen et al. (2009) included healthy young and older adult women to evaluate age-related differences in hippocampal and PFC (including dlPFC and OFC) volume and associated functional activations during retrieval. Findings revealed that successful encoding activated the bilateral middle temporal gyrus, which was correlated to greater gray matter density in the hippocampus and prefrontal gyrus, particularly for the older group (Brassen, Buchel et al. 2009). In a group of healthy older adults volume of the left entorhinal cortex was found to be positively associated with activation in the right inferior PFC/insula (BA47) during an incidental semantic memory encoding task (Rosen, Gabrieli et al. 2005). Trivedi et al. (2011) evaluated group differences between healthy older adults and those with amnesic mild cognitive impairment during memory recall and found that cognitively stable adults demonstrated a correlation between greater left entorhinal cortical volume and increased functional activation in the right mPFC (BA8; Trivedi, Stoub et al. 2011). Studies such as these clearly illustrate the utility of evaluating structure-function relations, as they have the potential to help explain the neurological basis behind cognitive alterations.

There is very little research examining the effects of cortical thickness alterations on functional brain activity. A study examining associative memory for word pairs in healthy older adults found that thicker left entorhinal cortex was correlated with functional activation in the ACC (BAs 24, 32) and mPFC (BAs 9, 10) during memory retrieval (Braskie, Small et al. 2009). Some additional evidence for altered relationships exists in evaluations of working memory deficits in patients with schizophrenia. A key feature of the disease profile for schizophrenia involves structural abnormalities (Olabi, Ellison-Wright et al. 2011), and there is growing interest in probing the influence of these changes on function and cognition. In a study comparing schizophrenia patients to healthy volunteers, Pujol et al. (2013) used an n-back working memory paradigm and found significant BOLD activations in areas comprising the Central Executive
Network (CEN; including the bilateral inferior, middle and medial frontal gyri [BA6], bilateral inferior and superior parietal lobe, bilateral precuneus [BA7], right lingual gyrus, bilateral middle occipital gyrus, and cerebellum) and deactivations in the Default Mode Network (DMN; including the bilateral ACC [BA32], PCC [BA31], and right middle temporal gyrus [BA39]) for patients. The patient group also showed significant left hemisphere thinning in the pars opercularis (BA44), insular and precentral cortex compared to healthy volunteers. Subsequent regression analysis revealed that the PFC thinning found for patients predicted 57% of the CEN activations/DMN deactivations (Pujol, Penades et al. 2013).

Focusing on BOLD activation in the dACC, an area found to be disturbed in response to working memory demands and structurally altered in schizophrenia (Minzenberg, Laird et al. 2009), Schultz et al. (2012) examined structure-function relations during a working memory Sternberg task. Patients with schizophrenia had attenuated activation in the dACC compared to healthy volunteers, and this deactivation was largely predicted (41%) by cortical thinning in the temporoparietal and dlPFC regions (Schultz, Koch et al. 2012). In a group of high functioning patients with schizophrenia, as assessed by performance on the Tower of London task, BOLD deactivation was found in the right PFC and superior/middle temporal gyrus, and the left occipital lobe, supramarginal gyrus, and pars opercularis. This reduced activation was significantly correlated with cortical thinning in the left prefrontal, dlPFC, and frontal regions, as well as the bilateral parietal cortex (Rasser, Johnston et al. 2005). In a group of patients with schizophrenia or schizoaffective disorder, a recent study probed illness awareness, which is often impaired in these patients, during fMRI and found that deficits in illness beliefs were associated with greater reactivity in the mPFC and temporoparietal-occipital junction; response in the latter region was associated with thinning of the left angular gyrus, parieto-occipital junction, and medial superior frontal gyrus (Gerretsen, Menon et al. 2015). Taken together,
these results suggest that underlying cortical alterations play a significant role in dysfunctional neuronal response to working memory tasks and anosognosia in schizophrenia.

The relationship between cortical thickness and amygdalae functionality has been evaluated in a group of healthy young adults using affective matching and labeling (compared to sensorimotor control) tasks (Foland-Ross, Altshuler et al. 2010). Greater thickness of the left temporoparietal junction (BAs 40, 22) was found to correlate with reactivity in the left amygdala during the negative affect matching task, and was attributed to temporal cortical involvement in emotion perception; whereas, thickness of the left vmPFC (BA 11) correlated with reduced activation in the left amygdala during the negative emotional labeling task, and was posited to reflect more complex cognitive control/regulatory processes involved in the labeling of affect (Foland-Ross, Altshuler et al. 2010). Another recent study by Motzkin et al. (2015) assessed the effects of bilateral focal lesions in the vmPFC (encompassing the medial [m] OFC [BA11], BAs 12, 24, 25, 32, and medial portion of BA10) in four older adults (age M = 58 years, SD = 6.2) compared to neurologically intact volunteers (a subset being age- and sex-matched). Amygdalae functioning were evaluated using an event-related fMRI valence-rating paradigm of negative and neutral scenes. While both healthy and lesioned groups elicited robust bilateral amygdalae activation to the negative versus neutral stimuli, vmPFC damaged patients demonstrated significantly greater activations in the right amygdala than intact and matched comparison volunteers (Motzkin, Philippi et al. 2015). While the latter study did not focus on cortical thickness measurement, these recent works do support the notion that alterations in PFC structure can have an effect on amygdalae functionality, and could be important towards the understanding of emotional alterations in aging, as well as affective processing deficits in mood disorders, in particular for older adults that naturally show cortical change. It is important to provide potential biomarkers of interest to help inform neuropsychiatric investigation, and this
can be accomplished by first evaluating the structure-function relationships involved in healthy aging.

1.10 Summary

- Despite age-related cognitive declines, older adults show preservation or improvements related to emotion, such as maintained affective detection, better emotional regulation, as well as preferences for positive valence in attention and memory (Scheibe and Carstensen 2010).

- Although SST proposes that older adults are motivated to focus on positive information to influence emotional satisfaction, aging may not necessarily disrupt the ability to process and respond to negative material. For example, positivity effects are eliminated in older adults when cognitive control is compromised (Reed, Chan et al. 2014), suggesting higher-order networks may become important to the processing of negative stimuli. Other theories suggest that neurologic alterations can expand explanations for age-related differences in affect.

- Limbic and frontal cortical regions (including areas such as the amygdalae, ACC and vmPFC) have been implicated in an emotional processing and regulatory network. These regions consistently show activity in response to affective content and become more or less activated in response to regulatory goals (Sabatinelli, Fortune et al. 2011; Frank, Dewitt et al. 2014).

- Aging does impact cortical structure; with volume reductions apparent in the PFC and amygdalae, and thinning of PFC regions, especially laterally (Fjell, Westlye et al. 2009;
Taki, Thyreau et al. 2013). However, reductions in the amygdalae are not as extensive as in other regions, and there is some evidence of a preservation of the OFC with aging (Grieve, Clark et al. 2005; Fjell, Westlye et al. 2014).

- Functionally, the amygdalae have shown both an attenuation and maintenance of response to negative stimuli across different tasks in older compared to young adults; as well, there is an increase of activations in higher-order, controlled, processing areas of the PFC for older adults (e.g., Tessitore, Hariri et al. 2005; St Jacques, Dolcos et al. 2009; Ebner, Johnson et al. 2013).

- Very little research has examined the relations between brain structure and functional activation, with the current literature typically focused on memory tasks as opposed to those related to emotional processing. However, in young adults, one study has revealed that the thickness of the OFC correlates with reduced amygdala reactivity to the labeling of negative affect (Foland-Ross, Altshuler et al. 2010). Yet, despite evidence for cortical thickness and amygdalae alterations with aging, this relationship has not been evaluated in an older population.

- It is important to consider the structural-functional relationships associated with affective processing in healthy aging to help understand the underlying neurobiology of age-related emotional change. The current investigation elucidates the effects of aging and cortical thickness on neuronal activation to an affective probe.
1.11 Study Objectives

1.11.1 Specific Aims

In a group of healthy adult men we will:

1. Investigate age effects on affective amygdalae reactivity using fMRI.

2. Investigate age effects on cortical thickness using structural magnetic resonance imaging (MRI).

3. Determine the relationship between aging, structural morphology, and functional activation.

1.11.2 Hypotheses

1. There will be an increase in amygdalae activation during an emotion-matching paradigm compared to a sensorimotor task in healthy adult men. However, based on the previous literature regarding affective facial processing of negative expressions, we expect our group of older men to show an attenuated level of amygdalae activation, coupled with an increase in vPFC and dmPFC activations, during the affective condition compared to our younger men.

2. Relative to healthy younger men, older men will show cortical thinning in the frontal (superior, middle, inferior), parietal (postcentral, supramarginal) and temporal (superior) lobes.

3. Greater amygdalae reactivity will be best predicted by cortical thinning in the PFC for older, but not young, adults.
Chapter 2
Study Design and Methods

2.1 Overview

Healthy older and young adult men (n = 10, respectively) underwent a structural brain scan followed by functional imaging, during which they completed an emotional matching paradigm and sensorimotor task.

2.2 Volunteer Recruitment

Volunteers were identified through the Rotman Research Institute (RRI) Healthy Volunteer Database at Baycrest Hospital (Toronto, Ontario, Canada), or referrals from the Centre for Addiction and Mental Health (CAMH; Toronto, Ontario, Canada). Twenty right-handed, non-smoking, Caucasian men (older group: aged ≥ 60 years; young group: aged 20 – 40 years) completed a brief pre-screening telephone interview to assess their suitability for full study screening. There is evidence for sex effects on measures of cortical thickness and it is recommended to control for these effects (Barnes, Ridgway et al. 2010), thus to reduce confounds we restricted recruitment to men.

2.3 Study Procedures

This study is an independent analysis of a portion of data from protocol approved by the Research Ethics Boards at Baycrest Hospital (REB#08-39) and CAMH (Protocol #343/2008-06). The larger protocol investigates the differences between healthy young and older adult men on affect-related neuronal activation to a serotonergic (5HT)
challenge. Procedures relevant to the current independent analysis are described, as follows.

2.3.1 Screening Visit

Screening visits were conducted at either the RRI or CAMH. All volunteers provided written informed consent, approved by the RRI and CAMH Research Ethics Boards, to participate in the study. The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID-I), Montgomery-Asberg Depression Rating Scale (MADRS), Beck Scale for Suicidal Ideation (SSI), and Beck Anxiety Inventory (BAI) were administered to ensure that all volunteers were free from current or past psychiatric diagnosis and symptomatology. History of substance abuse (within one year) and dependence (lifetime) were assessed as part of the SCID-I Module E. Substance abuse was further ruled out by urine toxicology screen. Screening procedures involved an assessment of medical history and a physical examination, including collection of heart rate and blood pressure measures. The Mini-Mental Status Exam (MMSE) was administered to rule out cognitive impairment. Volunteers were vetted for suitability to participate in the brain imaging procedures (e.g., absence of ferromagnetic materials; claustrophobia). Volunteers were free from unstable medical, cardiac, or neurological illness, psychiatric illness, substance abuse or dependence, and contraindication to imaging procedures. Details of the assessments of psychiatric status, cognitive function, affective awareness and mood are described in the following section. The latter two measures of emotion (i.e., the Twenty-Item Toronto Alexithymia Scale
[TAS-20] and the Positive and Negative Affect Schedule [PANAS]) were administered during the Scanning Visit.

2.3.1.1 Psychiatric and Affective Assessments

2.3.1.1.1 Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Research Version

The SCID-I is presented in a semi-structured interview format and is designed to assess major Axis I psychiatric diagnoses made by a clinician or trained interviewer (First, Spitzer et al. 2002). Items are generally rated on a four point scale: ?=inadequate information, 1=absent/false, 2=subthreshold, 3=threshold/true. Subscale items are summed according to diagnostic criteria to determine the presence or absence of a particular disorder. Time to complete the SCID-I varies between 30 to 60 minutes for a non-patient population. The SCID-I is designed for use with adults aged 18 years and older. The comprehensive research version includes 12 modules, as follows:

Module A: Evaluation of Mood Episodes, Dysthymic Disorder, Mood Disorder due to a General Medical Condition, and Substance-Induced Mood Disorder

Module B: Psychotic and Associated Symptoms

Module C: Differential Diagnosis of Psychotic Symptoms

Module D: Differential Diagnosis of Mood Disorders

Module E: Substance Use Disorders
Module F: Anxiety Disorders

Module G. Somatoform Disorders

Module H: Eating Disorders

Module I: Adjustment Disorders

2.3.1.1.2 Montgomery-Asberg Depression Rating Scale

The MADRS is a 10 item depression severity rating scale, administered in semi-structured interview format (Montgomery and Asberg 1979). Items are rated based on defined scale intensity of 0, 2, 4, 6, with lower ratings representing an absence or appropriate/fleeting level of occurrence (e.g., Item 1, Apparent Sadness, 0=no sadness) and higher scores representing significant presence (e.g., Item 10, Suicidal Thoughts, 6=Explicit plans for suicide when there is an opportunity/Active preparations for suicide). The interviewer also has the option of selecting 1, 3, or 5 ratings for each item, if appropriate. Scores range from 0 – 60, with 0-6=symptoms absent, 7-19=mild depression, 20-34=moderate depression, 35-60=severe depression. This scale has been validated for use with geriatric populations without dementia, and a clinical cut-off of ≥17 is recommended to indicate the presence of a major depressive disorder (Engedal, Kvaal et al. 2012). The time frame covered by the scale was: Screening = past week; Pre-Scanning = since the Screening Visit; Post-Scanning = since the last questionnaire. Time taken to complete the MADRS is approximately ten minutes.
2.3.1.1.3 Beck Scale for Suicidal Ideation

The SSI is a 19 item, semi-structured, assessment of suicidal intent taking into account the characteristics, prevalence, and intensity of self-destructive thoughts, wishes, or threats (Beck, Kovacs et al. 1979). The scale measures three dimensions of suicidal ideation: Active Suicidal Desire, Passive Suicidal Desire, and Preparation. Each item is rated on a three-point scale from 0 to 2, with each rating representing statements that differ in magnitude. Total scores range from 0 – 38, and a score of ≥ 6 has been used as a clinically significant cut-off (Sokero, Melartin et al. 2003). There have been no age-related differences found in the manifestation of low levels of suicidal ideation using this scale in a non-clinical population (Miller, Segal et al. 2001). Ideation is assessed for the past week from time of the scales administration. Task duration is approximately five minutes.

