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Interactions Among Amygdala Volume, Cortical Thickness, and Structural Connectivity in Youth: Relationship to Emotion Regulation

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INTERACTIONS AMONG AMYGDALA VOLUME, CORTICAL THICKNESS, AND STRUCTURAL CONNECTIVITY IN YOUTH: RELATIONSHIP TO EMOTION REGULATION

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List of Abbreviations

ACC	Anterior Cingulate Cortex
aIN	Anterior Insula
CG	Cingulum
DFN	Defensive Fear Network
dACC	Dorsal Anterior Cingulate Cortex
dlPFC	Dorsal Lateral Prefrontal Cortex
dmPFC	Dorsal Medial Prefrontal Cortex
FG	Fusiform Gyrus
GLM	General Linear Model
GNC	General Network of Cognition
GNC-1	Portion of the GNC related to unconscious emotion/emotion regulation
GNC-2	Portion of the GNC related to conscious emotion/emotion regulation
IN	Insula
UF	Uncinate Fasciculus
lOFC	Lateral Orbitofrontal Cortex
lPFC	Lateral Prefrontal Cortex
MASC	Multidimensional Anxiety Scale for Children
MCS	Monte Carlo Simulation
mOFC	Medial Orbitofrontal Cortex
mPFC	Medial Prefrontal Cortex
MTL	Medial Temporal Lobe
OFC	Orbital Frontal Cortex

PCS	Precuneus
PCL	Paracentral Lobule
pdACC	Posterior Dorsal Anterior Cingulate Cortex
PFC	Prefrontal Cortex
pgACC	Pregenual Anterior Cingulate Cortex
pIN	Posterior Insula
Post-CG	Postcentral Gyrus
pPL	Posterior Parietal Lobe
Pre-CG	Precentral Gyrus
rACC	Rostral Anterior Cingulate Cortex
rdACC	Rostral Dorsal Anterior Cingulate Cortex
RMF	Rostral Middle Frontal Cortex
SFG	Superior Frontal Gyrus
SPL	Superior Parietal Lobule
sgACC	Subgenual Anterior Cingulate Cortex
vlPFC	Ventral Lateral Prefrontal Cortex
vmPFC	Ventral Medial Prefrontal Cortex

Abstract

Emotion regulation includes adaptive (e.g., reappraisal) and non-adaptive behaviors (e.g., avoidance) designed to alter ones' affective responses. The central hypothesis is that emotional consciousness – being self-aware that you are currently in a particular emotional state – and emotion regulation share the same underlying brain mechanisms/networks. In addition, it is argued that the more appropriate dichotomy, in regard to non-adaptive and adaptive emotion regulation strategies, is dependent on whether they are unconscious or conscious (respectively), positing a two-system framework of emotion regulation. Evidence for the proposed framework draws and builds off of recent theories of higher-order emotional consciousness (LeDoux & Brown, 2017) and supported frameworks of fear/anxiety (LeDoux & Pine, 2016). The literature reviewed suggests that the difference between emotional consciousness and emotion regulation lies in the variations in recruitment of lower-order, subcortical networks and the higher-order interpretation by the same overarching general network of cognition. In the second portion, an empirical examination of this theory was conducted using neuroimaging and self-reported anxiety in a sample of youth. I provide evidence for my first hypothesis by identifying significant clusters of grey-matter thickness in the general linear analyses that qualitatively overlap with the general network of cognition proposed to underlie emotional consciousness. The second hypothesis was partially supported as grey-matter thickness of these regions of the PFC, but not amygdala volume, significantly related to self-reported anxiety. Next, it is demonstrated that this relationship was significantly moderated by youths' structural connectivity. Post-hoc analyses indicated that PFC grey-matter cortical thickness had a significant indirect effect on the relationship between amygdala volume and youth's self-reported anxiety. The current results

provide support for the central hypothesis that emotional consciousness and emotion regulation share many of the same underlying brain networks and mechanisms.

1. Introduction

1.1. Emotion Regulation

The ability to effectively regulate emotions is essential for an individual's well-being. Emotions ebb and flow over time and are crucial for our survival; signaling when our attention is needed elsewhere while facilitating the updating of goal progress (e.g., Carver & Scheier, 1990). However, our environment (external and internal), for better or for worse, is constantly changing; efficient and accurate updating of goal progress and emotional responses is essential for adaptive emotion regulation (Gross, 1999). Emotion regulation refers to adaptive (e.g., reappraisal problem solving), as well as long-term non-adaptive behavior (e.g., worry, rumination) to the inevitable fluctuations in affective responses (see Aldao, Nolen-Hoeksema, & Schweizer, 2010). It was once thought emotions influence behavior in an uncontrollable manner (Lyons, 1978). We now know that many stages of emotion processing are controllable. For instance, one can divert attention away from an emotional stimulus (e.g., Rothermund, Voss, & Wentura, 2008), reduce the physiological consequences of the emotions he or she is feeling (e.g., Porges, 2007), and/or cognitively reappraise a particular emotional experience (e.g., Gross, 1998). These processes are just a few examples of effortful (or conscious) emotion regulation strategies.

The amygdala is involved in a wide range of emotional processes. Broadly, elevated amygdala responses to emotional stimuli appear to reflect emotional intensity or arousal regardless of whether the emotional valence is positive or negative (Anderson & Sobel, 2003; Small et al., 2003). Amygdala activity is involved in evaluating potentially threatening stimuli (Shin, Rauch, & Pitman, 2006), encoding emotionally salient stimuli (Canli et al., 2000), affective recognition (Adolphs et al., 1994; Baird et al., 1999), fear conditioning (Garakani,

Mathew, & Charney, 2006; Olsson & Phelps, 2007; Schulkin, 2006), behavioral regulation (Dolan, 2007), and emotion regulation (Goldin et al., 2008; Ochsner et al., 2004).

Surprisingly, structural imaging studies have been inconsistent when linking amygdala volume to various affective disorders. Some researchers have found reduced amygdala volumes in youth with major depression (Rosso et al., 2005) but others have reported larger amygdala volumes in the same population (MacMillan et al., 2003). Research has indicated that bipolar youth typically display reduced amygdala volume (Blumberg et al., 2003; Pfeifer, Welge, Strakowski, Adler, & Delbello, 2003), but more recent research suggests that this may be, at least partially, attributed to a history of pharmacotherapy (i.e., lithium; Savitz et al., 2010). The literature in pediatric anxiety has also been equivocal (see De Bellis et al., 2000; Milham et al., 2005). Notably for the present study, in healthy youth amygdala volume has been found to be negatively (Blackmon et al., 2011), as well as positively related to amygdala volume across development (Albaugh et al., 2017). What accounts for these equivocal findings regarding amygdala grey-matter and negative affect?

One potential explanation for the discrepant findings list above is that the amygdala participates in emotion related processes as one element in a network of regions that also includes top-down frontoparietal areas associated with emotion regulation. Thus, it is not the amygdala volume alone that predicts emotional dysregulation but rather the relationship between amygdala volume and the grey matter makeup of cortical areas associated with emotion regulation. There is much functional evidence that frontoparietal areas are related to the amygdala, and to emotional reactivity more generally, as a function of their involvement in emotion regulation (Amting, Greening, & Mitchell, 2010; Greening, Osuch, Williamson, & Mitchell, 2013; McRae, Hughes, Chopra, Gabrieli, Gross, & Ochsner, 2010).

1.2. Aims and Purpose

Emotion regulation underlies nearly all diagnostic categories (Aldo et al., 2010), where adaptive emotion regulation is associated with better mental health (Gross & Muñoz, 1995), improved physical health (Sapolsky, 2007), healthier interpersonal relationships (Murray, 2005), and better work performance (Diefendorff, Hall, Lord, & Strean, 2000). Despite its transdiagnostic importance, and a large increase in emotion regulation research over the past decade, there is surprising lack of continuity within the field (see Gross, 2013). The confusion in the literature partially stems from the dubious distinction between emotion and emotion regulation, as well as poorly integrated literatures (e.g., clinical, neuroscience, emotion processing, and emotion regulation). For instance, it is not clear what constitutes emotion regulation versus other forms of emotional processing (Koole, 2009), and there is even dispute what defines an emotion (see Izard, 2007). Some view emotion generation and emotion regulation as not being mutually exclusive (see Gross & Barrett, 2011; Ochsner et al., 2009); experts in the field refer to the distinction as being "blurry at best" (pg. 3, Ochsner, Silvers, & Buhle, 2012; Ochsner et al., 2009) and note it is unclear ''where an emotion ends, and regulation begins'' (pg. 308, Davidson, 1998). This is further compounded by differences in terminology, level of analysis, and measurement (Izard, 2007; Nigg, 2017). By definition, an emotional state cannot last forever – every emotion one has experienced has been regulated in some way. Despite difficulty distinguishing these constructs they are frequently modeled independently.

Broadly, the aim of the dissertation is to review the literatures on emotional processing among various fields by providing evidence for a two-system framework of emotion regulation that scaffolds off of two similar theories of emotional consciousness (LeDoux & Brown, 2017) and a popular framework of fear/anxiety (LeDoux & Pine, 2016). The overall purpose of this

dissertation is to extend these two dominate theories of emotion with the hope that it will help integrate the fields of clinical psychology and neuroscience literatures. Utilizing neuroimaging and reported anxiety, I examine my central theoretical hypothesis.

1.2.1. Theoretical Overview

The dissertation is divided into two portions. First, a theoretical overview is followed by an empirical examination of this theoretical viewpoint. In the first portion, my central theoretical hypothesis is that emotional consciousness – being self-aware that you are currently in a particular emotional state – and emotion regulation share the same underlying brain networks/mechanisms. In addition, it is hypothesized that when evaluating the adaptiveness of emotion regulation strategies (i.e., non-adaptive or adaptive) the more appropriate dichotomy is between unconscious (termed type- or level-one throughout) and conscious (termed type- or level-two throughout) emotion regulation (respectively). Similar to theories of emotional consciousness (LeDoux & Brown, 2017) and an empirically supported framework of fear/anxiety (LeDoux & Pine, 2016), the differences between emotional consciousness and emotion regulation lies in the recruitment of lower-order, subcortical networks and their interpretation by higher-order structures. Evidence for this hypothesis will come from psychological neuroscience literatures and allows for the easy extension of LeDoux and Pine's (2016) two-system framework of fear/anxiety to one of emotion regulation. The review will end by positing specific circuits within the network as being type-one emotion regulation – often called emotion reactivity/responsivity/sensitivity – or type-two emotion regulation (i.e., effortful strategies). It should be noted early that the distinction made between conscious and unconscious processes is not perfect (e.g., do you remember the specifics of your drive to work this morning? See Bargh

& Williams, 2006); however, the conceptual distinction is important as it overlaps nicely with (and has direct implications for) the framework and theory that will be central to the current review. Given their intertwined nature, a framework of emotion regulation that scaffolds off dominate theories of emotional processing (i.e., LeDoux & Brown, 2017; LeDoux & Pine, 2016) has the potential to orient these two overlapping fields. Prior to going forward, it is important to define the terminology used, as well as review the two-system framework of fear/anxiety (LeDoux & Pine, 2016).