2.3.1.1.4 Beck Anxiety Inventory

The BAI consists of 21 items assessing somatic symptoms of anxiety and is administered in self report format (Beck, Epstein et al. 1988). Each symptom is rated on a four point scale indicating the extent to which that symptom has bothered the respondent, from 0=not at all to 3=severely, it bothered me a lot. Total scores range from 0 – 63, with 0-9=no/normal anxiety, 10-18=mild/moderate anxiety, 19-29=moderate/severe anxiety, and 30-63=severe anxiety. The psychometric properties of this scale have been evaluated as sufficient in older adults, and it is recommended for use in the detection of anxiety in both community-dwelling and psychiatric older adult populations (Therrien and Hunsley 2012). The time frame covered by the scale was: Screening = past month; Pre-Scanning
= since the Screening Visit; Post-Scanning = since the last questionnaire. This scale takes approximately five to ten minutes to complete.

2.3.1.1.5 Mini-Mental Status Exam

The MMSE is a 30 item screening for cognitive impairment administered as a semi-structured interview (Folstein, Folstein et al. 1975). The assessment includes items related to orientation to time and place, registration, attention and calculation, recall, language, repetition and complex commands. Items are scored as 0=incorrect or 1=correct. Total scores range between 0 – 30, with ≥ 27 representing normal cognitive function. The time taken to complete this assessment is approximately ten minutes.

2.3.1.1.6 Twenty-Item Toronto Alexithymia Scale

The TAS-20 consists of 20 items that assess the alexithymia construct, representing difficulties in identifying and describing emotions and limited emotional introspection (or externally oriented thinking), and is administered in self report format (Bagby, Taylor et al. 1988; Bagby, Parker et al. 1994). Respondents indicate the extent to which they agree with each statement as it applies to themselves based on a five point scale ranging from 1=strongly disagree to 5=strongly agree. All item scores are summed to generate a total score indicative of overall affective dysfunction. As well, summing responses to the items corresponding to each factor generates scores that reflect the three central components of alexithymia. Total score cut-offs representing alexithymia are ≥ 61, whereas scores of ≤ 51 are non-alexithymic. Prevalence of alexithymia has been found to be comparable between young and older adults (Gunzelmann, Kupfer et al. 2002). There
is no time frame associated with this measure. Scale duration is approximately ten minutes.

2.3.1.1.7 Positive and Negative Affect Schedule

The PANAS is a self report scale that includes 20 items measuring two mood factors known as positive and negative affect (Watson, Clark et al. 1988). High positive affect reflects enthusiasm, alertness, and enjoyable experiences, while low positive affect suggests lassitude and despondency. High negative affect represents subjective distress and unpleasant experiences, while low negative affect signifies calmness and tranquillity. For each item, respondents indicate to what extent they have experienced each mood state on a five point scale ranging from 1=very slightly/not at all to 5=extremely. Scores for each factor can range from 10 – 50. The time frame covered for this scale was relative to the past week at the time of completion. Normative data representing this time frame are, for positive affect: $M = 32.0$ (SD = 7.0) and for negative affect: $M = 19.5$ (SD = 7.0). Age-related influences on the PANAS scores have been found to be negligible, and are not considered to impact normative data (Crawford and Henry 2004). The duration for this scale is approximately five minutes.

2.3.2 Scanning Visit

Imaging procedures were completed at Baycrest Hospital’s MRI Suite. Upon arrival volunteers completed a mood evaluation with study personnel. Prior to entry into the MRI Suite, volunteers removed all magnetic materials from their person and were required to change into scrubs (gown and pants). An MRI Technologist reviewed the
completed MRI Safety Screening Form and the signature page of the Informed Consent Form with each volunteer. A brief explanation of the affective and sensorimotor tasks was given and volunteers were able to ask any questions at that time. These instructions were repeated, as a reminder, prior to each presentation of the tasks.

Volunteers were escorted into the MRI environment by the MRI Technologist and prepared for the scanning procedures, including positioning of cardiac and respiratory monitoring devices, earplugs, headphones, and foam cushions around the volunteer’s head to limit movement. Structural scanning was completed over 15 minutes, followed by three functional runs lasting eight minutes each. During each functional run, volunteers completed an affective and sensorimotor matching paradigm, selected based on its prior established success at eliciting robust amygdalae response (Hariri, Bookheimer et al. 2000; Hariri, Mattay et al. 2002; Bigos, Pollock et al. 2008).

Following study procedures volunteers were able to change back into their own attire, completed a final mood evaluation, including the TAS-20 and PANAS, to confirm stable mood and emotional awareness, and were provided transportation home. Compensation included up to $100 for time ($10 per hour for approximately 5 hours for the Screening and Scanning Visits), and imaging ($50), and volunteers were reimbursed for travel expenses (e.g., tokens, parking, taxi).

2.3.2.1 Image Acquisition

Structural and functional imaging was conducted using the Seimens TIM Trio 3.0 Tesla system (Siemens, Erlangen, Germany) with the standard 12-channel phased-array head
coil located at Baycrest Hospital. A high-resolution T1-weighted three-dimensional magnetization-prepared rapid gradient echo (MPRAGE) sequence obtained structural scans (repetition time [TR] = 2000 ms; echo time [TE] = 2.63 ms; Flip-angle = 9°, field of view [FOV] = 256 mm; acquisition matrix = 256 x 192 x 160; slice thickness = 1 mm; voxel size = 1 x 1 x 1 mm³; 160 oblique axial slices; scan time = 6.26 min) for co-registration to functional scans and cortical thickness analyses. Following the structural scan, fMRI scans were completed to measure local hemodynamic changes (BOLD signal) during task performance. A gradient-echo T2*-weighted echo planar imaging (EPI) acquisition obtained functional scans (TR = 2000 ms; TE = 27 ms; Flip-angle = 70°, FOV = 200 mm; acquisition matrix = 64 x 64; slice thickness = 3 mm; voxel size = 3.1 x 3.1 x 5 mm³; 40 oblique axial slices; scan time = 6.16 min).

2.3.2.2 Functional Imaging Matching Paradigm

2.3.2.2.1 Task Design

The fMRI tasks were administered according to a blocked design. There were three blocks with nine alternating conditions, beginning with a sensorimotor control condition (Shapes) followed by an affective experimental condition (Faces). Each condition began with a brief two-second instruction screen, followed by six randomized trials of five seconds each. Trials were separated by a one second fixation cross hair. The blocks took approximately eight minutes to complete, which included the presentation of instruction screens, preceding the onset of the conditions, describing the task with examples to ensure the response box was operational. Please see Figure 1 for an illustration of the task design.
Figure 1. Overview of the block design illustrating the (A) sequence of scans, (B) composition of functional runs alternating Shapes and Faces conditions, and (C) the trials associated with those conditions.
In each trial of the Faces condition three distinct faces were presented: a target face above two choice faces. One of the two choice faces expressed the same emotion as the target (i.e., anger, fear, surprise, or neutral expression). The volunteers selected the facial expression that best matched the target’s expression from the two presented choices by pressing a response button corresponding to each of the two choice faces. Six randomized trials per condition, consisting of three faces each, were presented, with emotional expression randomized within each block.

In each trial of the Shapes condition three geometric images were displayed: a target shape above two distinct choice shapes. One of the two choice shapes matched the target. The volunteers selected the choice shape that matched the target by pressing a response button corresponding to each of the two choice shapes. Six randomized trials consisting of three geometric images were presented during each block, with the shapes presented randomized within each block.

2.3.2.2.2 Stimuli

The paradigm used in the current study was developed by Hariri et al. (2000; 2002). The facial images used are available through the NimStim Set of Facial Expressions (www.macbrain.org/resources.htm; Tottenham, Tanaka et al. 2009). Images were presented in black and white to minimize slight differences in colour. For each trial all three faces were of the same sex and ethnicity (age range 21 – 30 years). We did not supplement facial stimuli with older-age faces as both young and older adults demonstrate amygdalae response to young-age faces, despite older adults showing increased reactivity to own-age faces (Ebner, Johnson et al. 2013). Caucasian and
African American ethnicities were included at a ratio of 2:1. In total, 216 facial images were used. An equal presentation of male and female faces expressing angry, fearful, surprised and neutral emotions were included. The sensorimotor images consist of circular and elliptical shapes in various combinations, which were manually reproduced for the current study. In total, three distinct shapes were used to derive ten geometric image combinations. The shapes condition has been used as a control task in this paradigm instead of neutral facial expressions as the latter stimuli are found to be perceived as emotionally ambiguous or even as negatively valenced and may differentially activate the amygdalae (Blasi, Hariri et al. 2009), potentially confounding response in these regions when utilized as a contrast (Hariri, Mattay et al. 2002). For example, meta-analysis has revealed that contrasting affective stimuli with similar non-affective comparators (e.g., neutral faces) reduces the magnitude of amygdalae response (Sergerie, Chochol et al. 2008). Thus, the matching paradigm conditions (Faces versus Shapes) were not altered from previously published reports. Please see Figure 1C for an illustration of a Faces and Shapes trial.

2.3.2.3 MRI Suite Software and Equipment

MR safe prescription glasses (+6.00 to -6.00 sphere; www.safevision.net/mri.html) were provided to those volunteers requiring corrective eyewear. A visual acuity test was performed with volunteers using a standardized Snellen chart at a distance of 109 cm. All volunteers were confirmed to have accurate vision. The software package Presentation (version 11.0, www.neurobs.com), installed on a standard Baycrest MRI Suite desktop computer, was used to run the paradigm. Accuracy and reaction time on the tasks was
recorded in Presentation from button presses of a response box held in the right hand of volunteers. The response box (model # HHSC-1x4-CR, Current Designs Inc., www.curdes.com) has four buttons on it and emulates computer key presses; only the first two buttons (numbers 1 and 2) were used. A button press of 1 with the volunteer’s index finger represented a left choice and a middle finger button press of 2 represented a right choice. Volunteers viewed images projected on a screen in the center of the bore of the magnet through a mirror positioned on the scanner head coil. The projector (model # NEC MT1065, www.projectorcentral.com) was located behind the magnet with a visual angle of 15.24° (height, H) x 12.33° (vertical, V), at a viewing distance of approximately 132 cm and a native resolution of 1024 x 768. The screen size is 35.3 cm (H) x 28.5 cm (V). Physiologic information was recorded using a Siemens PulseOx monitor that was attached to the volunteer’s left index finger, and a Siemens pneumatic belt respiration monitor placed around the volunteer just below the ribcage. A brief instruction period preceded all functional scans to ensure that volunteer’s were alert, that the response box was in working order, and that stimuli could be seen clearly, as verified by volunteer report.

2.4 Analysis of Data

2.4.1 Volunteer Demographics and Clinical Characteristics

A series of independent samples t-tests were used to examine differences between young and older adults on the demographic and clinical measures of age, education level, MMSE, SSI, PANAS and TAS-20 (total and factor) scores. Effect sizes were calculated
using Cohen’s d, where a value of 0.2 reflects a small effect, 0.5 a medium effect, and 0.8 signifies a large effect (Lakens 2013).

The MADRS and BAI were administered at three time points: Screening, Pre-, and Post-Scanning. Separate 2 x 3 repeated measures analysis of variance (ANOVA) were used to determine any significant interactions between age (young, older) by measure completion time (Screening, Pre-, Post-Scanning). The generalized eta square ($\eta_G^2$) was used to evaluate effects sizes, where a value of 0.01 indicates a small effect, 0.06 a medium effect, and 0.14 represents a large effect (Lakens 2013).

2.4.2 Behavioural Data

Accuracy and response latencies for the fMRI tasks were evaluated using separate 2 x 3 x 2 repeated measures ANOVA to test for a significant interaction of condition (faces, shapes) by time (BLOCK1, BLOCK2, BLOCK3) by age group (young, older). Effect sizes are reported using $\eta_G^2$.

2.4.3 Activation Data

2.4.3.1 Pre-processing

Processing of imaging data was completed using the Analysis of Functional NeuroImages (AFNI; version 2011_12_21_1014) software (Cox 1996). To offset magnetization equilibrium effects, the first 10 time points of each functional run were excluded from analysis. While efforts are made to reduce the motion of volunteers, it can still occur (e.g., physiologic motion from respiration and cardiac pulsations, rigid
motion from jaw movements, swallowing, and small head movements) resulting in adjacent voxels interfering in signal causing the detection of false activation, or signal loss due to the averaging of two different tissues occupying the same voxel (i.e., partial volume effects). Data were corrected for physiologic motion using collected measurements of cardiac and respiratory function entered into the 3dretroicor program. To reduce rigid motion artifact, data were spatially realigned to the 51st volume of the second functional run using the 3dvolreg program. Signal normalization was performed first by calculating the mean intensity value on a voxel-by-voxel basis using the AFNI program 3dTstat, then calculating the threshold for each run using the AFNI program 3dClipLevel, and finally calculating the percent signal change using the AFNI program 3dcalc. The three functional runs were then concatenated into a single time series and a mask image was created to limit voxel analysis to brain tissue, eliminating non-brain noise.