1.2.2. Empirical Support for A Two-System Framework

In the second portion of this dissertation, preliminary evidence will be provided for the two-system framework of emotion regulation. Specifically, I first look to determine regions of cortical thickness that are significantly associated with amygdala volume in a sample of typically functioning youth. I go on to examine whether this relationship is moderated by youths' structural connectivity, linking grey-matter thickness (i.e., regions that correlated amygdala volume) and subcortical areas (i.e., amygdala volume) with self-reported anxiety. In my exploratory analyses, a test of indirect effects was conducted. I examined whether the relationship between amygdala volume and anxiety is indirectly related once restrictive variance is accounted for by regions of grey-matter cortical thickness (thought to be associated with emotion regulation). Final evidence is provided for an indirect effect, by the follow-up analyses examining whether amygdala volume and self-reported anxiety is moderated by cortical thickness in areas associated with emotion regulation. Given the ambiguity in the literature, precisely defining the terminology, level of analysis, and theoretical viewpoint used throughout

the thesis – in both the emotion and emotion regulation literatures – is essential before moving forward.

1.2.3. Terminology

Emotion regulation is often divided into effortful, conscious, deliberate actions (termed type-two throughout; see LeDoux & Pine, 2016; Nigg, 2017) and noneffortful, unconscious, nondeliberate actions (termed type-one throughout). Diagnostically agnostic terms outlined by Nigg (2017) will be used when needing to differentiate among emotion regulation: type-one (non-effortful, unconscious, etc.) and type-two (effortful, conscious, etc.). Emotion regulation will be defined broadly as regulatory actions used to alter ones' behavior, physiological responses, and/or subjective experience. This includes both type-two, conscious emotion regulation strategies (e.g., problem-solving, cognitive reappraisal, mindfulness), as well as type-one, or unconscious emotion regulation (i.e., regulatory mechanisms that operate automatically and outside of one's awareness; see Bargh & Williams 2007).

Often emotional reactivity/responsivity/sensitivity (i.e., automatic behavioral and physiological changes in response to neutral or negative stimuli) is used to refer to type-one emotion regulation. They are identical semantically, but conceptually different. For instance, the emotion reactivity literature tends to focus on the change in an individuals' emotion reactivity over development. Here, it is argued that a more helpful way to view the same phenomenon would be to focus on the rise and changes in type-two emotion regulation (and its interaction with type-one emotion regulation) over development.

1.3. Two-System Neuroscience Framework of Fear (LeDoux & Pine, 2016)

LeDoux and Pine (2016) begin the journey of bridging the emotion-emotion regulation gap with their two-system neuroscience framework of fear. The framework provides evidence for the distinction and independence between the two threat systems. The first-system is thought to be primarily subcortical (e.g., sensory system, amygdala, bed nucleus of the stria terminalis, and striatum). The first-system leads to behavioral responses (i.e., the nucleus acumens facilitating escape and avoidance behaviors; Delgado, Jou, LeDoux, & Phelps, 2009; Schlund, Hudgins, Magee, & Dymond, 2013) and physiological changes in the brain and body – type-one, automatic, and non-effortful, termed defensive behaviors (i.e., DFN). LeDoux and Pine (2016) delineate specific neural correlates of the DFN, which gives rise to defensive behaviors and physiological changes. This first-system serves as the primary source of type-one emotion regulation, as the efficiency of the self-regulating lower-order process will determine if the combination of sensory input becomes a subjective conscious emotional state (see Figure 1.1).

The second system is posited to be an independent, higher-order cortical system that facilitates the subjective experience of emotion depending on the subcortical input (e.g., DFN). Specifically, LeDoux and Pine (2016) suggest that the GNC, which gives rise to perceptual (non-emotional) conscious experience (Craig, 2009; Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Frith & Dolan, 1996; Frifth, Perry, & Lumer, 1999; Lau & Passingham, 2006; Naccache, Blandin, & Dehaene, 2002; Rees & Frith, 2007), is not fundamentally different than the network that facilitates emotionally conscious experience. The key difference is in variation of the lower-order, subcortical input (e.g., autobiographical memory input, sensory systems, DFN). This dissertation aims to extend the reach of the GNC to emotion regulation (see Figure 1.1).

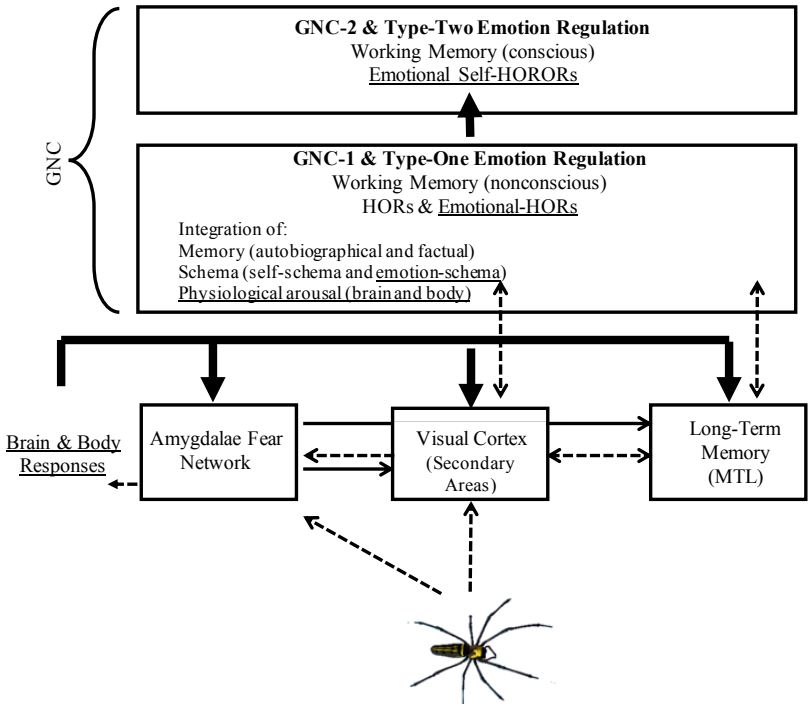


Figure 1.1. The two-system framework of emotion/emotion regulation. Note the difference between an emotional, non-emotional state of consciousness, as well as conscious (i.e., type-two) and unconscious (i.e., type-one) emotion regulation, is accounted for by the kinds of inputs processed by the GNC. Solid lines show network interactions that are especially important in emotional states. Underlined text indicates states/events that occur during emotional but not nonemotional experiences. See main text for additional details. Adapted from LeDoux and Brown's (2017) figure.

Evidence for the independence of the two-system (e.g., DFN and GNC) framework comes from a number of areas of research supporting the distinction between type-one (unconscious) and type-two (conscious) emotion regulation. While the first system (e.g., DFN) gives rise to type-one, unconscious defensive behaviors/physiological changes, the second system is needed to interpret this subcortical input to allow for the subjective experience of fear. Support for this notion is vast. For instance, those with amygdala damage do not demonstrate bodily reactions to threats but still report fear (Jack & Roepstorff, 2003; Metcalfe & Terrace, 2004; Morris, Öhman, & Dolan, 1999; Overgaard, 2003; Williams et al., 2006). While healthy

individuals demonstrate amygdala responses to threats (Hariri, Tessitore, Mattay, Fera, Weinberger, 2002; Morris et al., 1999), those with anxiety disorders demonstrate exaggerated amygdala activation (Mowrer, 1960; Panksep, Fuchs, & Iacobucci, 2011; Perusini & Fanselow, 2015). Moreover, fear and anxiety do not correlate well with physiological and behavioral measures (Jack & Shallice, 2001; Frith et al., 1999; Rosenthal, 1986). It has also been repeatedly demonstrated that subliminal threats elicit amygdala activity and trigger physiological and behavioral responses, but not feelings of fear (Baars & Franklin, 2003; Duhaene, 2014; Hariri et al., 2002; Jacobs & Silvanto, 2015; Kihlstrom, 1987; Morris et al., 1999; Overgaard & Sandberg, 2014). Finally, literature on patients with blind spots also support the two-system framework, where they exhibit amygdala activation to threat, defensive behaviors, and changes in physiology, despite not having conscious awareness of the threating stimuli (Lau & Passingham, 2006; Persaud et al., 2011). Collectively, these findings imply that the processing of threat information by the DFN is dissociable from the conscious awareness of threat, which requires a higher-order cortical interpretation (i.e., GNC). Importantly, it also suggests that conscious awareness of threats occur in the same higher-order structures that conscious awareness of non-emotional stimuli do, differing on subcortical input.

Neuroscience research on conscious experience has consistently provided evidence that the GNC is comprised of the pPL, IN, ACC, mOFC, lOFC, vlPFC, dlPFC, dmPFC, and vmPFC cortices (see Figures 1.1 & 1.2A; LeDoux & Pine, 2016). For instance, during subliminal or masking procedures, while areas of the visual cortex are activated, participants display activation in the aforementioned areas of the GNC only when they report the stimulus present (Craig, 2009; Craig, 2010; Dehaene, 2014; Dehaene et al., 2006; Frith et al., 1999; Frith & Dolan, 1996; Lau & Passingham, 2006; Naccache et al., 2002; Rees & Frith, 2007). Similar findings come from

blindsight patients, where the GNC is only activated when they report consciously seeing the stimulus (Lau & Passingham, 2006; Persaud et al., 2011). Moreover, The GNC involves regions associated with attention, working memory, and metacognition, providing theoretical support (see, Dehaene, 2014; Dehaene et al., 2006; Del Cul, Dehaene, Reyes, Bravo, Slachevsky, 2009; Fleming, Huijgen, & Dolan, 2012; Frith et al., 1999; Frith & Dolan, 1996; Goldman-Rakic, 1999; Lau & Passingham, 2006; Miller & Cohen, 2001; Naccache et al., 2002; Pascual-Leone & Walsh, 2001; Rees & Frith, 2007; Vuilleumier et al., 2008).