2.4.3.2 Individual Analysis

For each volunteer, the stimulus time series was convolved with the estimated hemodynamic response function on a voxel by voxel basis to find the estimated response, then a multiple linear regression analysis of the time series data generated contrast maps (i.e., Faces > Baseline, Shapes > Baseline; Faces > Shapes) using the AFNI 3dDeconvolve program. The contrast map of interest was extracted using the AFNI program 3dmerge. Data then underwent spatial normalization to standard stereotactic space (Talairach and Tournoux 1988) to allow for comparisons across volunteers (using
AFNIs TT_avg152T1 template at a 2mm³ resolution\(^1\) with the AFNI program @auto_tlrc (using a 12-parameter linear affine transformation), and were smoothed with a Gaussian filter set at 6 mm full width at half-maximum (FWHM) to increase signal-to-noise ratio using the AFNI program 3dmerge.

### 2.4.3.3 Group Analysis

The individual statistical contrast maps were used to investigate the main effects of task-specific BOLD activation for the young and older groups using one-sample t-tests. Group differences between BOLD activations were evaluated using a two-sample t-test. For whole-brain group analyses, the anatomical location of significant clusters were determined by the Talairach coordinates of peak activation voxels using the AFNI ‘whereami’ program. A statistical threshold of \( p < 0.05 \), corrected for multiple comparisons using the AFNI 3dClustSim program (average blur estimate: FWHM \( x,y,z \) = 4, 3, 4) and activation of at least 19 contiguous voxels were used to identify significance for analyses.

### 2.4.3.4 Region of Interest Evaluation

The primary ROIs, the amygdalae, were demarcated based on standard anatomical criteria (Kates, Abrams et al. 1997) and manually drawn on each volunteer’s functional

\(^1\) Both data from young and older volunteers were normalized to the same standard brain template, derived from younger adults. Previous research using the same paradigm have completed separate analyses using an older brain template for normalization and have found no differences in amygdala activation patterns from those revealed when using a typical anatomical template for their older sample (Tessitore, A., A. R. Hariri, et al. (2005). "Functional changes in the activity of brain regions underlying emotion processing in the elderly." Psychiatry Research: Neuroimaging 139(1): 9-18.)
data using their anatomical image as a guide. Briefly, the amygdalae were defined anteriorly in the coronal plane where the anterior commissure is clearly visible across the midline of the brain. The inferior border comprised a white matter tract extending medially from the temporal lobe. The superior border was enclosed by the entorhinal sulcus, and not extending superiorly beyond this boundary. Medially, the amygdalae were bounded by cerebrospinal fluid or high-intensity white matter, and laterally the boundary extended to the central white matter tract of the temporal lobe. Posteriorly, the amygdalae were demarcated based on the appearance of the hippocampus in slices where the temporal horn was observed to enlarge superiorly along the lateral side of the two structures. ROI analysis was used to restrict the search for significant voxels with a voxel-wise analysis using general linear model in AFNI. A statistical threshold of $p < 0.05$, corrected for multiple comparisons using the AFNI 3dClustSim program (average blur estimate: FWHM x,y,z = 3, 3, 4) and activation of at least 19 contiguous voxels were used to identify significance for analyses.

2.4.4 Cortical Thickness Data

2.4.4.1 Pre-processing

Structural imaging data were processed using the automated Corticometric Iterative Vertex-based Estimation of Thickness (CIVET) pipeline (version 1.1.10; Montreal Neurological Institute [MNI] at McGill University, Montreal, Quebec, Canada). T1-weighted images were registered to a standard stereotaxic space with the average MNI ICBM 152 template using a 9-parameter linear transformation (Collins, Neelin et al. 1994), and corrected for non-uniformity (Sled, Zijdenbos et al. 1998). Tissue was then
classified into white matter, gray matter, and cerebrospinal fluid (Zijdenbos, Forghani et al. 2002). For the surface extraction the left and right hemispheres were separated, then using deformable surface models, boundaries between white and grey matter were extracted, first by defining the white matter surface then by an outward expansion to determine the intersection of grey matter and cerebrospinal fluid. Four surfaces were derived with 40,962 vertices each (MacDonald, Kabani et al. 2000). The t-link metric then assessed the distance between white and grey matter surfaces to calculate cortical thickness, following which the data were subjected to a 20-mm-surface-based diffusion-blurring kernel (Lerch and Evans 2005). The Automatic Nonlinear Image Matching and Anatomical Labeling (ANIMAL) algorithm was then applied to segment each hemisphere into sub-regions (as illustrated in Figure 2), deriving measures of average cortical thickness for each of the lobes and sub-regions (Collins, Holmes et al. 1995). Cortical thickness is well preserved despite differences in head size and there are no relationships between the two, thus no adjustments were made to account for variations in head size (Barnes, Ridgway et al. 2010).

2.4.4.2 Group Analysis

Vertex-wise analysis was carried out using the general linear model in the R-MINC package (R version 3.1.1, R-MINC version 1.2.4.5), which runs a group contrast in a multiple regression to determine age-group differences in cortical thickness values at each vertex point using the R-MINC command: vs <- vertexLm(left_cortical_thickness ~ Group, data_table). The analysis was corrected for multiple comparisons using a False Discovery Rate (FDR) thresholded at 5%, such that significance was defined by q < 0.05.
Figure 2. Brain atlas segmented into 56 cortical structures (see Table 1 for the colour coding key). (A) Anterior, (B) superior, (C) left, and (D) right views. Adapted from Shattuck et al. (2008) with permission of the publisher (Elsevier Limited, Oxford, UK).
Table 1. Cortical structure colour coding for the segmentation atlas.

<table>
<thead>
<tr>
<th>Frontal Lobe</th>
<th>Parietal Lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left</strong></td>
<td><strong>Right</strong></td>
</tr>
<tr>
<td>Gyrus</td>
<td>Gyrus</td>
</tr>
<tr>
<td>Superior Frontal</td>
<td>Postcentral</td>
</tr>
<tr>
<td>Middle Frontal</td>
<td>Superior Parietal</td>
</tr>
<tr>
<td>Inferior Frontal</td>
<td>Supramarginal</td>
</tr>
<tr>
<td>Precentral</td>
<td>Angular</td>
</tr>
<tr>
<td>Middle Orbitofrontal</td>
<td>Precuneus</td>
</tr>
<tr>
<td>Lateral Orbitofrontal</td>
<td></td>
</tr>
<tr>
<td><strong>Occipital Lobe</strong></td>
<td></td>
</tr>
<tr>
<td>Rectus</td>
<td></td>
</tr>
<tr>
<td><strong>Temporal Lobe</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Left</strong></td>
<td><strong>Right</strong></td>
</tr>
<tr>
<td>Gyrus</td>
<td></td>
</tr>
<tr>
<td>Superior Temporal</td>
<td>Superior Occipital</td>
</tr>
<tr>
<td>Middle Temporal</td>
<td>Middle Occipital</td>
</tr>
<tr>
<td>Inferior Temporal</td>
<td>Inferior Occipital</td>
</tr>
<tr>
<td>Cuneus</td>
<td></td>
</tr>
<tr>
<td><strong>Cerebral Cortex</strong></td>
<td><strong>Other Structures</strong></td>
</tr>
<tr>
<td>Parahippocampal</td>
<td><strong>Left</strong></td>
</tr>
<tr>
<td>Lingual(^a)</td>
<td><strong>Right</strong></td>
</tr>
<tr>
<td>Insular Cortex</td>
<td></td>
</tr>
<tr>
<td>Fusiform(^a)</td>
<td>Caudate</td>
</tr>
<tr>
<td><strong>Limbic Lobe</strong></td>
<td>Cerebellum</td>
</tr>
<tr>
<td><strong>Left</strong></td>
<td><strong>Right</strong></td>
</tr>
<tr>
<td>Structure</td>
<td></td>
</tr>
<tr>
<td>Cingulate Gyrus</td>
<td>Putamen</td>
</tr>
<tr>
<td>Hippocampus(^b)</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>Brainstem</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\): structures considered to overlap both the temporal and occipital lobes; \(^b\): structure considered to overlap both the temporal and limbic lobes; adapted from Shattuck et al. (2008) with permission of the publisher (Elsevier Limited, Oxford, UK).
Lobe-segmented analyses were conducted using IBM SPSS Statistics for Windows (version 19.0; Armonk, NY: IBM Corp). Group differences in the cortical thickness segments were evaluated using a general linear model (multivariate analysis of variance, MANOVA) followed by a discriminant function analysis, with age (young, older) as the fixed factor and thickness measures encompassing the frontal, parietal, temporal, and occipital lobes as the dependent variables. For discriminant function analyses, multiple comparison correction was applied using a Bonferroni adjusted $\alpha$ level corresponding to the number of segments derived for each lobe (e.g., for the left frontal lobe there were nine segments, thus $\alpha = 0.05/9 = 0.005$). SPSS provides univariate tests of differences in follow-up to significant MANOVAs, which does not protect against inflated Type I error rates, thus multivariate discriminant function analyses were used to better predict which linear combination of variables defined group membership (Field 2013). The structure matrix of the discriminant function analysis provides the Pearson’s correlations between the predictors (i.e., the segmented cortical thickness values) and the discriminant function, much like the factor loading of a factor analysis. The $r$ values represent the largest absolute correlations that are associated with the function that distinguishes between the two age-groups and loadings of $r < 0.3$ do not contribute to the model (Burns and Burns 2009).

**2.4.5 Relationships Between Functional Activation to the Emotion Matching Paradigm, Cortical Structure and Aging**

The R-MINK package was used to carry out vertex-wise analysis with the general linear model using a multiple regression analysis to determine whether cortical thickness measures predicted amygdalae activations and whether there were age-group differences
at each vertex point using the R-MINK command: `vs <- vertexLm(left_cortical_thickness ~ MeanAct_Lamy_FvS + Age, data_table)`. Multiple comparisons were corrected with FDR $q < 0.05$.

For the lobe-segmented analysis, IBM SPSS Statistics for Windows was utilized. To examine the relationship between amygdalae activations and brain structure in each age group, regression analyses were performed on the mean BOLD response in the amygdalae ROIs for each volunteer using the mean lobe-segmented PFC thickness values as predictors for young and older adults separately. A Fisher’s Z test was employed to determine age-group differences for the fit of the respective models using their R-values, which are a measure of the quality of the prediction of the dependent variable. In particular, the R-value represents the multiple correlation coefficient between the predictors (i.e., cortical thickness measures) and the outcome (i.e., amygdala activation).
3.1 Volunteer Demographics and Clinical Characteristics

There were 23 volunteers eligible for full screening procedures following the prescreening telephone interviews. All volunteers provided written informed consent at the beginning of the Screening Visit. Three volunteers were withdrawn from the study following screening procedures. One older man was withdrawn after a finding of hypertension. Two young men were also withdrawn: one after a finding of a history of anxiety and panic attacks; and one for continual scheduling conflicts. Ten healthy older (age range 60 – 85 years, M = 70.60, SE = 2.84) and ten healthy young (age range 20 – 40 years, M = 27.30, SE = 2.08) adult men completed study procedures between June 2009 and July 2011. Please see Table 2 for a summary of the volunteer demographics and clinical characterization.

Independent samples t-tests revealed that the age groups did not significantly differ in their years of education (t\textsubscript{18} = -0.589, p = 0.563, d = 0.28), cognitive function as assessed by the MMSE (t\textsubscript{18} = -0.249, p = 0.806, d = 0.12), or low level of suicidal ideation as assessed by the SSI (t\textsubscript{18} = -1.213, p = 0.241, d = 0.57). Both young and older volunteers were found to have little difficulty in their overall affective awareness as seen by their low alexithymia scores on the TAS-20 (t\textsubscript{18} = -1.189, p = 0.250, d = 0.56). When looking at the separate factor subscales, the age groups did not differ in their ability to identify (t\textsubscript{18} = -0.538, p = 0.597, d = 0.25) or describe feelings (t\textsubscript{18} = 0.000, p = 1.000, d = 0.00); however, older volunteers were found to be more fixated on external details as opposed
Table 2. Demographic and clinical characteristics of the study volunteers by age group.

<table>
<thead>
<tr>
<th>Characteristica</th>
<th>Young</th>
<th>Older</th>
<th>t Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Enrolled</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>27.3 (6.6)</td>
<td>70.6 (9.0)</td>
<td>-12.316</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age Range, years</td>
<td>20 - 40</td>
<td>60 - 85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, years</td>
<td>16.8 (3.0)</td>
<td>17.6 (3.1)</td>
<td>-0.589</td>
<td>0.563</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.3 (1.1)</td>
<td>29.4 (0.7)</td>
<td>-0.249</td>
<td>0.806</td>
</tr>
<tr>
<td>SSI</td>
<td>0.1 (0.3)</td>
<td>0.6 (1.3)</td>
<td>-1.213</td>
<td>0.241</td>
</tr>
<tr>
<td>TAS-20 Total</td>
<td>36.2 (9.1)</td>
<td>41.3 (10.1)</td>
<td>-1.189</td>
<td>0.250</td>
</tr>
<tr>
<td>DIF</td>
<td>8.6 (3.1)</td>
<td>9.6 (5.0)</td>
<td>-0.538</td>
<td>0.597</td>
</tr>
<tr>
<td>DDF</td>
<td>10.0 (3.1)</td>
<td>10.0 (4.8)</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>EOT</td>
<td>17.6 (5.1)</td>
<td>21.7 (3.5)</td>
<td>-2.102</td>
<td>0.050</td>
</tr>
<tr>
<td>PANAS, PA</td>
<td>32.1 (8.5)</td>
<td>30.5 (9.4)</td>
<td>0.401</td>
<td>0.693</td>
</tr>
<tr>
<td>PANAS, NA</td>
<td>12.0 (3.0)</td>
<td>11.6 (2.9)</td>
<td>0.303</td>
<td>0.765</td>
</tr>
<tr>
<td>MADRS</td>
<td>2.2 (2.6)</td>
<td>0.4 (0.8)</td>
<td>0.2 (0.6)</td>
<td>1.0 (3.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAI</td>
<td>2.0 (2.3)</td>
<td>0.4 (0.7)</td>
<td>0.4 (0.8)</td>
<td>2.3 (4.0)</td>
</tr>
</tbody>
</table>

a: values presented are in the form of mean (standard deviation), unless otherwise specified; MMSE: Mini-Mental State Examination; SSI: Beck Scale for Suicidal Ideation; TAS-20: Twenty-item Toronto Alexithymia Scale; DIF: Difficulty Identifying Feelings; DDF: Difficulty Describing Feelings; EOT: Externally Oriented Thinking; PANAS: Positive and Negative Affect Schedule; PA: rating of positive affect; NA: rating of negative affect; MADRS: Montgomery-Asberg Depression Rating Scale; BAI: Beck Anxiety Inventory; b: F statistic shown for the Age * Completion Time interaction effect.
to internal states ($t_{18} = -2.102, p = 0.050, d = 0.99$). Young and older volunteers were also found to have experienced similar levels of high energy/mental alertness/enjoyable interactions (high positive affect: $t_{18} = 0.401, p = 0.693, d = 0.19$) and calmness/serenity (low negative affect: $t_{18} = 0.303, p = 0.765, d = 0.14$) as assessed by the PANAS within the past week, including the day of scanning, which are consistent with normative data for the particular timeframe (Watson, Clark et al. 1988).