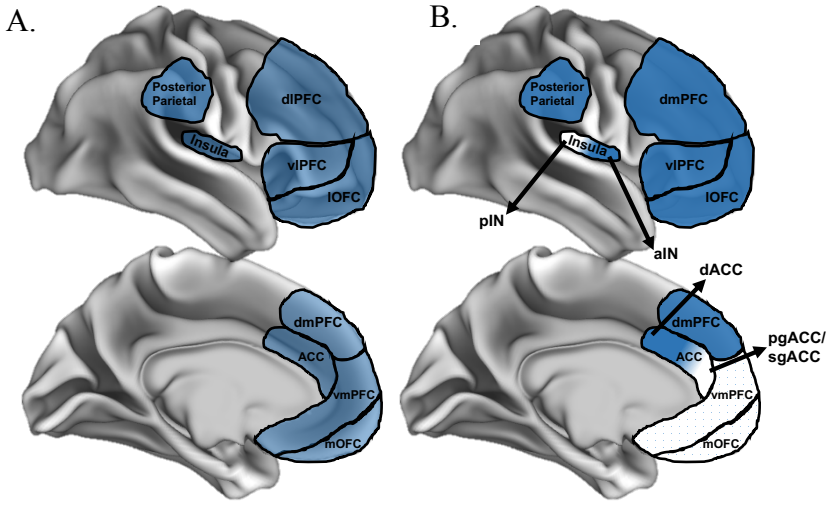


Figure 1.2. (A) The structures posited to comprise the GNC, as outlined by LedDoux and Pine (2015) and LeDoux and Brown (2016). (B) The same structures, some parcellated, to note which areas comprise the GNC-1 or type-one, unconscious, emotion regulation (white) and those that are part of the GNC-2 or type-two, conscious, emotion regulation (blue).

A dominant interpretation of these findings comes from the higher-order theory, which suggests that subjective experience arises from set circuitry, which supports thoughts about lower-order information (Cleeremans, Timmermans, & Pasquali, 2007; Cohen & Dennett, 2011; Dehaene et al., 2006). While attention, working memory, and their underlying circuits support consciousness, working memory can be engaged without generating conscious content (Brown,

2012; Carruthers, 2005; Firth & Dolan, 1996; Kouider, De Gardelle, Sackur, & Dupoux, 2010). Thus, an additional layer of cognitive representation, likely also involving the frontal cortex, is required beyond nonconscious representation in working memory (Cohen & Dennett, 2011).

1.4. Higher-Order Theory of Consciousness (LeDoux & Brown, 2017)

LeDoux and Brown's (2017) higher-order theory of emotional consciousness has its foundation in LeDoux and Pine's (2016) framework, importantly adopting the same terminology. It extends the two-system framework by incorporating psychological literature to posit a modified higher-order theory of emotional consciousness. They begin with agreeing that the underlying brain mechanisms that give rise to perceptual (non-emotional) consciousness are not fundamentally different than those that give rise to emotional consciousness. LeDoux and Brown (2017) go on to suggest that the subcortical regions that receive primary sensory signals from the body (Damasio, 1999), memory systems (Squire & Zola-Morgan, 1991), and the visual system (Van Essen, Anderson, & Felleman, 1992) are all involved in the first-order representations that indirectly influence higher-order assembly of conscious feelings by the GNC (see Figure 1.1). Thus, the subjective experience of fear, within this framework, is modulated by the DFN, along with the subcortical body sensing network, memory, and visual systems, but directly arises from other independent higher-order frontoparietal networks integrating the information (i.e., the GNC).

Directly in line with the central hypothesis, LeDoux and Brown (2017) delineate two GNCs: a first GNC is thought to integrate subcortical input outside of an individuals' conscious awareness, and a second GNC that receives this input and gives rise to the conscious experience of fear. No specific regions, nor networks, were posited to delineate the GNC-1 and GNC-2.

Identifying sub-networks, or circuits, that comprise the GNC-1 and GNC-2 will be central to the current framework of emotion regulation. First, however, the differences between these intertwined GNCs need to be reviewed.

LeDoux and Brown (2017) proposed that phenomenally conscious experiences result from lower-order representations that originate from the GNC-1. Specifically, the GNC-1 then creates a higher-order representation of the first-order representation outside of an individual's awareness, which can affect behavior (e.g., Siegel & Gallagher, 2015). The GNC-2 is then needed to incorporate information from lower-order systems and GNC-1, leading to a higher-order representation of the first nonconscious representation that is now. The integration of this information in GNC-2 allows for the emotional experience, and as argued here, emotion regulation, into an individuals' awareness.

LeDoux and colleagues (2016; 2017) argue that the GNC-1 serves as the basis for the higher-order representation of the first-order representation produced by the visual cortex with input from a number of subcortical regions (e.g., amygdala fear network). Actively attending to, and a deliberate focus on, one's emotional state (i.e., active introspection) requires an additional higher-order representation (i.e., a higher-order representation [active introspection] of the first higher-order representation [passive introspection], termed a higher-order representation of a higher-order representation; now occurring within the cortical structures of GNC-2). Furthermore, it was theorized that when the type-one, nonconscious higher-order representations (i.e., leading to defensive fear behaviors, e.g., increased arousal), along with the higher-order representation of the higher-order representation (i.e., being able to report fear if asked), occur within unconscious working memory and conscious working memory, respectively (Bor & Seth, 2012; Del Cul et al., 2009; Lau & Passingham, 2007; Soto & Silvanto, 2014).

Taken together, perceptual (non-emotional) and emotional consciousness both require the incorporation of higher-order representation of lower, subcortical information by the GNC-2; differences in consciousness (non-emotional and emotional) arise from the subcortical input and higher-order representations. For instance, when the first, type-one higher-order representation within the GNC-1 includes subcortical input about the self (e.g., through autobiographical knowledge), the GNC-2 a self-relevant higher-order representation manifests (i.e., one is able to report being afraid when asked). Finally, when the third higher-order representation (i.e., a higher order representation of two previous higher-order representations) are integrated in the GNC-2 and include subcortical input regarding schemas, autobiographical memory, input from the DFN, and sensory networks, a similar self-relevant conscious awareness of being afraid can occur (e.g., having the thought "I am feeling afraid right now").

1.5. Theoretical Hypotheses

Although broad structures are mentioned, a comprehensive review of the literature extending the theory of emotional consciousness to emotion regulation is sorely needed. The scaffolding nature of these parallel processes makes a unifying theory, pulling from psychological, neuroscience, and biological sciences, intuitive and potentially useful. In addition, As shown in Figure 1.2B, the theorized neural circuits or substructures which comprise GNC-2 (and GNC-1) are not fundamentally different than those involved in type-two (and type-one) emotion regulation. However, the regulatory strategy used will depend on the selective recruitment of higher-order, cortical substructures that comprise the GNC, as well as subcortical input.

A review of the functional literature (e.g., Silvers et al., 2015; 2016) supports the notion that the GNC-2 and type-two emotion regulation strategies heavily rely on the dlPFC, vlPFC, and dmPFC cortices, as well as the dACC, aIN, and portions of the OFC. When reviewing the literature, the GNC-1 and type-one emotion regulation are supported by the vmPFC, portions of the OFC, amygdala nuclei, and pIN. Extendedly, the proposed two-system framework of emotion regulation aims to provide evidence for specific structures and circuits within GNC that may be related to specific type-one and type-two emotion regulation strategies.

While, some have conceptualized emotion regulation as being on a continuum; from explicit, conscious, or effortful to implicit, unconscious, effortless, or automatic (Mauss, Bunge, & Gross, 2007), reviews of type-one and type-two emotion regulation support the extension of the two-system framework of fear/anxiety to type-one and type-two emotion regulation – hypothesized as distinct, but obviously interact (e.g., changing behavior and physiology can indirectly modulate the subjective states of fear because of the change in subcortical input; see Gyurak, Gross, & Etkin, 2011). For example, priming individuals with an emotional goal (e.g., stable, restrain) leads to reduced anger after an experimental provocation, despite being outside of participants awareness (Mauss, Cook, & Gross, 2007; Williams et al., 2006). These results indicate that nonconscious, type-one emotion regulation, such as goal direction, can aid one in controlling emotional states without effort or conscious awareness, which provides further evidence for their distinction.

People engage in numerous behaviors to regulate their emotions (Parkinson & Totterdell, 1999), where it could be argued that all the behaviors one engages are simply various efforts to regulate an emotional response. Emotion regulation can fall into four categories depending on the goal; to decrease negative emotions (Gross, Richards, & John, 2006), increase positive

emotions (Quoidbach, Berry, Hansenne, & Mikolajczak, 2010), increase negative emotions (Sutton, 1991), and to decrease positive emotions (Gruber, Mauss, & Tamir, 2011). For instance, one may suppress a laugh during a funeral (i.e., decrease positive emotions), think of a happy memory when missing a loved one (i.e., increase positive emotions), become angry to increase adrenaline before a sporting event (i.e., increase negative emotions), or inhibit a frown during a date (i.e., decrease positive emotions).

Although on a continuum and not categorical, conceptualizing emotion regulation as top-down and bottom-up processes can be useful in better understanding emotion and distinguishing the GNCs. Top-down processes are defined as being deliberate (i.e., type-two, effortful), slow, sequential, require working memory, but limited by capacity (Nigg, 2017). In contrast, bottom-up processes are automatic, stimulus-provoked, and have a quick onset (i.e., type-one, emotion reactivity), but are posited by some to not require working memory (Nigg, 2017). While top-down processes can activate or suppresses bottom-up responses (Avital-Cohen & Tsal, 2016), bottom-up regulation can alter behavior via priming, effecting top-down processes (Verbruggen, McAndrew, Weidemann, Stevens & McLaren, 2016).

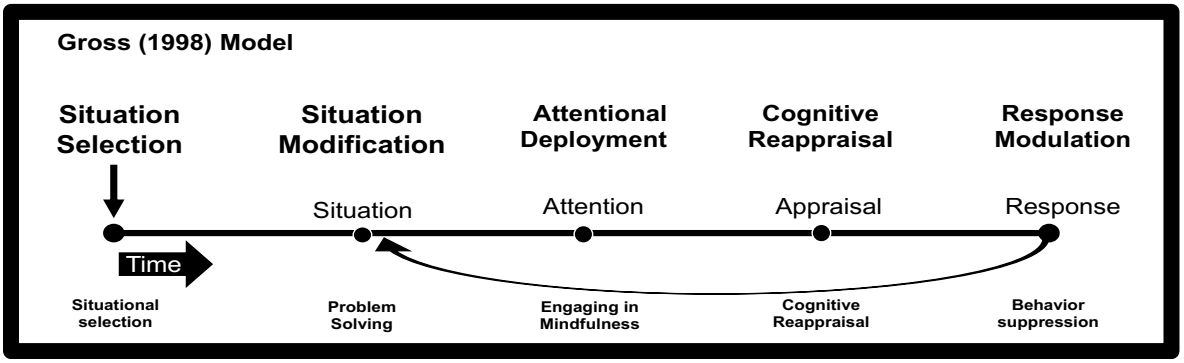
Importantly, cognitive reappraisal – the most commonly studied method of effortful (type-one) emotion regulation – is often split into studies of distancing and cognitive restructuring. A large problem in the field is that these methods are taken as being synonymous, when there are many reasons that this should not be the case. Unlike distancing, cognitive restructuring is central to cognitive-behavioral therapy, which is an empirically supported treatment for anxiety and depression (see Hollon & Ponniah, 2010). While distancing – another word for internal distraction or possibly avoidance – can reduce cognitive fixation (e.g., rumination) and alleviate subjective negative emotional experiencing during and directly after an

acute, distressing situation (Gerin et al., 2006) it can be maladaptive strategy in the long-term. For example, when participants were not allowed to ruminate (versus those that were allowed to ruminate), they demonstrated increased physiological responses to the stressor a week later (Glynn, Christenfeld, & Gerin, 2007). Overall, mentally processing the experience seems to confer some long-term benefits. In contrast, cognitive restructuring is thought to create schematic change (or changes in beliefs) that have been found to have long-term positive effects (see Clark 2013).