A two-way mixed ANOVA examining the differences between the age groups on their low levels of depression, as assessed using the MADRS completed at the Screening Visit, Pre-, and Post-Scanning, found that there was no significant main effect of age ($F_{1,18} = 0.082, p = 0.778, \eta^2_p < 0.01$). Thus, young and older volunteers reported similar low levels of depressive symptomatology. Using a Greenhouse-Geisser correction, there was a significant main effect of MADRS completion time ($F_{1.302, 23.431} = 4.081, p = 0.045, \eta^2_p = 0.08$). However, Bonferroni corrected post hoc pairwise comparisons revealed that reported levels of depression did not significantly differ between the Screening Visit ($M = 1.600, SE = 0.645$) and Pre- ($M = 0.700, SE = 0.423; t_{19} = 2.131, p = 0.086, d = 0.38$) or Post-Scanning ($M = 0.200, SE = 0.141; t_{19} = 2.152, p = 0.138, d = 0.81$), nor did scores differ between Pre- or Post-Scanning ($t_{19} = 2.152, p = 0.723, d = 0.40$). Without stringent correction applied, scores do differ between the Screening Visit and Pre- ($p = 0.029$) and Post-Scanning ($p = 0.046$), but not between Pre- and Post-Scanning ($p = 0.241$). However the differences are clinically insignificant, with MADRS scores in the range of 0 – 6 indicating absence of depressive mood symptoms. There was no significant interaction between age and MADRS completion time ($F_{1.302, 23.431} = 1.703, p$}
0.207, \eta_G^2 = 0.04), indicating that MADRS scores were similar between young and older volunteers at Screening, Pre- and Post-Scanning.

When evaluating group differences on low levels of anxiety, as measured by the BAI completed at Screening, Pre-, and Post-Scanning, a two-way mixed ANOVA revealed no significant main effect of age (F_{1,18} = 0.068, p = 0.797, \eta_G^2 < 0.01). Young and older volunteers reported similar low levels of anxiety symptomatology overall. Using a Greenhouse-Geisser correction, there was a significant main effect of when the BAI was completed (F_{1.029, 18.525} = 5.741, p = 0.027, \eta_G^2 = 0.14). Although, post hoc tests with Bonferroni correction revealed that reported low levels of anxiety did not significantly differ between the Screening Visit (M = 2.150, SE = 0.730) and Pre- (M = 0.500, SE = 0.229; t_{19} = 2.368, p = 0.100, d = 0.79) or Post-Scanning (M = 0.400, SE = 0.240; t_{19} = 2.574, p = 0.066, d = 0.83), nor did scores differ between Pre- or Post-Scanning (t_{19} = 1.000, p = 0.992, d = 0.10). Again, with no corrections applied, pairwise comparisons do find differences between BAI scores at the Screening Visit and Pre- (p = 0.033) and Post-Scanning (p = 0.022), but no Pre- and Post-Scanning differences (p = 0.331). However, BAI scores ranging between 0 – 9 indicate no or normal anxiety levels, and as such changes are not clinically meaningful. There was no significant interaction between age and BAI completion time (F_{1.029, 18.525} = 0.035, p = 0.861, \eta_G^2 < 0.01), indicating that young and older volunteers reported similar low levels of anxiety on the BAI at Screening, Pre- and Post-Scanning.
3.2 Functional Imaging Matching Paradigm

3.2.1 Performance Accuracy

A repeated measures ANOVA revealed that there was no significant difference in performance accuracy between young (M = 94.23%, SE = 1.77) and older (M = 90.99%, SE = 1.77) volunteers for the conditions overall (F_{1, 18} = 3.784, p = 0.07, \eta^2_G = 0.17).

Separating the task conditions did reveal a significant main effect (F_{1, 18} = 99.163, p < 0.001, \eta^2_G = 0.67), in that accuracy for the tasks was lower for the Faces condition (M = 86.06%, SE = 1.46) compared to the Shapes condition (M = 99.16%, SE = 0.35; see Figure 3A).

There was also a significant effect of block presentation (F_{2, 36} = 6.243, p = 0.005, \eta^2_G = 0.07). The first block showed slightly, but significantly, lower accuracy (M = 90.60%, SE = 0.82) than the second (M = 93.59%, SE = 1.12; t_{19} = -2.935, p = 0.031, d = 0.64) and third presentations (M = 93.64%, SE = 1.07; t_{19} = -3.302, p = 0.012, d = 0.70), which were not different from each other (t_{19} = -0.042, p = 1.000, d = 0.01; see Figure 3B).

There was a significant interaction between the task condition and the presentation of the blocks (F_{2, 36} = 9.194, p = 0.001, \eta^2_G = 0.07). Pairwise comparisons with Bonferroni correction revealed that performance accuracy for the Shapes condition was similar across all three blocks. However, accuracy for the Faces condition was significantly lower at its first presentation (M = 81.87%, SE = 1.74) than at the second (M = 88.52%, SE = 1.93; t_{19} = -3.796, p = 0.001, d = 0.81) and third presentations (M = 87.77%, SE = 1.99; t_{19} = -3.089, p = 0.006, d = 0.71), which were not different from each other (t_{19} = -0.438, p = 0.666, d = 0.09; see Figure 3C).
Figure 3. The impact of task condition and presentation on performance accuracy for the Matching Paradigm across all volunteers. (A) Percent correct responding to the Faces condition was lower than the Shapes condition. (B) Volunteers showed lower accuracy on the first compared to the second and third block presentations. (C) While the Shapes condition was completed with similar accuracy throughout the block presentations, the Faces condition showed lower percent correct responding at the first compared to the second and third presentations.

* $p_{corrected} < 0.05$; Error Bars: 95% Confidence Intervals.
There was a significant interaction between the task conditions and age ($F_{1, 18} = 4.846, p = 0.041, \eta^2_G = 0.06$). For the Shapes condition accuracy was similar between the age groups (Young: $M = 99.33\%$, $SE = 0.18$, Older: $M = 98.99\%$, $SE = 0.68$; $t_{18} = 0.486$, $p = 0.633$, $d = 0.21$). However, accuracy for the Faces condition was lower in the older volunteers ($M = 82.99\%$, $SE = 2.18$) as compared to the young volunteers ($M = 89.12\%$, $SE = 1.94$; $t_{18} = 2.103$, $p = 0.05$, $d = 0.99$), although this comparison does not survive Bonferroni correction. There was no significant interaction between the presentation of the blocks and age ($F_{2, 36} = 0.795$, $p = 0.459$, $\eta^2_G = 0.18$). Both age groups were similarly accurate over each of the blocks. There was no significant interaction between the task condition, block presentation, and age ($F_{2, 36} = 0.869$, $p = 0.428$, $\eta^2_G < 0.01$). Young and older volunteers showed similar patterns of accuracy on the Shapes and Faces conditions over all three blocks.

3.2.2 Response Speed

A repeated measures ANOVA showed no significant differences in overall response speed between young ($M = 1.78$ seconds [s], $SE = 0.12$) and older ($M = 2.03$s, $SE = 0.12$) volunteers ($F_{1, 18} = 2.123$, $p = 0.162$, $\eta^2_G < 0.01$). A significant effect of task condition was found ($F_{1, 18} = 398.344$, $p < 0.001$, $\eta^2_G = 0.05$; see Figure 4A) showing that response speed for the tasks was slower for the Faces condition ($M = 2.67$s, $SE = 0.11$) compared to the Shapes condition ($M = 1.141$s, $SE = 0.07$). There was a significant effect of block presentation ($F_{2, 36} = 24.650$, $p < 0.001$, $\eta^2_G < 0.01$). Thus, response speed for the conditions overall differed between the block presentations. Volunteers were significantly slower at responding over the first block presentation ($M = 2.03$s, $SE = 0.08$) than the second ($M = 1.89$s, $SE = 0.09$; $t_{10} = 4.036$, $p = 0.003$, $d = 0.33$) and third
Figure 4. The impact of task condition and presentation on reaction time for the Matching Paradigm across all volunteers. (A) Response speed to the Shapes condition was faster than the Faces condition. (B) Volunteers showed slower reaction time on the first compared to the second and third block presentations, with the third presentation being the fastest to complete. (C) The Shapes condition was completed slower at its first presentation compared to the second and third presentations, which showed no differences in speed. The Faces condition showed slower responding at the first compared to the second and third presentations, with the third being the fastest to complete. * $p_{corrected} < 0.05$; Error Bars: 95% Confidence Intervals.
presentations (M = 1.80s, SE = 0.08; t_{19} = 6.381, p = 0.010, d = 0.59), with the second presentation also taking significantly longer than the third to complete (t_{19} = 3.469, p < 0.001, d = 0.23; see Figure 4B).

There was a significant interaction between the task condition and the presentation of the blocks (F_{2,36} = 6.663, p = 0.003, \eta^2_{G} = 0.01). Pairwise comparisons with Bonferroni correction reveal that response speed for the Shapes condition was slower during its first presentation (M = 1.01s, SE = 0.07) than at the second (M = 1.12s, SE = 0.07; t_{19} = 4.151, p = 0.001, d = 0.27) and third presentations (M = 1.09s, SE = 0.07; t_{19} = 4.102, p = 0.001, d = 0.38), which were not significantly different from each other (t_{19} = 0.964, p = 0.347, d = 0.09). For the Faces condition, response speed was significantly slower at the first presentation (M = 2.84s, SE = 0.11) than at the second (M = 2.67s, SE = 0.13; t_{19} = 3.026, p = 0.007, d = 0.32) and third presentations (M = 2.51s, SE = 0.11; t_{19} = 5.666, p < 0.001, d = 0.65), and the second presentation of the blocks also took longer to complete than the third (t_{19} = 3.122, p = 0.006. d = 0.28) for this condition (see Figure 4C).

There was a significant interaction between the task condition and age (F_{1,18} = 5.357, p = 0.033, \eta^2_{G} = 0.05), suggesting the effect of the conditions on response speed was different between young and older groups. However, pairwise comparisons did not find any significant differences between groups, before or after Bonferroni correction for multiple comparisons. Results from this analysis show that the reaction time during the Shapes condition was similar between the age groups (Young: M = 1.11s, SE = 0.10, Older: M = 1.18s, SE = 0.10; t_{18} = -0.492, p = 0.629, d = 0.23), as well as for the Faces condition (Young: M = 2.46s, SE = 0.16, Older: M = 2.88s, SE = 0.16; t_{18} = -1.900, p = 0.074, d = 0.90). The significant main effect of the interaction was likely driven by
greater group differences for the Faces condition. There was no significant interaction between the presentation of the blocks and age ($F_{2, 36} = 0.517, p = 0.601, \eta^2_G = 0.04$), indicating that both age groups responded at a similar speed over each of the blocks. There was also no significant interaction between the task condition, block presentation, and age ($F_{2, 36} = 0.495, p = 0.614, \eta^2_G < 0.01$), showing that the pattern of response speed is similar between young and older volunteers on the Shapes and Faces conditions over all three blocks.

3.3 Functional Activation to the Matching Paradigm

3.3.1 Amygdalae Response

The first specific aim of this investigation was to evaluate amygdalae reactivity to the matching paradigm and determine any differences between young and older men. A one sample t-test revealed that young volunteers exhibited greater BOLD activation in the bilateral amygdalae ROIs for the affective, Faces, condition compared to the sensorimotor, Shapes, condition. Figure 5 illustrates the statistical Faces > Shapes group maps of significant amygdalae activations, and Table 3 displays the associated voxel-level statistics, including peak voxel coordinates and cluster size of contiguous voxels activated. Similarly, older volunteers were found to have increased affect-related BOLD response in the bilateral amygdalae ROIs (see Figure 6 for the statistical contrast maps and Table 4 for voxel-level statistics). A two-sample t-test found that there were no significant differences in task-specific bilateral amygdalae ROI activations between young and older volunteers.
Figure 5. Statistical contrast maps (radiologic convention) illustrating significant BOLD activations in the bilateral amygdalae to the emotional > sensorimotor task for healthy young adults ($p_{\text{FWE-corr}} < 0.05$; coordinates of peak voxel activation differences are shown in Table 3; statistical maps overlaid on the average anatomical scan derived from the young volunteers).

Table 3. Task specific bilateral amygdalae activations for healthy young adults

<table>
<thead>
<tr>
<th>Amygdalae ROIs</th>
<th>Peak Voxel Talairach Coordinate (x, y, z)</th>
<th>Cluster Size ($k_E$)</th>
<th>t-score</th>
<th>$p_{\text{FWE-corr}}$</th>
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<tbody>
<tr>
<td>Left</td>
<td>-26, 4, -16</td>
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<td>Right</td>
<td>18, -4, -8</td>
<td>37</td>
<td>2.963</td>
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Figure 6. Statistical contrast maps (radiologic convention) illustrating significant BOLD activations in the bilateral amygdalae to the emotional > sensorimotor task for healthy older adults ($p_{\text{FWE-corr}} < 0.05$; coordinates of peak voxel activation differences are shown in Table 4; statistical maps overlaid on the average anatomical scan derived from the older volunteers).