1.5.1. The Process Model (Gross, 1998)

The Process Model proposed by Gross (1998) is an information-processing model, where each step in the emotion-generative process is a potential point of regulation. Five points were identified that reflect families of emotion regulation processes: situation selection, situation, modification, attentional deployment, cognitive change, and response modulation (Gross & Thompson, 2007). The model is situated in time, where movement from left (situation selection) to right (response modulation) reflect movement through time within the emotion-generative cycle (see Figure 1.3).

A.



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B.

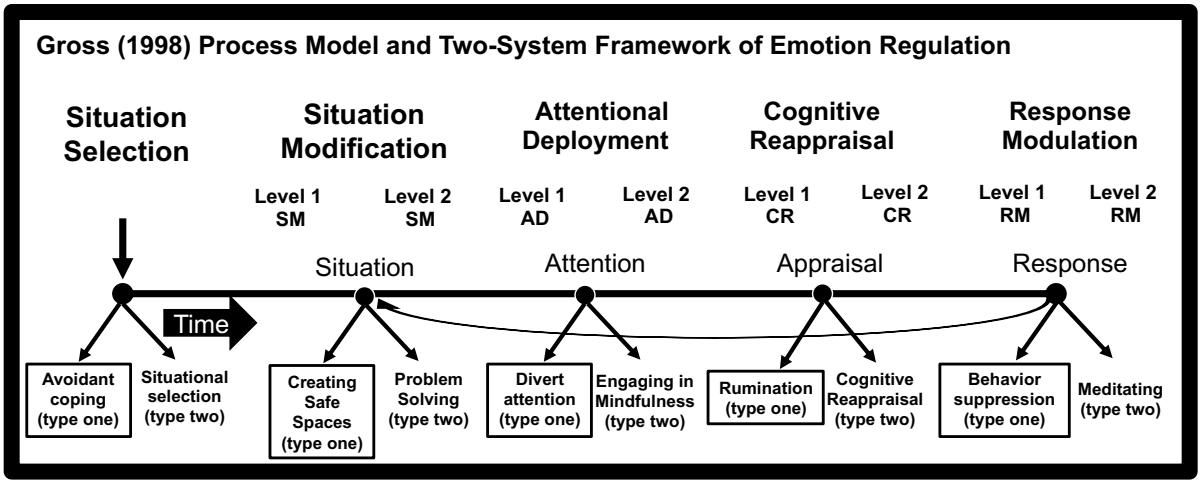


Figure 1.3. (A) Gross' (1998) Process Model specifying the four points of emotion regulation, with an example of emotion regulation processes at each stage. (B) Gross' (1998) Process Model and the complementary two-system framework of emotion regulation. All four stages, with eight substages, of emotion/emotion regulation are outlined, with an example of emotion regulation processes at each stage; processes in boxes represent type-one emotion regulation (i.e., unconscious, GNC-1) where emotion regulation strategies (i.e., type-two, GNC-2) are not boxed.

Briefly, situation selection, an individual can control the appraisal process before it ever begins by choosing a particular context to minimize the emotional burden. Situation modification entails attempts to directly change the situation to modify its emotional impact. The first two emotion regulation strategies modify appraisal inputs, thus controlling the cues available to generate specific emotions (Gross, 2001). An individual can divert their attention to environmental cues that promote desired emotions and/or ignore cues that promote negative emotions. Attentional deployment is important as it serves as a gate, allowing particular cues into the reappraisal process, while making others not possible. Cognitive change includes altering the meaning of a specific stimuli. Cognitive reappraisal, the most common form of cognitive change, includes changing beliefs about stimuli in an effort to decrease negative and/or increase positive emotions. Finally, response modulation only affects the behavioral output of the reappraisal

process. Therefore, response modification, such as behavioral suppression (e.g., hiding a grimace) or augment behavioral manifestations (e.g., slowly approach the stimulus).

Extending the process model to the higher-order theory of emotion regulation, all five points of the emotion regulation process could be regarded as type-one or type-two regulatory processes, depending on subcortical input (e.g., context) and higher-order connectivity (Gold, Morey, & McCarthy, 2015). For example, an individual may consciously choose not to go to the school dance due to fear or unconsciously avoid a particular stimulus ("I just don't want to go"), where both relate to subcortical and cortical activity within the same networks (i.e., DFN and GNC). By definition, cognitive change may be an exception, as this point typically refers to type-two emotion regulation strategies one can use in response to a current appraisal (i.e., the byproduct of type-one emotion regulation). However, some view that cognitive reappraisal can occur outside one's conscious awareness (e.g., Williams et al., 2006), as one does not consciously choose to be in denial or maybe to use humor in an uncomfortable situation, for example. The current two-system framework of emotion regulation emphasizes the difference between whether a particular emotion regulation strategy (of the five) is type-one or type-two. This vantage point will be shown to be advantageous and complementary to the Process Model, indicating the importance of a two-system framework of fear regulation (see Figure 1.3).

The Process Model also posits that different forms, or families, of emotion regulation have different consequences, as they are deployed at different stages of the emotion-generative process. Gross (2013) captures this idea with an illustration contrasting suppression (i.e., part of the response modulation family, in this case type-one) and reappraisal (i.e., part of the cognitive change family, in this case type-two). He notes that while both are commonly used to down-regulate emotions, only suppression is behaviorally oriented, where an individual attempt to

decrease emotion-related behaviors (e.g., altering your facial expression to not appear scared) while emotionally aroused. On the other hand, reappraisal is cognitively oriented, where an individual attempt to think about a situation to alter his/her emotional response, often termed cognitive restructuring (see Webb, Miles & Sheeran, 2012 for a review).

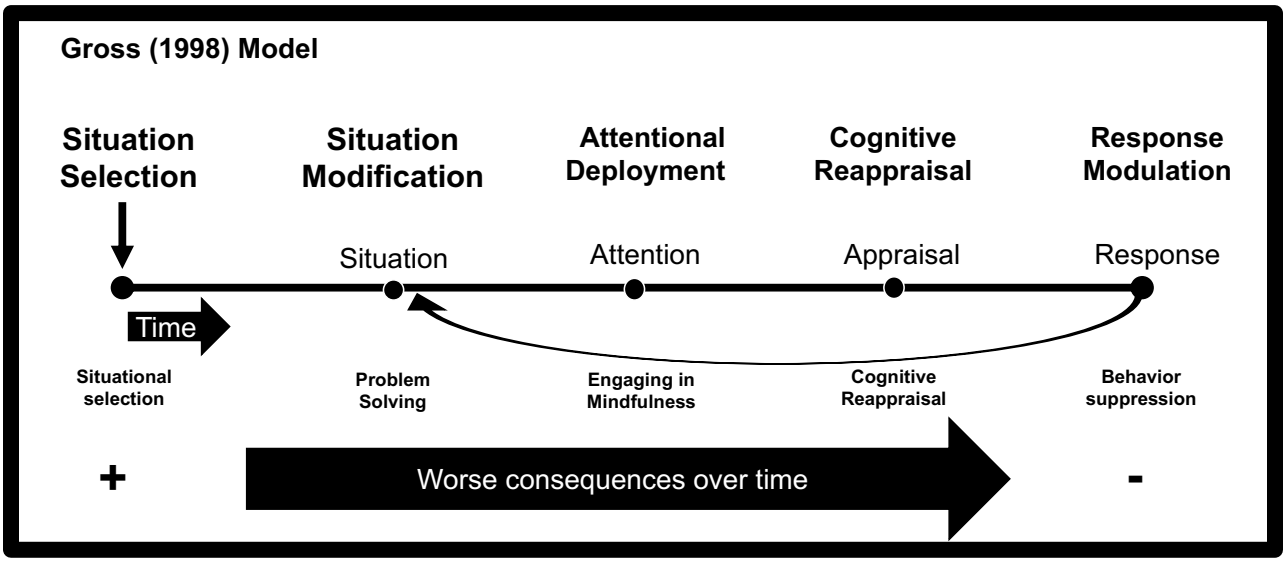
Gross (2013) continues the juxtaposition between suppression and reappraisal by noting affective, cognitive, and social differences the use of these two strategies can have. Suppression decreases positive, but not negative emotional experiences, increased physiological response, and greater activation in subcortical emotion-generative regions (e.g., amygdala). Conversely, cognitive reappraisal has been shown to decrease negative emotional experiences, increase positive emotional experiences, does not affect arousal, and leads to reduced activity in emotion-generative regions (e.g., amygdala; see Gross & Thompson, 2007). Where suppression leads to worse memory, reappraisal either has no effect or improves memory and performance (Jamieson, Mendes, Blackstock, & Schmader, 2010; Richards & Gross, 2000). Socially, suppression is less tolerated by partners and is associated with increased blood pressure, whereas reappraisal is not associated with adverse social consequences (Butler et al., 2003).

Aldao, Nolen-Hoeksema, and Schweizer (2010) provide further support for this notion in their meta-analysis of six emotion regulation strategies (i.e., acceptance, avoidance, problem solving, reappraisal, rumination, and suppression) and symptoms of four psychopathologies (i.e., anxiety, depression, eating, and substance-related disorders). They found large effect sizes for rumination, medium to large for avoidance, problem-solving, and suppression, and a small to medium effect size for reappraisal and acceptance. In addition, clinical versus normative samples significantly moderated these relationships. Given the prominence of reappraisal and acceptance in treatment models (e.g., cognitive-behavioral therapy), their findings were surprising. In all,

these results suggest that the presence of a maladaptive emotion regulation strategy is much more deleterious than the absence of an adaptive emotion regulation strategy.

As mentioned, adaptive and maladaptive emotion regulation strategies are often differentiated in the literature. For example, reappraisal, problem-solving, and acceptance are seen as adaptive (Gross, 1998; Gratz & Roemer, 2004). In contrast, maladaptive strategies are thought to underlie models of depression and anxiety (Beck & Clark, 1988), which led to cognitive-behavioral therapies focus on teaching reappraisal skills (Beck, Rush, Shaw & Emery, 1979). While adaptive emotion regulation strategies tend to be type-two, whereas maladaptive emotion regulation strategies are often type-one (do you choose to worry?), this is not always the case. For example, type-one (unconscious) reappraisal of goals is thought to be associated with positive outcomes (e.g., Williams et al., 2006) and type-two emotion regulation strategy of using humor is associated with poorer outcomes (Samson & Gross, 2012). Therefore, the two-system framework of emotion regulation explains this discrepancy (See Figure 1.4)

A.



(fig. cont'd.)

B.

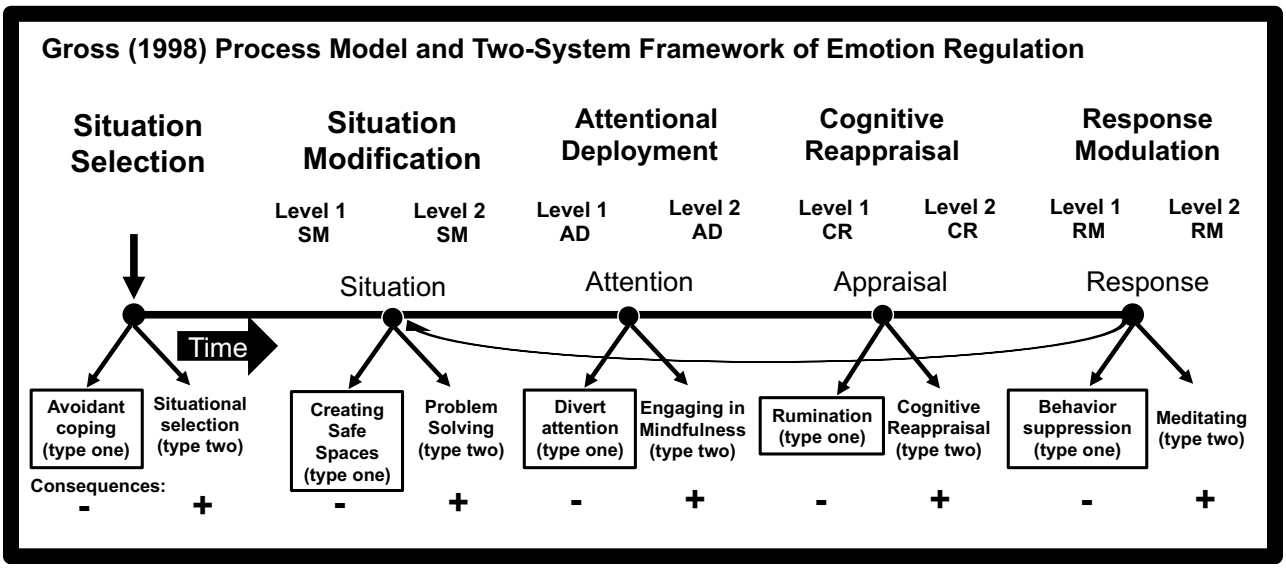


Figure 1.4. (A) Gross' (1998) Process Model specifying that it hypothesizes that emotion regulation strategies have worse consequences over time (or over the four stages of emotion regulation), with an example of emotion regulation processes at each stage. Gross' (1998) Process Model and the two-system framework of emotion regulation. All four stages and eight substages of emotion/emotion regulation are outlined, with an example of emotion regulation processes at each stage, and the typical consequences.

Problem-solving is a type-one, conscious (effortful) attempt to modulate a situation or consequences; typically involving specific actions directed at solving the problem. Evidence for problem-solving as an adaptive strategy comes from studies finding low problem-solving is associated with many internalizing disorders (e.g., Kant, D'Zurilla, & Maydeu-Olivares, 1997) and is a component taught during cognitive-behavioral therapy (e.g., Beck et al., 1979). Mindfulness is a regulation strategy that involves the non-judgmental acceptance of emotions (Bishop et al., 2004). Thus, it is conceptualized as a non-elaborative, non-judgmental, present-centered awareness and acceptance of thoughts, feelings, and sensations (Kabat-Zinn, 2003). High acceptance has been found to produce good outcomes (e.g., Hayes, Strosahl, & Wilson, 1999), where low-levels of acceptance have long been associated with various internalizing (e.g.,

McLaughlin, Mennin, & Farach, 2007) and personality disorders (Gratz, Rosenthal, Tull, & Lejuez, 2006).

Maladaptive regulation strategies such as suppression and avoidance are risk factors for anxiety, depression, and substance abuse (Carver et al., 1989; Folkman & Lazarus, 1980). While Gross' model (1998) emphasizes suppression of emotional expression; providing evidence of the long-term negative outcomes (e.g., increased physiological arousal; see Gross & Thompson, 2007; John & Gross, 2004). Others have focused on cognitive suppression (Wenzlaff & Wegner, 2000), providing substantial evidence that effortful suppression of thoughts increases their accessibility (Wegner & Erber, 1992; Wegner, Schneider, Carter, & White, 1987) and physiological arousal (Wegner, Broome, & Blumberg, 1997).

Historically, avoidance has been conceptualized in the behavioral domain. Mowrer (1947) posited the two-stage theory of fear, where 1) fear is learned through classical conditioning and 2) through (behavioral) avoidance extinction cannot occur, maintaining the fear response through operant conditioning. This model has been applied to post-traumatic stress disorder (Foa & Kozak, 1986), panic disorder (Barlow, Craske, Cerny, & Klosko, 1989), and specific phobia (Merckelbach, de Jong, Muris, & van den Hout, 1996). Experiential avoidance, in contrast, is the avoidance (or suppression) of thoughts, emotions, physiological responses, memories, and urges (Hayes et al., 1999). Hayes and colleagues proposed acceptance as the alternative to experiential avoidance, central to the treatment they developed, acceptance and commitment therapy (Hayes et al., 1999).

Instead of suppressing unwanted cognitions or emotions, some individuals repetitively focus on the cause of their negative emotions, and the undesirable outcomes (i.e., rumination; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Similarly, worry (i.e., a repetitive focus on an

anticipated adverse event in the future) is associated with a tendency to attempt to control and avoid negatively evaluated internal experiences (i.e., emotion regulation; Roemer, Salters, Raffa, & Orsillo, 2005) and with a tendency to react to emotional responses as if they are threatening (i.e., emotional reactivity; Roemer et al., 2005; Mennin et al., 2005). Worry is hypothesized to negatively reinforced by diminishing negative emotions and physiological arousal (Borkovec, Alcaine, & Behar, 2004; Borkovec & Hu, 1990; Wells & Papageorgiou, 1995), and a conditioned response activated by negative emotional states (Startup & Davey, 2001). Worry is thought to be Clinical and subclinical populations can be differentiated on their self-reported reason to worry, where the latter reports using this strategy to distract themselves from other negative topics.

Both rumination and worry facilitate the avoidance of emotional processing, leading to less adaptive functioning and increased distress. Individuals reporting chronic rumination and/or worry state they use the strategy to solve the problem at hand, despite both being negatively related to problems solving (Dugas, Letarte, Rhéaume, Freeston, & Ladouceur, 1995; Papageorgiou & Wells, 2003). For instance, worry has been found to be related to problem orientation (i.e., emotional reactivity; immediate cognitive-behavioral-affective reactions to problematic situations) but not to problem-solving skills (i.e., adaptive emotion regulation; creating goals, brain storming solutions, making decisions, and implementing the solutions; Dugas et al., 1995). Unsurprisingly, rumination also interferes with good problem solving and has been found to foster indecisiveness (Ward, Lyubomirsky, Sousa, & Nolen-Hoeksema, 2003).

Taken together, it is clear that not all emotion regulation strategies are equal. When viewing it from a two-system framework, it appears that positive outcomes are associated with an individual being aware of the emotion regulation occurring. This would suggest that strategies

typically viewed as maladaptive, such as rumination, are adaptive if one is aware they are occurring, which is exactly what is found (Glynn et al., 2007). This viewpoint fits nicely with the literature and what is observed clinically as well. The developmental process hinders children's ability to bring emotion regulation strategies within awareness (i.e., type-two), leaving them with nearly only type-one emotion regulation processes. Thus, explaining the difficulties of teaching cognitive restructuring or mindfulness to very young children, as well as their trouble reporting and managing their internal world (see Christophersen & VanScoyoc, 2013). While research has been able to delineate adaptive and maladaptive emotion regulation strategies, current evidence suggests a two-system framework. Emphasizing what strategies not to use (medium to large effect sizes) while teaching adaptive strategies (small to medium effect sizes) is certainly an avenue of future treatment research.

1.6. The General Network of Cognition and Emotion Regulation

Neuroimaging studies of these emotion regulation strategies (e.g., Otto, Misra, Prasad, & McRae 2014; Zilverstand, Parvaz, & Goldstein, 2017) map on to the GNC outlined by Ledoux and Brown (2017), where the various strategies differ only on lower-order, subcortical input. As seen in Figure 1.2A, they broadly implicate the pPL, IN, ACC, and a number of areas in the PFC (i.e., ventral-lateral, dorsal-lateral, orbital-lateral, orbital-medial, dorsal-medial, and ventral-medial cortices). In terms of functional neuroimaging, these same regions are involved in type-two emotion regulation strategies such as cognitive reappraisal (Zilverstand et al., 2017), active suppression (Goldin et al., 2008; Wyland, Kelley, Macrae, Gordon, & Heatherton, 2003), as well as type-one regulatory processes such as the initiation of defensive behaviors (e.g., Mogenson,

Jones, & Yim, 1980), rumination (Cooney, Joormann, Eugène Dennis, & Gotlib, 2010), and worry (Paulesu et al., 2010).

Further evidence comes from the structural (i.e., cortical thickness, subcortical volumes) differences (and overlap) found between self-reported anxious apprehension (largely mapping on to type-two emotion regulation strategies such as worry) and anxious arousal (capturing type-one defensive behaviors/changes in physiology). In line with structures comprising the GNC, anxious apprehension, but not anxious arousal, correlated with clusters in the dlPFC, dmPFC and vlPFC, whereas anxious arousal, but not anxious apprehension, produced clusters in the aIN and the amygdala (Castagna et al., 2017). Again, these findings are congruent with the two-system framework of fear/anxiety (LeDoux & Pine, 2016). Interestingly, a conjunction analysis revealed the importance of a number of frontoparietal regions with strong relationships to both systems (Castagna et al., 2017). The overlap among the GNC and regions involved in emotion regulation, broadly, is fairly evident; however, my aim is to extend LeDoux and Brown's (2017) distinction between GNC-1 and GNC-2.

Support for my hypothesis is first provided by a review of the literature on the function of neurocognitive structures thought to comprise the GNC. It is suspected that the literature will support neural circuits or substructures that map on to the GNC-2 (and GNC-1), and that they are not fundamentally different than those involved in type-two (and type-one) emotion regulation. Each structure posited by LeDoux and Pine (2016) will be reviewed to highlight their function in emotion regulation. Evidence of their role in perceptual consciousness (Craig, 2009; Dehaene, Changeux et al., 2006; Frith & Dolan, 1996; Frifth et al., 1999; Lau & Passingham, 2006; Naccache et al., 2002; Rees & Frith, 2007) and emotional consciousness (LeDoux & Brown, 2017; LeDoux & Pine, 2016) has been extensively reviewed elsewhere.