<table>
<thead>
<tr>
<th>Amygdalae ROIs</th>
<th>Peak Voxel Talairach Coordinate (x, y, z)</th>
<th>Cluster Size ($k_E$)</th>
<th>t-score</th>
<th>$p_{\text{FWE-corr}}$</th>
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</table>
3.3.2 Prefrontal Cortical Response

Focusing on the PFC region results of the whole-brain general linear model analysis, both young and older volunteers exhibited several activations. One-sample t-test identified affective-task related activation for young adults in the right frontopolar cortex (BA10, extending into BA46) and bilateral dlPFC (left inferior BA9; right middle BA 46, 9). Deactivations were also found in the bilateral mPFC (BA10). Figure 7A (top panel) illustrates the statistical contrast maps and the left panel of Table 5 reports the voxel-level statistics for the young volunteers. Older volunteers also showed activations in the bilateral dlPFC (left middle and inferior BA9; right middle BA46 and inferior BA9) to the Faces > Shapes task. In addition, older volunteers activated the bilateral vlPFC (left inferior BA44; right inferior BA47) and the left dmPFC (BA8). Figure 7B (bottom panel) presents the statistical contrast maps and the right panel of Table 5 displays the voxel-level statistics for the older group.

3.3.3 Remaining Whole-Brain Regional Activations

Results from one-sample t-tests for the young and older volunteers, respectively, revealed several activations across the remainder of the whole-brain during the processing of affective facial expressions compared to a sensorimotor task. Young volunteers activated the left parietal lobe at the paracentral, inferior, and angular gyri, as well as in the insula and cerebellum; right hemisphere activations occurred in the superior temporal, and middle occipital lobes, and the claustrum; bilateral activations presented in the precuneus, fusiform, lingual gyrus, inferior occipital lobe, and cuneus, as well as in the limbic lobe, including the ACC, lentiform nucleus, thalamus, and also the
Figure 7. Statistical contrast maps (radiologic convention) of significant BOLD prefrontal cortical (PFC) activations for healthy young and older adults to the emotional > sensorimotor task (p_{FWE-corr} < 0.01; Talairach coordinates of peak voxel activations are shown [x, y, z]; statistical maps overlaid on the average anatomical scan derived from the young [panel A] and older [panel B] volunteers, respectively). (A) Young adults show task-related activation in the right frontopolar cortex and bilateral middle/inferior dorsolateral PFC (dPFC), and deactivations in the bilateral medial PFC (mPFC). (B) Older adults show affective response in bilateral middle/inferior dPFC, bilateral ventrolateral PFC (vPFC) and left mPFC.
Table 5. Task specific prefrontal cortex activations for healthy young and older adults

<table>
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<tr>
<th>Region</th>
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<th>YOUNG</th>
<th>Cluster Size (kE)</th>
<th>t-score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OLDER</th>
<th>Peak Voxel Talairach Coordinate (x, y, z)</th>
<th>Cluster Size (kE)</th>
<th>t-score&lt;sup&gt;a&lt;/sup&gt;</th>
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BA: Brodmann area (approximation); a: Significant at p<sub>FWE-corr</sub> < 0.01; b: Decreased activity
cerebellar culmen. Affective-task related deactivations were also seen for young
volunteers in the left postcentral gyrus, superior and middle temporal lobes, and
supramarginal gyrus; the right paracentral gyrus; and bilaterally in the precentral gyrus,
ACC and PCC. The voxel-level statistics of significant activations for the young
volunteers are displayed in the left panel of Table 6.

The emotional matching paradigm elicited several activations for the older volunteers in
the left precentral gyrus, inferior parietal lobe, cuneus, and cerebellum; the right
cerebellar pyramis and uvula; and bilateral activations were evident in the precuneus,
fusiform, lingual gyrus, inferior occipital lobe, midbrain (red nucleus), and cerebellar
culmen. The only deactivation to the affective task for older volunteers was found in the
right insula. The right panel of Table 6 presents the voxel-level statistics of significant
activations for the older volunteers.

3.3.4 Age-Related Differences in Activation Patterns

While both healthy young and older volunteers recruited a wide-spread network of
regional activations to the affective task, a two-sample t-test revealed limited group
differences. Young volunteers were more likely to activate in posterior brain regions,
including the left fusiform gyrus, and bilateral middle and inferior occipital cortices as
compared to older volunteers. Figure 8A (top panels) demonstrates the statistical Faces >
Shapes group maps of significant activations, and Table 7 reports the voxel-level
statistics. In contrast to the young group, older volunteers activated in more regions,
including the right fusiform gyrus, bilateral cerebellum (tonsil and culmen), superior and
middle temporal cortices, and frontal regions including the vPFC extending to the ACC,
Table 6. Task specific remaining whole-brain activations for healthy young and older adults

<table>
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<tr>
<th>Region</th>
<th>BA</th>
<th>Peak Voxel Talairach Coordinate (x, y, z)</th>
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<th>t-score</th>
<th>pFWE-corr</th>
<th>Peak Voxel Talairach Coordinate (x, y, z)</th>
<th>Cluster Size (kE)</th>
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<tr>
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<td>Lentiform nucleus (putamen, globus pallidus)</td>
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<tr>
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<td>BA</td>
<td>YOUNG</td>
<td></td>
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<td>t-score</td>
<td>pfwe-corr</td>
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<td>(x, y, z)</td>
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<td>Bilateral culmen</td>
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<td>88</td>
<td>3.292</td>
<td>&lt;0.05</td>
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<tr>
<td>Left culmen</td>
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<td>Region</td>
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<td>BA: Brodmann area (approximation)</td>
<td>a: Decreased activity</td>
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<td>Peak Voxel Talairach Coordinate (x, y, z)</td>
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<td>pFWE-corr</td>
<td>&lt;0.01</td>
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Figure 8. Statistical contrast maps (radiologic convention) of significant differences in BOLD activation between healthy young and older adults to the emotional > sensorimotor task ($p_{\text{FWE-corr}} < 0.05$; coordinates of peak voxel activation differences are shown in Table 7; statistical maps overlaid on the average anatomical scan derived from all volunteers). (A) Compared to older adults, young adults show greater activation in the left fusiform gyrus and bilateral middle/inferior occipital (MOC, IOC) cortices. (B) Compared to young, older adults show increased response in right ventral (vPFC) and left medial prefrontal (mPFC) cortices, left precentral gyrus (PG), right superior (STC) and left middle temporal (MTC) cortices, right fusiform gyrus, and bilateral cerebellum (tonsil and culmen).
Table 7. Significant differences in BOLD activation between healthy young and older adults

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>Peak Voxel Talairach Coordinate ((x, y, z))</th>
<th>Cluster Size ((k_E))</th>
<th>t-score</th>
<th>(p_{\text{FWE-corr}})</th>
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<tr>
<td><strong>Young&gt;Older</strong></td>
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<tr>
<td>Temporal cortex</td>
<td></td>
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</tr>
<tr>
<td>Left fusiform</td>
<td>37</td>
<td>-40, -58, -14</td>
<td>67</td>
<td>2.880</td>
<td>&lt;0.04</td>
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<td>Occipital cortex</td>
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<td>Left middle</td>
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<td>-44, -84, 10</td>
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<tr>
<td>Right middle/inferior</td>
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<td>32, -92, -2</td>
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<td><strong>Older&gt;Young</strong></td>
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<td>Ventral prefrontal cortex</td>
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<tr>
<td>Right inferior (extending to ACC)</td>
<td>47/32</td>
<td>34, 32, 4</td>
<td>68</td>
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<td>&lt;0.03</td>
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<td>Medial prefrontal cortex</td>
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<td>-4, 4, 52</td>
<td>35</td>
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<td>Precentral gyrus</td>
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<tr>
<td>Left</td>
<td>6</td>
<td>-46, -4, 54</td>
<td>79</td>
<td>2.880</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Temporal cortex</td>
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<tr>
<td>Left middle</td>
<td>21</td>
<td>-62, -22, -6</td>
<td>118</td>
<td>2.633</td>
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<tr>
<td>Right superior</td>
<td>38</td>
<td>50, 16, -8</td>
<td>95</td>
<td>2.880</td>
<td>&lt;0.01</td>
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<td>Right fusiform</td>
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<td>48, -46, -18</td>
<td>22</td>
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<td>Peak Voxel Talairach Coordinate ( (x, y, z) )</td>
<td>Cluster Size ( (k_E) )</td>
<td>t-score</td>
<td>( p_{FWE-corr} )</td>
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<tr>
<td>Cerebellum</td>
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<td>Bilateral culmen (peak activation, left)</td>
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<td>30, -60, -50</td>
<td>135</td>
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BA: Brodmann area (approximation)
mPFC and precentral gyrus. The statistical contrast maps are visualized in Figure 8B (bottom panels), with voxel-level statistics described in Table 7.

3.4 Differences Between Young and Older Volunteers on Measures of Cortical Thickness

3.4.1 Voxel-Wise Measures

A general linear analysis evaluating cortical thickness changes with increasing age revealed significant age-related thinning of regions including the bilateral superior, middle, and inferior frontal gyri, lateral (l) OFC, pre- and post-central gyri, supramarginal gyrus, superior and middle temporal gyri, medial superior frontal gyrus, paracentral lobule, left superior parietal lobe, and right inferior parietal lobe. The greatest magnitude of between-group thinning was apparent in the lateral and medial posterior portion of the superior frontal gyrus, pre- and para-central gyri, supramarginal and superior temporal gyri. Some thickening occurred at the right posterior lateral occipital lobe, and right cuneus. Most medial frontal and lateral/medial occipital regions showed no age-related differences. Figure 9 illustrates areas of significant cortical change at an FDR corrected rate of $q < 0.05$. Separate analyses for the extracted segmentation-wise values confirm these findings, as outlined in the following sections.

3.4.2 Lobe-Segmentation Measures

MANOVAs were conducted on the segmented regional thickness measurements, separated by lobes. Significant aging effects were found for the left frontal ($V = 0.81$, $F_{9,10} = 4.633$, $p = 0.013$), bilateral parietal (Left: $V = 0.74$, $F_{5,14} = 7.791$, $p = 0.001$;
Figure 9. Cortical thickness differences between older and young adults. Compared to healthy young adults, older adults demonstrated significant cortical thinning in regions of the left (A) frontal, parietal, and temporal lobes, (B) medial superior and paracentral lobes, right (C) frontal, parietal and temporal lobes, and (D) medial superior and paracentral lobes. Some thickening occurred at the (C) posterior lateral occipital lobe, and (D) cuneus. Values on the left of colour bars refer to the left hemisphere and on the right refer to the right hemisphere. Colour bars represent t values of significant cortical thinning (blue) and thickening (pink) at $p_{\text{FDR-corr}} < 0.05$. Statistical maps overlaid on the average anatomical scan derived from all volunteers.
Right: $V = 0.723$, $F_{5,14} = 7.308$, $p = 0.001$), and bilateral temporal (Left: $V = 0.696$, $F_{6,13} = 4.964$, $p = 0.008$; Right: $V = 0.783$, $F_{6,13} = 6.115$, $p = 0.003$) lobes. The general linear model for the right frontal lobe did not reveal any significant age distinctions ($V = 0.667$, $F_{9,10} = 2.228$, $p = 0.114$), nor for the bilateral occipital lobes (Left: $V = 0.395$, $F_{4,15} = 2.446$, $p = 0.092$; Right: $V = 0.311$, $F_{4,15} = 1.693$, $p = 0.204$). Subsequent discriminant analyses for the significant effects feature the specific differences between younger and older volunteers for each lobe’s segmentation.

### 3.4.2.1 Frontal Lobes

Predictor variables entered into the discriminant analysis for the left frontal lobes were the superior frontal gyrus, rostral middle frontal gyrus inferior tier, rostral middle frontal gyrus superior tier, caudal middle frontal gyrus, inferior frontal gyrus, precentral gyrus, middle OFC, lOFC, and gyrus rectus. The discriminant function revealed a significant association between the age groups and left frontal lobe segments ($\Lambda = 0.193$, $\chi^2_9 = 22.18$, $p = 0.008$), accounting for 80.64% of the variance between groups. Significant mean differences were found for all cortical thickness segments between young and older volunteers except for the gyrus rectus (Figure 10).

However, the structure matrix found six significant predictors best differentiated the groups. Older volunteers exhibited thinning in the precentral gyrus ($r = 0.594$), rostral middle frontal gyrus superior tier ($r = 0.579$), superior frontal gyrus ($r = 0.567$), caudal middle frontal gyrus ($r = 0.541$), rostral middle frontal gyrus inferior tier ($r = 0.392$), and inferior frontal gyrus ($r = 0.320$), with the other three regions being poor predictors of group membership.
Figure 10. Discriminant analysis of segmented left frontal lobe reveals significant mean differences between young and older volunteers for eight of the nine segments. Box highlights results of structure matrix indicating most significant predictors of age group membership. PFG: Prefrontal Gyrus; rMFG-Sup: Rostral Middle Frontal Gyrus, Superior Tier; SFG: Superior Frontal Gyrus; cMFG: Caudal Middle Frontal Gyrus; rMFG-Inf: Rostral Middle Frontal Gyrus, Inferior Tier; IFG: Inferior Frontal Gyrus; mOFG: Middle Orbitofrontal Gyrus; IOFG: Lateral Orbitofrontal Gyrus; GR: Gyrus Rectus. * $p_{corrected}$ < 0.05; ** $p_{uncorrected}$ < 0.05; Error Bars: 95% Confidence Intervals.
3.4.2.2 Parietal Lobes

For the discriminant analysis of the parietal lobe segmentation, predictor variables included the postcentral gyrus, superior parietal gyrus, supramarginal gyrus, angular gyrus, and precuneus. The discriminant function highlighted a significant differentiation between young and older volunteers for the parietal lobe segmentation (Left: $\Lambda = 0.264$, $\chi^2_5 = 20.622$, $p = 0.001$; Right: $\Lambda = 0.277$, $\chi^2_5 = 19.898$, $p = 0.001$), with 73.62% of the between group variance accounted for in the left lobe and 72.25% in the right. Mean cortical thickness was found to be significantly different between younger and older volunteers for all bilateral segments, excluding the precuneus (Figure 11). Analysis of the structure matrix revealed four of the five segments included best predicted group membership, where the precuneus was a poor predictor. Older volunteers were characterized by thinning in the bilateral postcentral gyrus (Left: $r = 0.707$; Right: $r = 0.753$), supramarginal gyrus (Left: $r = 0.665$; Right: $r = 0.584$), angular gyrus (Left: $r = 0.545$; Right: $r = 0.372$), and superior parietal gyrus (Left: $r = 0.522$; Right: $r = 0.438$).