Each paragraph will pull from functional imaging studies and meta-analyses, where the literature generally supports the notion that the GNC-2 and type-two emotion regulation strategies heavily rely on the dlPFC), vlPFC, dmPFC cortices, as well as the dACC, aIN, and portions of the OFC. The GNC-1 and type-one emotion regulation, in contrast, appear to be supported by the vmPFC, portions of the OFC, amygdala nuclei, and pIN. See Figure 1.2B.

1.7. Neuroanatomy of Emotion and Emotion Regulation

1.7.1. Posterior Parietal Lobe (pPL)

When an individual is aware of a visual stimulus, PFC and pPL circuits are engaged; however, as awareness dissipates, the circuit is no longer recruited (Block, 2007; Rees & Frith, 2007; Lau & Rosenthal, 2011; Rosenthal, 2005), which has been extended to threat awareness (Baars & Franklin, 2003; Dehaene, 2014; Block, 2007; Jacobs & Silvanto, 2015; Kihlstrom, 1987; Morris et al., 2004; Overgaard et al., 2014). Functional imaging has consistently implicated the pPL, vlPFC, and superior temporal as regions involved in linguistic processing (Anderson & Phelps, 2002). These findings suggest that these regions are likely important in higher-order emotional consciousness (i.e., GNC-2) and regulation (i.e., type-two). Evidence supporting this claim comes from a meta-analysis where the pPL engagement was related to cognitive reappraisal (Zilverstand et al., 2017). Furthermore, Goldin et al. (2008), found pPL recruitment during two types of effortful (i.e., type two) emotion regulation strategies. Therefore, it is posited that the pPL predominantly coactivated with other regions of the GNC-2.

1.7.2. Insula (IN)

The IN is broadly associated with internal bodily sensations and interoceptive representations that can substantialize into conscious awareness of one's arousal (Craig, 2009). For instance, Critchley et al. (2004) found strong activity in the IN when participants were aware of their heart-beat, an interoceptive measure that correlates with individual subjective emotional awareness. A posterior-anterior IN cortex distinction is important, and likely explains why previous clinical literature has been, at times, equivocal. For instance, some find greater bilateral activation (along with the amygdala) to emotional faces in individuals' prone to anxiety (when compared to anxiety-normative controls; Stein et al., 2007). Within a sample of clinically anxious participants and healthy controls, the aIN, specifically, shows hyper-reactivity in response to fearful faces, which also involves reduced connectivity with the lPFC (implicated in type-two emotion regulation). A recent, comprehensive meta-analysis, however, did not find evidence for differences in IN activity between those with social anxiety disorder and healthy controls when viewing faces (Gentilli et al., 2016).

This discrepancy may stem from differential functions by the aIN and pIN. Interestingly, objective, unconscious representations of internal sensations are represented linearly in the dorsal pIN, but subjective (conscious) ratings of these interoceptive representations correlate with activation of the aIN and the adjacent OFC (Rolls, 2015; 2016). Moreover, the pIN has been implicated in heautoscopy (i.e., a dissociative experience of feeling as though one is in two bodies at once; Heydrich & Blanke, 2013). In contrast, the aIN is thought to receive input from the OFC and ACC (Price, 2006; 2007); the OFC and ACC decode and represent the reward and punishment-related signals that can produce autonomic (visceral) responses (Rolls, 2014; 2016). Activity in the aIN is often found in neuroimaging studies examining type-two emotion

regulation strategies (e.g., Goldin et al., 2008). Together, this suggests that the integration of interoceptive information may occur in a posterior-anterior pattern.

Four functional groups that comprise the IN shed light on its various functions. Kurth et al. (2010) identified sensorimotor, cognitive, social-emotional, and an olfacto-gustatory domain within the IN. They provided converging evidence for the current theory. The mid-posterior regions were found to be densely connected to primary and secondary sensory and motor areas. Therefore, it appears likely that the pIN is essential to the GNC-1, where it may integrate subcortical information from the DFN regarding behavioral and physiological arousal. In contrast, the anterior-dorsal regions have stronger connections with frontal regions (see Augustine, 1996), likely indicating its importance as a substructure of the GNC-2. Further evidence comes from literature demonstrating the robust relationship between the anterior-dorsal regions of the IN is part of the frontoparietal network, important in language processing, as well as working memory and attention tasks (Price, 2000). These processes directly overlap with type-two emotion regulation strategies such as cognitive reappraisal (i.e., language processing) and attentional deployment (i.e., attention).

Taken together, a modest hypothesis would be that the pIN provides input on internal sensations, outside of one's awareness (i.e., GNC-1) to the DFN (e.g., amygdala). In contrast, the aIN is posited to be important for emotional consciousness (GNC-2), as it provides input on arousal to higher-order cortical areas that give rise to emotional consciousness. (i.e., mPFC, aIN; see Cardinal et al., 2002).

1.7.3. Anterior Cingulate Cortex (ACC)

LeDoux and Pine (2017) specifically implicate the ACC as being central to the GNC. The ACC is known to play an important, albeit broad, role in higher-order appraisals and decision making (Bush et al., 1999; Mars et al., 2011). The function of the ACC directly maps on to type-two emotion regulation strategies such as cognitive reappraisal. The focus will be on specific substructures of the ACC, as various parcellations demonstrate different functions that relate to the GNC-1 and GNC-2.

Broadly, the ACC is a limbic structure correlated with pleasantness or unpleasantness of stimuli (Rolls, 2015). It receives strong input from the amygdala and OFC regarding value and outcome value representations. It has strong projections to the midcingulate cortex that facilitate action-outcome learning (Rolls, 2014). Some have suggested that the ACC mediates the orbitofrontal cortex representations of current and future value with behaviors (Rolls, 2015; 2014).

The ACC is typically parcellated by its ventral (i.e., pgACC and sgACC) and dorsal portions (i.e., dACC). (Etkin, Egner, & Kalisc, 2011; Vogt, Berger, & Derbyshire, 2003). Emotion-processing regions (e.g., amygdala, hypothalamus) have strong connectivity with the dACC and pgACC (Amaral et al., 1992; An et al., 1998; Beckmann et al., 2009; Chiba, Kayahara, & Nakano, 2001; Ghashghaei, Hilgetag, & Barbas, 2007; Rempel-Clower & Barbas). The dACC has the strongest connectivity with the premotor and lPFC (Bates & Goldman-Rakic, 1993; Beckman et al., 2005). Overall, the pgACC and portions of the sgACC interact with lower-order cortical structures (i.e., DFN) indicating that they likely are important structures in the GNC-1 and facilitate type-one emotion regulation. On the other hand, dACC communicates with dorsal and lateral regions of the PFC important in type-two, conscious emotion regulation. It

follows that the dACC would predominantly be involved in emotional consciousness (GNC-2) and type-two emotion regulation. For this to be correct, functional neuroimaging studies should find differences among the subregions of the ACC that map on to type-one (and GNC-1) and type-two (and GNC-2). Activity in the dACC, specifically, has been correlated with fear-conditioned skin conductance (Milad et al., 2007) and increased heart rate during social evaluation (Wager et al., 2009). Moreover, direct stimulation of the dACC creates the subjective state of fear (Meyer, McElhaney, Martin, & McGraw, 1973) – in line with the dACC being essential to the GNC-2.

Where the dACC is associated with imminent threats, the pgACC and sgACC typically activate during a distal threat, extinction, and recall of extinction (Etkins et al., 2011). Moreover, a meta-analysis found that the dACC, but not the pgACC or sgACC, is consistently recruited during type-two emotion regulation functional neuroimaging studies (Kalisch, 2009). Consistent with this view, the pgACC and sgACC (along with the mPFC) may mediate the dorsomedial and lPFC central to reappraisal. They may serve a similar function with the amygdala, as the amygdala has little to no connectivity with the lPFC (Amaral et al., 1992; Kalisch, 2009). Finally, type-one emotion regulation, which can be examined through distraction and emotion labeling tasks, activates the pgACC, sgACC, and mPFC (Delgado et al., 2008; Lieberman et al., 2007); hypothesized to reflect the structures' generic inhibition of negative emotional processing (i.e., GNC-1 or type-one emotion regulation) to the amygdala and can be recruited by higher-order regions of the GNC-2 (e.g., dACC or lPFC).

In a review of the literature, Kalisch and Gerlicher (2014) suggested similar division of the dACC but into rostral and posterior portions. The rdACC – not the pdACC, is associated with cognitive reappraisal, conscious worrying, and catastrophizing (i.e., type-two). Thus, the rdACC,

more specifically, may be related to type-two emotion (i.e., GNC-2) and type-two emotion regulation. Further evidence comes from functional connectivity studies, which indicate that the rdACC has reciprocal connections with the pdACC (i.e., physiological processing), the periaqueductal gray, the amygdala, and aIN (Chiba et al., 2001; Gashghaei et al., 2007; Grupe & Nitschke, 2013). Finally, with increased connectivity between the rdACC-amygdala positively correlates with individuals' trait anxiety, indicating that threat appraisal processes in the rdACC activates portions of the amygdala, alerting one to potentially threating stimuli (Etkin et al., 2011). Collectively, the literature supports the distinction between dACC and the ventral ACC (i.e., pgACC and sgACC), where the latter is an important component is central for type-two emotion regulation (and GNC-2), but the former facilitates processes primarily related to type-one (and GNC-1) emotion regulation.

1.7.4. Medial-Lateral Orbitofrontal Cortex (mOFC; lOFC)

It is unsurprising that the OFC has been implicated as being a part of the GNC (LeDoux & Pine, 2016), as it often associated with the integration of information vital for consciousness (see LeDoux & Brown, 2017). The OFC is often divided into mOFC and lOFC portions that have been shown to have differential functions and connectivity. Broadly, the OFC is involved in emotion, reward valuation, and reward-related decision making, where it projects its representations to the dACC for action-outcome learning (Rolls, 2015). The OFC has direct connections to the amygdala, and receives input from each sensory modality (e.g., visual, olfactory), providing "what" information (Rolls, 2015).

The mOFC has consistently been associated with taste, oral texture, olfaction stimuli, and subjective pleasantness (Grabenhorst, Rolls, & Bilderbeck, 2007; Kringelbach & Rolls, 2004;

Rolls, 2004; Rolls 2015; Rolls, Kringelbach, & De Araujo, 2003; Rolls, O'Doherty, Kringelbach, Francis, Bowtell, & McGlone, 2003). A meta-analysis (Kringelbach & Rolls, 2004) found that the mOFC is related to contextual evaluation of stimuli and updating the meaning of emotional stimuli as they change over time, which is essential to altering stimulus meaning during reappraisal. As well, during gambling tasks, the monetary reward value is presented in the mOFC, but the monetary outcome loss is presented in the lOFC (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). However, the OFC has been conceptualized as a convergence zone for afferents from limbic and association areas; therefore, evidence for the OFC contribution of the GNC-1/GNC-2 and relating to both type-one and type-two emotion regulation will be provided as well.

The lOFC activity is consistently related to the evaluation of punishers and future value of stimuli, which can lead to a change in ongoing behavior (De Araujo et al., 2003; Rolls, 2015). Activation of lOFC is noted when stimulus-reward mappings are changed (O'Doherty et al., 2003). This is consistent with neuroimaging studies showing activation of lOFC and related areas of vlPFC when participants are performing the Stroop task (Bench et al., 1993), providing responses opposite of what is cued (Paus et al., 1993), inhibiting an attentional shift (Nobre et al., 1999), inhibiting motor movement (Krams et al., 1998), changing entrenched responses (Taylor, Kornblum, Minoshima, Oliver, & Koeppe, 1994), and deductive and inductive reasoning (Goel et al., 1997).

The OFC, broadly, is associated with cognitive reappraisal (Banks et al., 2007; Goldin et al., 2008; Ochsner et a., 2004; Etkin et al., 2011). Specifically, the connectivity between the amygdala, OFC, and dmPFC seem to be essential to type-two emotion regulation, where the amygdala coupling with the OFC and dmPFC significantly predicts the attenuation of an

individual's self-reported negative affect following cognitive reappraisal (Banks et al., 2007). This has led some to speculate that the OFC may serve as a mediator between the lower-order DFN (e.g., amygdala) and the higher-order cortical structures (e.g., PFC).

In line with this notion, it has been posited that the OFC with the vmPFC are implicated in the integration of bodily signals that help decision making, termed the somatic marker hypothesis (see Dunn, Dalgleish, & Lawrence, 2006 for a critical review). For instance, the OFC receives information from a number of regions in the sensory cortex (e.g., Rolls, 2015). Moreover, the OFC has inputs from somatosensory cortex, inferior temporal cortex, temporal pole, and the visual association areas (Barbas, 1995; Morecraft, Geula, & Mesulam, 1992; Petrides & Pandya, 1988). The amygdala has direct projections that reach the OFC (Krettek & Price, 1977; Ray & Price, 1993). The OFC then provides input to the ACC, hypothalamus, ventral tegmental area and caudate nucleus inferior temporal and entorhinal cortices (Nauta, 1964; Kemp & Powell, 1970; Insausti, Amaral, & Cowan, 1987). The diverse pattern of connectivity suggests that the OFC may serve as a convergence region for afferents from both emotion and sensory regions. A wide-range of connectivity is also consistent with either a wide range of functions or an integrative role; therefore, it is likely to be important for both type-one (i.e., GNC-1) and type-two (i.e., GNC-2) emotion regulation.

1.7.5. Dorsomedial and Ventral Medial Prefrontal Cortex (dmPFC; vmPFC)

The mPFC is typically parsed into the dmPFC and vmPFC, which have been found to have differential functions. For instance, meta-analytic studies show reappraisal of negative stimuli typically recruit the lateral and dorsomedial PFC (e.g., Banks et al., 2007). Further, the inverse relationship between activation in the dmPFC, vlPFC, OFC, and dlPFC (but not vmPFC)

and reduced activity in the DFN (e.g., amygdala) is frequently considered an index of cognitive reappraisal (Banks et al., 2007; Buhle et al., 2014). Broadly, dmPFC is thought to moderate the significance of a stimuli (i.e., salience) through the regulation of attention to sensory input regions in the amygdala and hippocampus (Kolb, 1984) and by mediating amygdala input to the nucleus accumbens, facilitating motivation and learning (Jackson & Moghaddam, 2001). While dmPFC activation is consistently found during effortful emotion regulation (i.e., type-two), the vmPFC likely serves a more domain-general role, useful for a number of various goal-directed behaviors (see Nakamura-Palacios et al., 2016).

The inverse relationship between cortical-subcortical activity is consistent with a "top-down" model of emotion regulation that involves the dmPFC, along with domain-general cognitive control regions: dlPFC, vlPFC, and pPL (Buhle et al., 2014; Diekhof, Geier, Falkai, & Gruber, 2011; Kalisch 2009; Ochsner et al. 2012; Ochsner & Gross 2005, 2008; Schiller & Delgado 2010). Again, directly mapping on to structures hypothesized to comprise the GNC-2 and type-two emotion regulation. Interestingly, electrolytic lesions of the vmPFC (but not the dmPFC, vlPFC, nor IN cortex) interfere with type-one emotion regulation, such as freezing (Morgan, Romanski, & LeDoux, 1993; Morgan & LeDoux, 1995); evidence that the vmPFC is more likely important to type-one (i.e., GNC-1) emotion regulation.

The dmPFC is positively correlated with reappraisal (e.g., Buhle et al., 2014), associated with rule-based processing, and controls motor activity through its connections with the motor cortex, which, in turn, directs the execution of movement (Narayanan & Laubach, 2008). Using principal component analysis to examine the neurofunctional organization of regions implicated in reappraisal (Klumpp, Bhaumik, Kinney, & Fitzgerald, 2018), the dmPFC was found to have the most robust factor loading. Moreover, a meta-analytic study of psychotherapy in anxiety and

depression showed more controlled dmPFC activity following psychotherapy (Messina, Sambin, Palmieri, & Viviani, 2013; Messina, Sambin, Beschoner, & Viviani, 2016). Together, it appears that the dmPFC relates to emotional perceptual and emotional consciousness through its recruitment during rule-based processing and reappraisal (possibly respectively). Support converges for the dmPFC serving as a pivotal structure within the type-two emotion regulation circuit and GNC-2.

Broadly, the vmPFC has largely been implicated in decision making (e.g., Koob, 2013), fitting well with the necessity of this structure in both perceptual and emotional consciousness (see LeDoux & Pine, 2016). However, significant evidence has related the vmPFC to various aspects of emotion and emotion regulation, as activation is associated with behavioral rigidity (Killcross & Coutureau, 2003). Interestingly, broad mPFC lesions often lead to depressive-like behaviors, such as learned helplessness (Klein et al., 2010), but inactivation of the vmPFC is likened to an antidepressant response (Slattery, Neumann, & Cryan, 2011). The primarily efferent projections from the vmPFC are to the nucleus accumbens shell, but the dmPFC mainly projects to the nucleus accumbens core (Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). Notably, experiments have found that the dmPFC- nucleus accumbens core and vmPFC- nucleus accumbens shell pathways are essential to a) drug-seeking behavior and b) promotion/inhibition of those behaviors (depending on learning history), respectively (Bossert et al., 2012; LaLumiere & Kalivas, 2008; McFarland, Lapish, & Kalivas, 2003). By extension, the vmPFC has efferent projections (Peters, Kalivas, & Quirk, 2008), with evidence that this circuit is essential for the suppression of inappropriate behavior – possibly promoting or sustaining the extinction of unreinforced actions. vmPFC promotes actions through its primarily GABAergic projections to the phasically inhibited neurons of the nucleus accumbens (Riga et al., 2014). Kim

et al. (2011) provided evidence that fear extinction or acquisition, in large, is mediated by whether glutamatergic or GABAergic neurons are activated. The release of glutamatergic/GABAergic is triggered by the lateral nucleus of the amygdala, an area with robust connections with the nucleus accumbens shell. The vmPFC (limbic and infralimbic subdivisions) also receives input from the hippocampus and thalamic nuclei, critical in short- and long-term memory, contextual memory, and spatial navigation (Varela, Kumar, Yang, & Wilson, 2014).

Together with the strong connections between the vmPFC, lateral nucleus of the amygdala, and nucleus accumbens (Cardinal et al., 2002), it may be hypothesized that the vmPFC serves as a type-one, unconscious working memory hub, integrating information from many subcortical and cortical structures, modulating the acquisition, as well as extinction, of defensive fear behaviors. Ochsner et al. (2012) provide further support, as the vmPFC is described as integrating affective valuations of specific stimulus (e.g., DFN, ventral striatum). Specifically receiving input from the MTL, brainstem, and lPFC. Therefore, the vmPFC is hypothesized to primarily comprise the GNC-1 and be important for type-one emotion regulation, potentially influencing the particular emotion regulation strategy used. If this hypothesis is correct, one would suspect that the vmPFC would mediate emotion reappraisal, such notion has robust support (Motzkin, Phillippi, Wolf, Baskaya, & Koengs, 2015; Gold et al., 2015; Oschner et al., 2012).

1.7.6. Ventral Lateral and Dorsolateral Prefrontal Cortex (vlPFC; dlPFC)

Broadly, the lPFC has been most consistently associated with conscious awareness (Del Cul et al., 2009; Pascual-Leone & Walsh, 2001; Vuilleumier et al., 2008). It is unsurprising that it is likely essential for the GNC in facilitating both perceptual and emotional consciousness.

Therefore, both of these structures are thought to reflect type-two (and GNC-2) emotion regulation. The vlPFC has been consistently implicated with the selection/inhibition and maintenance of goal-relevant information (e.g., reappraisals; Blumfield, Lee, & D'Esposito, 2014; Buhle et al., 2014), verbal retrieval (Wolf, Vasic, & Walter, 2006), verbal fluency (Hanslmayr, Matuschek, & Fellner, 2014), and various other aspects of semantic retrieval (see Diamond & Levine, 2017).

Thus, the vlPFC, along with the dlPFC, have strong reciprocal connections with the hippocampus through the retrospenial and parahippocampus cortices (e.g., Goldman-Rakic et al., 1984). The vlPFC is consistently found to be activated during type-two emotion regulation, reappraisal (Wager et al., 2008) Specifically, the vlPFC is critical in top-down modulation of activity for the retrieval of specific features of information when familiarity and/or stimulus-stimulus relations are not sufficient for memory retrieval (Kostopoulos & Petrides, 2016). In contrast, evidence suggests that the dlPFC has long been implicated in storing, maintaining, and manipulating working memory representations (e.g., Goldman-Rakic, 1995). This would include appraisals, suggesting that the dlPFC may be more involved with episodic encoding than the vlPFC (Buhle et al., 2014; Diamond & Levine, 2017). The results consistently have indicated that patients with affective disorders tend to over recruit the dlPFC, when compared to controls (Campbell-Sills et al., 2011; Greening et al., 2013; Johnstone et al., 2007).