3.4.2.3 Temporal Lobes

The segments of the temporal lobes entered as predictors in the discriminant analysis were the superior, middle, and inferior temporal gyri, fusiform gyrus, lingual gyrus, and parahippocampal gyrus. Significant differences were found between age groups for the bilateral temporal lobe segmentation (Left: $\Lambda = 0.304$, $\chi^2_6 = 17.869$, $p = 0.007$; Right: $\Lambda = 0.262$, $\chi^2_6 = 20.113$, $p = 0.003$), accounting for 69.56% of the variance between groups in the left and 73.79% in the right lobes. Younger and older volunteers differed in their mean cortical thickness for the bilateral superior (p < 0.001) and middle (Left: $p < 0.001$;
Figure 11. Discriminant analysis of segmented bilateral parietal lobes reveals significant mean differences between young and older volunteers for eight of the nine segments. Boxes highlight results of structure matrix indicating most significant predictors of age group membership. Top panel: left lobe; bottom panel: right lobe. PCG: Postcentral Gyrus; SPG: Superior Parietal Gyrus; SMG: Supramarginal Gyrus; AG: Angular Gyrus; PC: Precuneus. *$p_{\text{corrected}} < 0.05$; Error Bars: 95% Confidence Intervals.
Right: \( p = 0.011 \) temporal gyri, left inferior temporal gyrus (\( p = 0.043 \)), and right fusiform gyrus (\( p = 0.039 \); Figure 12). Evaluation of the structure matrix determined group membership was best predicted by three of the six segments, though differing slightly by hemisphere. The bilateral lingual and parahippocampal gyri, left fusiform and right inferior temporal gyri were poor predictors of age group separation. Best describing the older volunteers were thinning in the bilateral middle (Left: \( r = 0.683 \); Right: \( r = 0.397 \)), and superior (Left: \( r = 0.657 \), Right: \( r = 0.653 \)) temporal gyri, left inferior (\( r = 0.339 \)) temporal gyrus, and right fusiform gyrus (\( r = 0.312 \)).

### 3.5 Predicting Affect-Related Activation in the Amygdalae from Cortical Thickness Measures

Whole-brain vertex-wise analyses exploring correlations between amygdalae activations and cortical thickness for young and older volunteers separately were non-significant at an FDR corrected \( q \) of 0.05. Multiple linear regression analyses were performed with amygdalae activations as the outcome and the six lobe-segmented regions comprising the PFC as the predictors (i.e., the middle and lOFC, superior and inferior rostral middle frontal gyri, and the superior and inferior frontal gyri) for each age group. For older volunteers, a significant model was revealed for the right amygdala (\( F_{6,9} = 9.902, p = 0.043, R^2 = 0.852 \)). Greater mean right amygdala activation was best predicted by a pattern of thicker left middle OFC (\( t = 7.068, p = 0.006 \)) and superior rostral middle frontal gyrus (\( t = 5.031, p = 0.015 \)) and thinner left lOFC (\( t = -6.109, p = 0.009 \)) and inferior rostral middle frontal gyrus (\( t = - 4.060, p = 0.027 \)). Please see Figure 13 for the partial regression plots of the residuals illustrating the associations between amygdala activation and each individual thickness.
Figure 12. Discriminant analysis of segmented bilateral temporal lobes reveals significant mean differences between young and older volunteers for three of the six segments. Boxes highlight results of structure matrix indicating most significant predictors of age group membership. Top panel: left lobe; bottom panel: right lobe. MTG: Middle Temporal Gyrus; STG: Superior Temporal Gyrus; ITG: Inferior Temporal Gyrus; FG: Fusiform Gyrus; LG: Lingual Gyrus; PHG: Parahippocampal Gyrus. * $p_{\text{corrected}} < 0.05$; ** $p_{\text{uncorrected}} < 0.05$; Error Bars: 95% Confidence Intervals.
Figure 13. Regression plots of mean right amygdala BOLD response for older volunteers and (A) left middle OFC thickness, (B) left superior rostral middle frontal thickness, (C) left lateral OFC thinning, and (D) left inferior rostral middle frontal thinning. Data points reflect the association of a predictor with amygdala activation, after removing the effects of the other predictors. For example, panel (A) shows the amygdala activation residuals in predicting mOFC thickness from all other predictors plotted on the Y-axis, and on the X-axis are the mOFC thickness residuals from predicting amygdala activation from all other predictors in the model.
predictor, after removing the effects of all other predictors. This relationship between right amygdala response and left regional prefrontal thickness was not significant in the younger age group (F_{6, 9} = 0.720, p = 0.666, R^2 = 0.590).

A comparison of the fit of the models from the older and young groups revealed that there was a significant difference between the respective R values (Z = 2.226, p = 0.03), whereby PFC thickness measures did predict amygdala activation uniquely for the older group.

Models examining right functional activation and right regional thickness, as well as left function and bilateral PFC structures were non-significant for both older and young volunteers.
4.1 Functional Imaging Matching Paradigm

Overall, healthy young and older adults were comparable in their performance accuracy and reaction time to the matching paradigm, showing similar performance across each condition over each of the blocks. The Faces condition generally was more challenging than the Shapes condition, with lower accuracy and slower reaction time. There were no differences between the age groups during the Shapes condition, and any differences for the Faces condition do not survive multiple comparison corrections. The initial presentation of the tasks is more challenging, taking longer to complete with lower accuracy than the second and third presentations. While the second and third presentations show similar rates of accuracy, the final presentation shows the fastest reaction time. This is particularly true for the first presentation of the Faces condition compared to the second and third (which do not differ in terms of accuracy but do when considering response speed). The Shapes condition also showed slower response speeds at first presentation compared to second and third (which did not differ). The occurrence of the blocks was randomized, thus any differences likely reflect practice effects, where volunteers improved following the first presentation of the tasks.

Although some significant differences were found between task conditions and presentations, and marginal differences were observed between young and older adults, it is important to note that both accuracy and reaction time remained quite high. Over the three presentations, accuracy for the Faces condition ranged between 84.56 to 92.48%.
correct and reaction time between 2.28 to 3.02 seconds, and for the Shapes condition accuracy ranged between 98.34 to 99.67% correct and reaction time between 1.05 to 1.17 seconds. Specifically for the age by condition interactions, older volunteers exhibited 83% accuracy and a reaction time of 2.88 seconds for the Faces task, compared to 89% accuracy and 2.46 second response speed for the young group. It is noteworthy that performance for this study was similar to that of other studies using the same paradigm. For example, Hariri et al. (2000) reported accuracy rates of 81.30% correct and response speed of 2.50 seconds for the Faces condition and 95.70% correct and 1.30 seconds for the Shapes condition in a group of 16 healthy young adults (Hariri, Bookheimer et al. 2000). Several other studies have reported equally high accuracy and response speeds (Tessitore, Hariri et al. 2002; Hariri, Drabant et al. 2005). Thus, any differences are regarded to be negligible.

4.2 Affective-Task Related Functional Activations

4.2.1 Amygdalae Activations to Negative Facial Affect are Maintained in Aging

While many studies of facial processing of negative or combined negative and positive affect have shown attenuations of amygdalae activation in healthy older adults (e.g., Iidaka, Okada et al. 2002; Gunning-Dixon, Gur et al. 2003; Tessitore, Hariri et al. 2005), our study did not bear out these results. Our findings do, however, provide important support to the affective facial processing literature with respect to a comparable magnitude of amygdalae reactivity to predominantly negative valence between older and young adults. Facial stimuli have been shown to be effective in eliciting amygdalae
activation in a study of age in- versus out-group membership (Ebner, Johnson et al. 2013), as well as novel fear processing in healthy older adults (Wright, Wedig et al. 2006). In the latter study, peak coordinate response for older adults was located in a dorsal region of the right amygdala (Talairach z coordinate: -14), and as such was attributed to possible arousal effects (Wright, Wedig et al. 2006). Peak activation coordinate discrepancies in Wright et al.’s (2006) study between their older and young groups were similarly located to the coordinates found in our current work, particularly in the right amygdala for older (i.e., more dorsal, Talairach z coordinate: -14) and left amygdala for the younger group (i.e., more ventral, Talairach z coordinate: -16), where we found the most robust activations to be localized. Further implicating arousal effects, a recent study directly assessing amygdalae response to varying levels of arousing stimuli found that both young and older adults exhibited common activation in the right amygdala to high arousing negative scenes, but a reduction in amygdalae signals to low arousal images for older adults (the latter stimuli being rated as less arousing by the older group; Dolcos, Katsumi et al. 2014).

A lack of group differences between healthy older and young adults in amygdalae reactivity to this affective facial matching task suggests that our paradigm was successful in creating sufficient arousal in this region to largely negative stimuli, a proposition discussed by St. Jacques et al. (2009). There is evidence for a maintenance of the amygdalae’s response when older adults view stimuli including positive affect (Mather, Canli et al. 2004; Kensinger and Schacter 2008; Leclerc and Kensinger 2008; Moriguchi, Negreira et al. 2011; Ritchey, Bessette-Symons et al. 2011). Although our paradigm did not directly assess the processing of positive valence, some facial expressions of
happiness were included as incorrect, non-target, comparators to negative expressions, and it could be that the incidental processing of these images influenced activity in the amygdalae regions in our group of older adults. Likewise, the valence of the facial expressions of surprise could have been perceived as positive and may have affected amygdalae response.

Surprised expressions can be interpreted in either a negative or a positive way and their valence is contextually dependent. For instance, during a valence-rating task, Neta et al. (2011) found that young adults rated surprised faces as more negatively valenced than happy faces. When expressions of surprise were presented in blocks of either angry or happy faces, their ratings became more congruent with the respective negative or positive valence of the co-occurring faces. However, presenting surprised faces within the context of negative expressions elicited ratings that were more similar to ratings of angry faces, whereas happy faces continued to be rated as far more positive than surprised faces in the positive context (Neta, Davis et al. 2011). Thus, surprise may still be interpreted in a more negative direction (Neta, Norris et al. 2009; Neta and Whalen 2010; Neta, Davis et al. 2011). Kim et al. (2004) found negatively cued expressions of surprise activated the left ventral amygdala, while positively cued expressions increased right vmPFC response. While Kim et al.’s (2004) peak activation locations for the amygdala and vPFC were divergent from our own, their reported left amygdala cluster overlapped our older group’s amygdala cluster extent (though in our study that cluster was found to span more dorsally). Nonetheless, the better proximity of our cluster to a negatively primed amygdala response is suggestive that the surprised facial expressions included in our study may have been interpreted in a more negative (versus positive) context, especially
considering they were presented among far greater negative (e.g., fear, anger) than
positive expressions (i.e., happy). We did not, however, collect ratings of valence for our
facial stimuli and as such it remains speculative that surprised faces were indeed
interpreted as negatively valenced.

The stimuli set used in the current investigation has been described as including facial
expressions that are particularly intense (Tottenham, Tanaka et al. 2009), which could
have influenced amygdala reactivity. Several studies including young adults have
confirmed that the NimStim faces are rated as highly arousing. For instance, direct
comparisons to other widely used facial stimuli sets revealed that the NimStim faces are
attributed higher arousal and intensity ratings overall, compared to the Karolinska
Directed Emotional Faces (Adolph and Alpers 2010), and the Ekman Pictures of Facial
Affect (cf. AppendixA.xls data of Palermo and Coltheart 2004). Furthermore, research
evaluating amygdala reactivity to the processing of racial in-groups versus out-groups
has demonstrated that young adults exhibit greater regional response to out-group faces,
which might be attributable to an in-group habituation effect (Hart, Whalen et al. 2000).
While we enrolled only Caucasian volunteers, our paradigm included both Caucasian and
African-American faces, and the presence of these out-group faces may have contributed
to sustaining amygdala responses in both age groups.

It is possible that the attenuation of the amygdala’s responses to negative facial
expressions found in prior studies could be a result of greater habituation effects for older
volunteers, for instance if volunteers viewed only ethnic in-group face stimuli.
Habituation was not evaluated in these studies, nor was the ethnicity of volunteers
reported, and only half of those studies described their stimuli set, using databases
including Caucasian faces only (Fischer, Sandblom et al. 2005; Tessitore, Hariri et al. 2005; Fischer, Nyberg et al. 2010). The habituation of the amygdalae to affective facial expressions has been evaluated in young adults and reveals that the right amygdala attenuates in response to fearful and happy facial expressions over time (Breiter, Etcoff et al. 1996; Phillips, Medford et al. 2001; Wright, Fischer et al. 2001; Fischer, Wright et al. 2003). To our knowledge, only one study including older adults has assessed habituation of the amygdalae to faces and did so using only neutral expressions (Wedig, Rauch et al. 2005). While this study found a differential pattern of habituation, where older adults habituated more to neutral faces in the left than right amygdala, and young adults had the reverse pattern, there were no significant age-related differences in bilateral amygdalae habituations, which was consistent with the findings for young adults of prior studies including neutral stimuli. However, this effect may be different when considering emotional stimuli. It might be that the amygdalae will habituate more extensively in older individuals when viewing negative stimuli that are not sufficiently arousing (e.g., when volunteers view faces of their same ethnicity), and activation may be maintained when stimuli remain salient across time (e.g., by including ethnic out-group faces, novel, or intensely arousing stimuli). Supporting this proposition is a study by Roalf et al. (2011) that evaluated habituation to affective scenes using a paradigm sensitive to these effects by repetitive presentation of emotional stimuli. Particularly for negative scenes, which were intentionally selected to elicit high arousal (based on normative ratings, and confirmed by subjective volunteer ratings), young and older adults were found to exhibit similar magnitudes of amygdalae response. Furthermore, the responses were maintained, and arousal ratings remained high, between early to late presentations of negative scenes, indicating that the amygdalae did not habituate to these highly arousing stimuli (Roalf,
Pruis et al. 2011). Elucidating the affective conditions under which the amygdalae may differentially habituate to stimuli with aging remains an avenue of future study that could explain some of the discrepancy between research findings of attenuated versus preserved amygdalae activations, particularly for facial stimuli.

4.2.2 Age-Related Differences in Prefrontal Cortical Activation with Affective Processing

During the emotion-matching paradigm, we did observe PFC activation patterns consistent with the literature. Our whole-brain, voxel-wise, analysis found older adults showed greater vPFC (extending to the ACC [BA47/32]) and mPFC (BA6) activations. Similar regional activations have been reported for subjectively rated negative scenes (St Jacques, Dolcos et al. 2010), explicit processing of affective facial expressions (Gunning-Dixon, Gur et al. 2003), and passive viewing of angry faces (Fischer, Sandblom et al. 2005). Increased functional connectivity has been found between the ACC and amygdalae (St Jacques, Dolcos et al. 2010), and has been posited to reflect greater affective regulatory attempts by older individuals. The vPFC/ACC and mPFC have been implicated in emotional processing and automatic affective regulation (Bush, Luu et al. 2000), as well as effortful processing (Ritchey, Bessette-Symons et al. 2011). This suggests that even when regulatory attempts are unsuccessful (in that amygdalae reactivity were maintained in our group), older adults may continue to engage cognitive control mechanisms during the processing of salient negative material.

These results do provide some support for greater anterior regional recruitment with aging, as only the older group exhibited greater activation in any frontal region compared
to their younger counterparts. This is consistent with the PASA pattern, suggesting that older adults recruit frontal and parietal regions more so than younger adults to maintain a similar level of task accuracy (Grady, Maisog et al. 1994; Dennis and Cabeza 2008). Indeed, in our younger adult group, there were enhanced activations in the left fusiform gyrus (BA37), and bilaterally in the middle and inferior occipital gyri (BA19/18). Greater activation in posterior cortical regions (e.g., fusiform, lingual, angular gyri) have been consistently reported for healthy young relative to older adults during the processing of negative facial expressions (bilateral fusiform BA19 [Tessitore, Hariri et al. 2005]; BA19, 37 [Wright, Wedig et al. 2006]; right lingual BA18, angular BA39 [Iidaka, Okada et al. 2002]), and scenes (left: BA19/37, right: BA19/31 [St Jacques, Dolcos et al. 2010]; left: BA18, right: BA19 [St Jacques, Dolcos et al. 2009]; BA19/37 [Ritchey, Bessette-Symons et al. 2011]). However, we did observe greater right fusiform (BA37) activation in the older group. This is consistent with another study finding right fusiform (BA19/37) response, in addition to preserved amygdala activation, in the context of successfully encoded negative imagery in their older group (Kensinger and Schacter 2008). This particular region has been shown to be activated during the processing of the perceptual details of negative material, and corresponds to subsequent memory for visual specifics (Kensinger, Garoff-Eaton et al. 2007), suggesting that our older group was particularly attentive to the perceptual content of the negative facial expressions.

4.3 Cortical Thickness Differs Between Healthy Young and Older Adults

We found a regional pattern of cortical thinning which differentiated young and older adults. Voxel-wise analysis found widespread frontal, parietal, and temporal cortical
thinning between the age groups, with particularly significant reductions seen for older adults in the dorsolateral and dorosmedial frontal cortex, pre/postcentral gyri, supramarginal gyrus, and superior temporal gyrus. Further analysis of the segmented lobes confirmed that older adults were best differentiated from young adults by mean cortical thickness reductions across the frontal (left precentral, middle, and inferior frontal gyri), parietal (bilateral postcentral, superior, supramarginal, and angular gyri), and temporal (bilateral superior, middle, left inferior, right fusiform gyri) lobes. Thinning in the frontal and parietal lobes is regularly demonstrated in studies of age-related structural loss (Salat, Buckner et al. 2004; Driscoll, Davatzikos et al. 2009; Taki, Thyreau et al. 2013; Fjell, Westlye et al. 2014). We found overlap between thinning in the frontal, parietal and superior temporal areas between our study and another cross-sectional analysis of six separate samples (n = 883) that consistently demonstrated age-related thickness differences in these regions (Fjell, Westlye et al. 2009). We did not find differences between young and older adults in the thickness of the occipital cortices, which is also in agreement with studies demonstrating less volumetric decline in this region (Raz, Gunning-Dixon et al. 2004), as well as a lack of age-related differences in cortical thickness (Fjell, Westlye et al. 2009). Furthermore, while reduced thickness was observed in OFC regions (particularly laterally), there were generally greater reductions in other prefrontal areas. This result is consistent with the literature, particularly for the mOFC, in both assessments of volume and cortical thickness (Salat, Buckner et al. 2004; Fjell, Westlye et al. 2009; Taki, Thyreau et al. 2013; Fjell, Westlye et al. 2014). Despite a small sample size, our findings do provide some support for the relative vulnerability of much of the PFC with advancing age, which is in line with previous research from larger scale studies.
4.4 Prefrontal Cortical Thickness Influences Amygdala Function in Older Adults

In our group of healthy older adults, mean BOLD reactivity of the right amygdala to an emotional facial processing task was predicted by the overall thickness of the left mOFC and superior rostral middle frontal gyrus and thinning in the left IOFC and inferior rostral middle frontal gyrus. This relationship was not found in the younger age group, and the between group difference was significant, suggesting this particular structure-function connection is unique with aging. The amygdalae are shown to be concurrently activated with PFC regions, including the OFC and middle frontal gyrus, in the evaluation of affective imagery (Fusar-Poli, Placentino et al. 2009; Sabatinelli, Fortune et al. 2011). The lateral and orbital PFC and rostral middle frontal gyrus are associated with affective regulation and experience, with lateral regions being implicated in inhibitory processes and medial regions associated with increasing arousal for negative material (Ochsner, Ray et al. 2004). The co-activation of more medial PFC regions, such as the OFC, and the amygdalae has been observed in relation to negative affective attention and interpretation (Adolphs 2002; Bishop 2007). A relative structural preservation of these PFC regions in our current investigation could reflect that older adults maintain the ability to attend to particularly arousing negative material. Lateral PFC regions, overlapping with the IOFC and inferior middle PFC regions observed in our current study, have been shown to be activated during the controlled suppression of sadness (Levesque, Eugene et al. 2003). Greater activation in the lateral inferior middle PFC has shown to be associated with decreased amygdalae activation during the reappraisal of negative scenes (Winecoff, Labar et al. 2011). Thus, it is possible that thinning of these
lateral regions in older adults makes it more difficult for them to suppress amygdala reactivity when viewing highly arousing negative stimuli. We have found that areas important for the regulation, understanding, and perception of affective information show relatively less age-related thickness change medially (perhaps reflecting preserved attention to, and interpretation of, emotional information) and lateral thinning (suggesting disrupted inhibitory connections when faced with arousing stimuli) with aging, and that this structural pattern predicts the maintenance of amygdala activation to a salient negative affective task distinctively in older adults.

Our results are in line with recent evidence from a lesion study which indicates that structural damage of vPFC regions (including the OFC) in older adults results in greater hyperactivity of the right amygdala to negative imagery (Motzkin, Philippi et al. 2015). Patients with bilateral damage to the amygdalae, resulting from Urbach-Wiethe disease, have shown an association with increased thickness of the bilateral vPFC (encompassing the lateral and medial OFC) compared to neurologically intact volunteers (Boes, Mehta et al. 2011), strengthening the inverse connection between these structures. Furthermore, Foland-Ross et al. (2010) demonstrated negative correlations between OFC thickness and amygdala response in a group of healthy young adults during a cognitively demanding affect labeling task. Although this latter group did not find PFC-amygdalae correlations during the process of affective matching, their result is consistent with other studies in young adults that utilize this paradigm and fail to find activations in PFC regions (Hariri, Bookheimer et al. 2000; Lieberman, Eisenberger et al. 2007). However, the few studies employing this matching paradigm to evaluate age-related effects of negative facial processing do show PFC activations in older adults to this task (Tessitore, Hariri et al.)
2005; Bangen, Bergheim et al. 2014), and we have also demonstrated this with our current evaluation. This type of reliance on PFC areas is consistent with the PASA pattern, suggesting that higher-order cognitive control processes may become increasingly important for older adults to maintain task accuracy (Grady 2000), and could indicate that affective perception also becomes more demanding with aging. This could explain why our result of greater amygdala reactivity predicted by PFC thickness measures was specific to our older group.

These results may be relevant to the study of affective disorders occurring in late-life. Our findings of OFC/middle frontal gyrus thickness changes complement research in late-life depression (LLD) showing more extensive thinning in these regions for depressive individuals (Lim, Jung et al. 2012; Mackin, Tosun et al. 2013), and the relationship to greater amygdala reactivity in our healthy older population underscores the significance of these regions as neuroanatomical markers for investigation.

Furthermore, there is a correlation between greater thinning in the OFC and treatment non-response (Mackin, Tosun et al. 2013), highlighting the importance of defining pathophysiologic changes that have the potential to influence the identification of patients at greater risk for unfavourable therapeutic outcomes. Changes in cortical morphometry with aging could increase functional reactivity of structures that are implicated in mood disorder, which could explain, in part, why the etiology of LLD differs from that of early onset depressive illness.
4.5 Methodological Considerations

A major strength of our current investigation was that our sample of healthy young and older adults was well characterized. All volunteers were right-handed and men, mitigating the potential confounding effects of handedness and sex on the neuroimaging results. Furthermore, all volunteers underwent a thorough screening process including medical and psychiatric evaluation, and there were no significant differences between age groups in level of education, and on measures of cognitive function, affect, depression, or anxiety.

A limitation is that the modest number of volunteers in the current study could have lead to insufficient power to detect small between-group differences. It is worth noting that the older volunteers did exhibit greater bilateral mean amygdalae activations to the faces task than did the younger group, albeit not statistically significant. Similarly, Wright et al. (2006) and Ebner et al. (2013) reported greater activation in their groups of older volunteers, countering other reports of decreased activation in these regions. However, we were unable to confirm the small exploratory effects observed by Foland-Ross et al. (2010) in their group of healthy young adults, which indicated a positive correlation between temporoparietal thickness and amygdala reactivity to the affective matching paradigm. Subsequent studies employing larger samples would be of benefit in replicating the preliminary results presented herein, and could potentially reveal age-related activation differences that were not currently detectable (such as group activation discrepancies in the supramarginal and superior temporal gyri).
We did not directly assess the arousal level of the stimuli used in the current investigation, and thus arousal effects are speculative. However, the locations of peak activations in the amygdalae were different between the young and older adults, and consistent with the literature implicating ventromedial localization for valence effects and dorsolateral localization to arousal effect (Whalen, Rauch et al. 1998; Whalen, Shin et al. 2001; Wright, Wedig et al. 2006). Furthermore, the facial stimuli set used for the emotion matching paradigm has been shown to elicit high arousal and intensity ratings in young adults (Palermo and Coltheart 2004; Adolph and Alpers 2010). Ebner et al. (2013) found that including older adult facial stimuli resulted in augmented amygdalae response in their older age group to those own-age faces, suggesting stimuli of greater salience to older adults may further potentiate amygdalae activity. Future investigations should account for ratings of the subjective intensity or arousal experienced by volunteers when viewing affective stimuli, as there is evidence for age-related differential amygdalae response attributed to low versus high arousing negative images (e.g., Dolcos, Katsumi et al. 2014). In addition, employing stimuli sets that are particularly relevant to older adults (e.g., own-age faces) may reveal interesting age-related activation differences during the evaluation of affective material.

Amygdalae volumetry could have impacted the functional results as well as the structure-function relations that we have described. We carried out an exploratory analysis using amygdalae volumes produced by the Multiple Automatically Generated Templates (MAGeT) brain segmentation algorithm (Entis, Doerga et al. 2012; Pipitone, Park et al. 2014; Treadway, Waskom et al. 2015). A 2 x 2 ANOVA was conducted to determine any significant interactions between age (young, older) by amygdalae volumes (left, right).
The main effect of age approached significance \( (F_{1,18} = 4.183, p = 0.056, \eta_G^2 = 0.18) \), suggesting the young group had a tendency towards larger amygdalae volumes compared to the older group (Young: \( M = 1260.40 \text{ mm}^3, \ SE = 37.72 \); Older: \( M = 1151.30 \text{ mm}^3, \ SE = 37.72 \)). A significant main effect of laterality revealed that overall the left amygdala was smaller in volume than the right (Left: \( M = 1186.20 \text{ mm}^3, \ SE = 28.79 \); Right: \( M = 1225.50 \text{ mm}^3, \ SE = 26.56 \); \( F_{1,18} = 6.941, p = 0.017, \eta_G^2 = 0.03 \)). There was no significant interaction found \( (F_{1,18} = 0.028, p = 0.869, \eta_G^2 < 0.01) \), indicating that the pattern of lateralized volumetric differences were similar between the age groups. Re-analyzing BOLD activations within and between age groups with the general linear model in AFNI, using amygdalae volumes of each group as a covariate, achieved similar results as we have originally reported. Likewise, including the volume of the right amygdala as a covariate in the multiple regression analysis evaluating the predictability of right amygdala activation by left PFC thickness measures did not reduce the significance of the reported results. The models were found to be significant for the older group \( (F_{7,9} = 91.917, p = 0.011, R^2 = 0.997) \), not significant for the younger group \( (F_{7,9} = 0.473, p = 0.809, R^2 = 0.623) \), and the comparison of the fit of the respective models revealed that there was a significant difference, such that the structure-function relationship found was specific to the older group \( (Z = 4.461, p < 0.001) \). Thus, it is unlikely that a lack of age-related functional differences, or discrepancies in structure-function relations, were attributable to amygdalae volumes.
4.6 Future Directions

4.6.1 Meta-Analysis of Functional Activation to Affective Processing Tasks in Aging

It is generally accepted that healthy older adults show a pattern of attenuated amygdalae activations coupled with increased prefrontal signals, particularly to negative affective tasks. However, closer evaluation of the existing literature suggests that there may be preserved amygdalae responses, even to negatively valenced material, especially when stimuli appear to be arousing. While fMRI analyses are beginning to include investigations of age effects on the neural correlates of affective processing, generally studies are limited in power due to small sample sizes. Meta-analysis is a powerful technique that allows the evaluation of the convergence of brain activation results across studies. A meta-analysis by Fusar-Poli et al. (2009) evaluated the regional BOLD activation patterns during tasks utilizing affective facial stimuli. In a sub-analysis of those studies including older adults no age related differences were found between young and older adults in the amygdalae or PFC when viewing negative facial expressions (Fusar-Poli, Placentino et al. 2009). However, this evaluation included studies with young and middle age ranges in their 'older' group (subgroup average age M = 55, SD = 14, range 23 – 80 years old, n = 111). The literature would benefit from a meta-analysis with more restricted criteria for older group inclusion to ensure that age differences are not mitigated by the inclusion of younger adults. Our group is currently undertaking such an endeavour. We used the coordinate-based quantitative activation likelihood estimation method to evaluate peak activation coordinate data from nine fMRI studies comparing healthy young (average age M = 25, SD = 3.6, range = 18 – 40, n = 131, 112 foci) and
older adults (average age M = 71, SD = 5.7, range = 57 – 90, n = 135, 100 foci) on negative affective processing tasks.

Preliminary results show that both young and older adults activate frontal, parietal, limbic and cerebellar regions when viewing predominantly negative stimuli. When directly comparing groups, older adults show greater activations in an anterior region of the insula (BA13) and the cerebellum, while young adults showed more activation in the right ventromedial amygdala. However, conjunction analysis revealed common activations in the left cerebellar declive, right middle frontal cortex (BA9) and in the right dorsolateral amygdala. While we continue to evaluate potential studies for inclusion and complete data extraction, these initial findings show promise towards providing a more accurate distinction between negative emotional processing differences associated with aging. While it appears that a ventromedial region of the amygdala is more activated to negative stimuli in young compared to older adults, results from conjunction analysis reveal that an arousal related region of the dorsolateral amygdala is similarly activated to negative material in both age groups. This finding suggests that amygdalae activations can be maintained with aging, particularly when affective information is salient and arousing, whereas differences in amygdalae activations attributable to valence effects are more pronounced in younger adults. This study will provide valuable, up-to-date, evidence for age-related changes in the fronto-limbic network across affective tasks, and help guide selection of neuroanatomical targets of interest for continued study in both healthy and pathological aging.
4.6.2 Prefrontal Cortical Thinning Effects on Amygdalae Function in Late-Life Depression and Treatment Refractoriness

4.6.2.1 Major Depressive Disorder in the Aging Population

While it may appear that aging improves the affective well-being of healthy individuals, emotional dysfunction can occur in late-life. In particular, major depression is a significant problem in aging. Its presentation and prognoses are distinct from that of early life depression. LLD is more chronic and severe, with greater incidence of medical and psychiatric comorbidity, disability, and mortality (Kohn and Epstein-Lubow 2006). It causes great burden to the patient, as well as significant strain on the health care system, for example in relation to disability claims (Dewa, Goering et al. 2002) and adverse drug reactions (Yee, Hasson et al. 2005). Treatment non-response and relapse are common, with as many as 30 – 50% of patients failing to respond (Lenze, Sheffrin et al. 2008) and up to 30 – 40% not achieving remission (Fava and Davidson 1996; Fava 2003; Kozel, Trivedi et al. 2008). Even when affective symptoms do remit, cognitive impairment develops or persists in a substantial proportion of patients (Bhalla, Butters et al. 2006). Additionally, initial treatment can confer significant risk for completed suicide in older patients (Juurlink, Mamdani et al. 2006). Cortical alterations in both structure and function have been demonstrated in LLD, including regions of the affective fronto-limbic network, such as the OFC and amygdalae.

4.6.2.2 Structural Change in Late-Life Depression

Cortical volume loss has been demonstrated in LLD patients compared to healthy volunteers, including regions such as the dIPFC, ACC, and OFC (Lai, Payne et al. 2000;
Lee, Payne et al. 2003; Lavretsky, Ballmaier et al. 2007; Chang, Yu et al. 2011). An ROI based analysis found LLD patients to have decreased volume across the PFC (medial superior, inferior frontal gyri, OFC), insulae, and amygdalae compared to healthy volunteers; with superior, medial superior, middle frontal and OFC regions correlating with older age at illness onset (Andreescu, Butters et al. 2008). Additionally, the amygdalae have been shown to be smaller in volume bilaterally in patients versus non-depressed controls (Burke, McQuoid et al. 2011). Using voxel-based morphometry, Egger et al. (2008) examined patients with LLD emerging at or past the age of 60 years (late-onset depression) and found decreased gray matter volume in the right amygdala, hippocampus, and bilateral mOFC. Furthermore, severity of depression was significantly correlated with smaller mOFC volume (Egger, Schocke et al. 2008).

Some studies have failed to find disease specific cortical thinning in LLD. In two studies, both healthy and depressed older adults showed a similar pattern of cortical gray matter loss, which was unrelated to cognitive and depressive measures (Koolschijn, van Haren et al. 2010; Colloby, Firbank et al. 2011). These studies suggested that cortical thinning is more a function of age, whereas measures of white matter or subcortical gray matter may be more important to the pathophysiology of LLD. However, more recently other investigations have demonstrated differences in thickness measures between LLD patients and healthy older adults. Lim et al. (2012) found that depressed older patients exhibited thinning in regions including the bilateral dLPFC, the left mOFC, pars triangularis, and rostral ACC, the right rostral middle frontal cortex, pars opercularis and PCC compared to healthy older volunteers. Depression severity was correlated with thinning in the left rostral ACC for patients (Lim, Jung et al. 2012). Subsequent studies
have gone on to confirm that, relative to healthy older adults, individuals with LLD show greater thinning in the frontal pole, superior frontal cortex, rostral and caudal middle frontal cortex, OFC, pars triangularis, and ACC (Sheline, Disabato et al. 2012; Mackin, Tosun et al. 2013; Kumar, Ajilore et al. 2014). Furthermore, thinning in several regions, including the frontal pole (Sheline, Disabato et al. 2012) and right mOFC (Mackin, Tosun et al. 2013), have been shown to be greater in LLD treatment non-responders. Discrepancies between studies may be a result of differences in the clinical classifications of participants (e.g., early-onset versus late-onset LLD), illness severity or duration, or treatment effects, including refractoriness (e.g., LLD patients with prior antidepressant exposure exhibit larger OFC gray matter volume than drug-naïve patients [Lavretsky, Roybal et al. 2005]; or, cortical thinning may be more relevant to treatment non-response, in that such patients may exhibit unique biomarkers of disease). In light of some of the inconsistencies between studies assessing cortical thickness in LLD patients, it is important to improve the evidence for thickness changes considered to be a part of normal, healthy, aging in order to better ascertain where differences may lie in the neurobiology of LLD.

4.6.2.3 Functional Changes with Late-Life Depression

Regions including the PFC and amygdalae have been implicated in studies of early-onset major depression (Rigucci, Serafini et al. 2010; Hamilton, Etkin et al. 2012), but there is a paucity of data evaluating the functional activity of these areas in LLD. Using a valence rating paradigm, one study found LLD patients to show decreased vmPFC (including ACC and mOFC) activation to negative words compared to healthy volunteers, which
was correlated with depression severity (Brassen, Kalisch et al. 2008). In response to an emotional odd-ball task, compared to healthy volunteers, negative distractors activated two small clusters of the bilateral amygdalae in LLD patients, while attentional targets attenuated signal in the right middle frontal gyrus for acutely depressed patients (also compared to remitted patients; Wang, Krishnan et al. 2008); response in the middle frontal gyrus was correlated with depression severity. A study measuring cerebral glucose metabolism using positron emission tomography (PET) has shown greater metabolism in frontal regions, including the right middle, bilateral superior (BA9), and inferior (BA45) frontal gyri, for LLD patients compared to healthy older adults (Smith, Kramer et al. 2009). In this study, Smith et al. (2009) demonstrated that greater depression and anxiety severity were correlated with augmented metabolism in the bilateral superior and middle frontal gyri, and left ACC; depression severity was further correlated with greater metabolism in the left inferior frontal gyri and insula (Smith, Kramer et al. 2009).

Some research has assessed the functional connectivity between frontal and limbic structures and found that it is affected by LLD. Compared to healthy older adults, apathetic LLD patients have been shown to have greater functional connectivity between the nucleus accumbens (a region involved in motivation and perception of positive stimuli) and the left OFC and middle frontal gyrus, and poorer connectivity between the nucleus accumbens and the right amygdala and lentiform nucleus compared to both non-apathetic patients and healthy volunteers (Alexopoulos, Hoptman et al. 2013). Non-apathetic LLD patients show decreased connectivity between the right nucleus accumbens and bilateral OFC compared to healthy adults (Alexopoulos, Hoptman et al. 2013).
2013), a finding which has since been replicated and associated with severity of depression (Tadayonnejad, Yang et al. 2014). Reduced functional connectivity between the left amygdala and right middle frontal gyrus and left superior frontal gyrus has also been observed in late-onset LLD patients as compared to healthy volunteers (Yue, Yuan et al. 2013).

4.6.2.4 Antidepressant Treatment Alters Cortico-Limbic Activity in Late-Life Depression

Pharmacotherapies of depressive disorders often target the 5HT system, which has been shown to influence PFC and amygdalae function. For example, in patients with LLD, eight weeks of treatment with the selective serotonin reuptake inhibitor (SSRI), citalopram, resulted in decreased glucose metabolism in regions including the bilateral medial frontal gyri (BA10) and amygdalae; metabolic reductions in the left amygdala, ACC, bilateral middle (BA46) and superior frontal (BA6/9) cortex, and insula (BA13) were correlated with the affective improvement seen in patients (Diaconescu, Kramer et al. 2011). However, in a group of healthy young adults, BOLD amygdalae activity was increased over the course of acute administration of citalopram to a negative affect matching task, indicating that initial pharmacologic treatment may augment functional activation, an effect that is hypothesized to be a precursor to the eventual down-regulation that is seen during chronic treatment (Bigos, Pollock et al. 2008). Lee et al. (2013) found older depressed patients, that were treatment refractory at six months into primarily 5HT interventions, exhibited greater activations to a working memory task in regions including the left middle frontal lobe (BA9) and amygdala, compared to non-depressed individuals. Depression severity and comorbid anxiety were significantly
correlated with left amygdala hyperactivity in their LLD group (Lee, Liu et al. 2013), highlighting this region as a neuroanatomical target. In another recent study, poor response to sertraline treatment over the course of 12-weeks was related to thinning in the PFC (frontal pole; Sheline, Disabato et al. 2012), suggesting that cortical thinning may also impede affective improvement. Thus, if greater cortical thinning affects increased functional activation in the amygdalae, and initial antidepressant treatment further amplifies this reactivity, this interaction could explain some of the variability in responding to SSRIs, such as treatment non-response or increased risk for suicide in older patients. However, cortical thickness measurement remains a relatively unexplored avenue in LLD, and thus no studies to date have examined the effect on limbic activity.

4.6.2.5 Summary

To our knowledge, our current study is the first to provide a link between PFC thickness and functional amygdala response during a negative affective task, which was specific to healthy older adults. Our results of cortical thinning with advancing age are consistent with prior work assessing age-related structural alterations. Recent studies including patients with LLD have found greater thinning in PFC areas, overlapping with regions we have implicated, and other investigations have observed evidence for amygdalae dysfunctions in LLD. Future work should extend our results into an examination of these structure-function relations that are relevant to psychiatric populations. It is conceivable that patients with LLD, and perhaps in particular those that are treatment refractory, may exhibit greater middle PFC and OFC thinning which could potentially moderate amygdalae hyperactivity to negative stimuli. Depression severity has been shown to
correlate with increased amygdalae responses. Treatments aimed at ameliorating affective symptoms have been shown to acutely increase the reactivity of this region to negative affects. It would be important to evaluate the effects of treatments, such as the commonly prescribed SSRIs, on the relationship between PFC thinning and amygdalae function as activation in this region may be further potentiated by structural alteration. Moreover, patients that do not remit with treatment may be especially vulnerable to these effects and it would be critical to distinguish whether there are differences in PFC thinning and amygdalae reactivity between treatment responders versus non-responders.

4.7 Concluding Remarks

We demonstrate that healthy older adults can show similar amygdalae reactivity during an affective facial expression matching task compared to young adults. Furthermore we present the first preliminary investigation that the thickness of middle PFC and thinning of lateral PFC regions augments amygdala activation distinctively in older adults. The pattern of more medial thickness and lateral structural decrease may reflect a maintenance of attention for highly arousing negative stimuli that becomes difficult to inhibit during aging. This work highlights neuroanatomical targets relevant to investigations of healthy aging and late-life disorders of mood. Moreover, we suggest a possible underlying structure-function relationship that may be particularly significant in the therapeutic interventions of LLD.
References


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