Four meta-analyses provide overwhelming evidence for the notion that the lPFC is critical for perceptual and emotional consciousness, and extendedly, type-two (and GNC-2) emotion regulation. Of 23 functional imaging studies of healthy participants engaging in cognitive reappraisal, results indicated that significant (bilateral) dlPFC, vlPFC, dACC, pPL, as well as the supplementary/premotor area activation (Kohn et al., 2014). Downregulation,

specifically, was found to correspond to activation in the dlPFC, dACC, and supplementary/premotor area activation in another meta-analysis of 44 functional imaging studies (Frank et al., 2014). Buhle et al. (2014) identified the same regions as Kohn et al. (2014), the dlPFC, vlPFC, dACC, supplementary/premotor area activation, and pPL as important in type-two emotion regulation. A final meta-analysis, which examined emotion regulation among clinical populations, consistently found that reduced recruitment of the vlPFC and dlPFC was related to impaired down-regulation of negative emotion, across clinical populations (Zilverstand et al., 2017). Not only do the four meta-analyses provide support for the role of the lPFC in type-two emotion regulation, they also provide substantial converging evidence for the first overarching hypothesis: regions involved in emotional consciousness are not fundamentally different than those that facilitate type-one and type-two emotion regulation.

Many researchers have suggested that the lPFC may be better organized along its rostral-caudal axis, where more rostral regions are involved in more complex, abstract, control functions (Badre & D'Esposito, 2007; Koechlin, Ody, & Kouneiher, 2003; Koechlin & Summerfield, 2007; Nee & Brown, 2012). Extendedly, the mid dlPFC has been associated with imposing higher-order constraints on more concrete processing in the vlPFC. Other research groups have suggested that the lPFC is involved in diverse types of cognitive demands, but lacks regional specificity (e.g., Crittenden & Duncan, 2012). Functionally, the vlPFC seems to be more generally associated with contextual rules and selection of task-relevant information. In contrast, the dlPFC seems to be more strongly related to working memory and resolving interference of task-irrelevant information (Muhl-Karbe et al., 2016). Put differently, the vlPFC may contribute to cue interpretation and task initiation, but the dlPFC processes task-specific information, allowing for adjustments in control to be made. Together, the vlPFC may be accurately viewed

as a central bottleneck between type-one (unconscious, bottom-up) and type-two (conscious, top-down) processing. Moreover, rostral regions of the dlPFC appear to be increasingly important for type-two, as it aids in the protecting task-goals from interfering stimuli (Muhl-Karbe et al., 2016). Therefore, it is surmised that the vlPFC and dlPFC appear to be structures central to GNC-2 and type-two emotion regulation.

1.8. Amygdala Connectivity and Emotion

More evidence of the two-system framework comes from examining the functional connectivity between lower- (i.e., GNC-1) and higher-order structures (i.e., GNC-2). Clearly, the amygdala does not operate in isolation, but it appears to serve as a junction within multiple neural networks (Pessoa, 2008). During resting state fMRI, the amygdala is functionally correlated with cortical brain regions such as the inferior frontal gyrus and superior frontal gyrus (Roy, et al. 2009). These results were corroborated by a recent meta-analysis of amygdala functional connectivity using meta-analytic connectivity modeling (Robinson, Laird, Glahn, Lovallo, & Fox, 2010).

Overall, amygdala-PFC connectivity has been found to play a critical role in emotion regulation (Wager et al., 2008), interpretation of emotionally ambiguous facial expressions (Kim, Somerville, Johnstone, Alexander, & Whalen, 2003), fear conditioning and extinction (LeDoux 2000; Morgan et al., 1993; Quirk, Likhtik, Pelletier, & Paré, 2003; Rosenkranz, Moore, & Grace, 2003), elevated trait anxiety (Kim & Whalen, 2009), and pathological anxiety (Hahn et al., 2011). Specifically, using resting-state fMRI, Hahn and colleagues (2011) found that individuals with social anxiety disorder had reduced functional connectivity between the amygdala and the mOFC. Similar results were found when relating amygdala and mOFC connectivity with anxiety

in a healthy sample (Kim, Gee, Loucks, Davis, & Whalen, 2010). As well, state anxiety levels in individuals with social anxiety was inversely correlated with the functional connectivity strength between the amygdala and the OFC. The latter provides credence for the view that amygdala-PFC circuitry plays a significant role in pathological, as well as trait, anxiety.

Structural connections (i.e., axonal connections) between the amygdala and parts of the cortex are also associated with emotional processing and anxiety. More recently, anxiety has been linked to a number of white matter tracts. Specifically, the UF has been found to be perturbed in individuals with social anxiety disorder, when compared to healthy controls (Phan et al., 2009). This finding extends to healthy individuals without a history of psychiatric disorders; where there is a negative correlation between UF volume and trait anxiety (Baur, Hänggi, & Jäncke, 2012). Moreover, these authors found that the volumes of the left UF and left amygdala were inversely associated. Overall, the UF has been posited to allow temporal lobe-based mnemonic associations to alter behavior through interactions with the lOFC, where the lateral OFC provides information on the valence of a decision (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). This view suggests that disruption of the UF may cause problems in the use of memory to guide behavior, as well as in the acquisition of certain types of learning and memory (e.g., fear learning).

Additionally, there is growing research on the association between the CG white matter tract and anxiety. The CG tract links within the limbic-cortical networks. The tract begins within the white matter of the temporal pole, extending to the posterior and superior parietal lobe, down to the corpus callosum, into the frontal lobe, ending in the anterior and inferior to the genu of the corpus callosum in the OFC (Schmahmann & Pandya, 2007). Therefore, damage to the CG bundle is likely to disrupt cognition and emotion regulation, increasing one's vulnerability for

the development of mood and anxiety disorders. Diagnostically, deficits in the CG tract have been linked to panic disorder (Han et al., 2008; Yu et al., 2013), posttraumatic stress disorder (Abe et al., 2006; Kim et al., 2006), and obsessive-compulsive disorder (Cannistraro et al., 2007; Chiu et al., 2011). Cognitively, CG integrity is associated with verbal memory (Delano-Wood et al., 2012), visual memory (Kantarci et al., 2011), executive functioning (e.g., inhibition; Metzler-Baddeley et al., 2012; Schermuly et al., 2010), and impairments that are also found in anxious samples (Bremner et al., 2004; Gilbertson et al., 2001; Vasterling et al., 1998; Vasterling et al., 2002; Yehuda et al., 1995). Relatedly, there is some evidence that CG tract integrity is likely to have a role in the development of anxiety symptoms, possibly via effects on fear-extinction processes (Fani et al., 2014).

1.9. Empirical Support

1.9.1. Testing the Two-System Framework

Given the two-system framework of emotion regulation, it is unsurprising that the literature on the relationship between amygdala volume and anxiety has been inconsistent (see De Bellis et al., 2000; Milham et al., 2005). This is partially attributed to the fact that amygdala volume is hypothesized to be a proxy for the GNC-1. Without the complementary second system (i.e., cortical GNC-2), only half a picture is painted. Importantly, amygdala volume during development has been found to significantly correlate with cortical thickness in the regions that comprise the GNC (Albaugh et al., 2013).

1.9.2. Current Study

The current study looks to build on previous literature by determining regions of cortical thickness that relate to amygdala volume in a sample of typically functioning youth (Albaugh et al., 2013), with the goal of delineating cortical regions implicated in emotion regulation (i.e., GNC-2), demonstrate this relationship is moderated by their structural connectivity, and link grey-matter thickness (i.e., regions that correlated amygdala volume) and subcortical (i.e., amygdala volume) and anxiety symptoms in youth. To this end, utilizing a publicly available database, the relationship between cortical thickness and right and left amygdala volume was examined utilizing general linear models. Next, diffusor tensor imaging was used to determine if white matter structural connectivity moderated the relationship between amygdala volume and correlated individual cortical thickness. Given the discrepant literature on the relationship between amygdala volume and anxiety, I suspected that PFC cortical thickness clusters may control for individual differences in emotion regulation. Therefore, in an exploratory nature, I then examined whether regions of cortical thickness (determined from the first analyses) indirectly effect the relationship between youths' amygdala volume and self-reported anxiety.

Given previous research on the effects of age on the correlation between cortical thickness and anxiety (Ducharme et al., 2014; Gee et al., 2013; Newman et al., 2016) and the well-established sex differences in anxiety prevalence (Cartwright-Hatton et al., 2006; Merikangas et al., 2010), the analyses will be controlled for the effects of age and sex. Furthermore, youth younger than 10 years of age will be excluded from analyses, given the literature on the positive to negative shift in connectivity between the amygdala and PFC that occurs during development (Gee et al., 2013).

1.10. Hypotheses

Hypothesis 1: amygdala volume in youth will be negatively correlated with regions involved in the top-down regulation of amygdala activity, such as the lPFC, lOFC, mOFC, aIN, rACC, and pPL.

Hypothesis 2: volumetric and fractional anisotropy differences in the UF and CG will moderate the relationship between the amygdala and correlated PFC regions.

Hypothesis 3: gray-matter thickness and amygdala volume will significantly relate to anxiety symptoms.

Exploratory Hypothesis: the relationship between amygdala volume and anxiety will be strengthened by the restriction of variance of cortical regions involved in top-down emotion regulation.

2. Methods

2.1. Subjects

The present study included a total of 34 typically developing youth (10-17 years; M_{age} = 13.9, *SD* = 2.21; 17 females, 17 males; see Table 4.1) from the Nathan Kline Institute Rockland Sample, which is provided by the Nathan Kline Institute (NY, USA) and publicly available at the International Neuroimaging Data-sharing Initiative online database. The Nathan Kline Institute institutional review board approved all procedures for collection and sharing of data. All subjects were administered the Wechsler Abbreviated Scale of Intelligence, a Full-Scale Intelligence Quotient over 80 (see Table 4.1). At the time of data acquisition from the Nathan Kline Institute Rockland Sample database, T1-weighted MRI scans were available for 46 children and adolescents. Four youth were excluded from the analyses because their MRI scan did not survive quality control inspection. Seven participants were excluded because of missing data (i.e., missing anxiety scores). One participant was excluded because they were younger than 10 years-old. Written informed consent and child assent was obtained from each participant. Further details regarding the image acquisition protocol is available on their website (http://fcon_1000.projects.nitrc.org/indi/pro/nki.html; Nooner et al., 2012).

2.2. Imaging Protocol

The following description of the imaging protocol is taken from Nathan Kline Institute source (http://fcon_1000.projects.nitrc.org/indi/enhanced/mri_protocol.html): "All subjects were scanned using a Siemens TrioTM 3.0 T MRI scanner. The 3D T1-weighted images were acquired using a magnetization-prepared rapid gradient echo sequence (repetition time/echo time = 2500/3.5 ms, inversion time = 1200 ms, field angle = 8°, field of view = 256 × 256 mm^2, voxel

size = 1.0 ×1.0 × 1.0 mm^3, number of slices = 192) and were used for spatial normalization and group-specific template generation. More details of the MRI protocol are available online (http://fcon_1000.projects.nitrc.org/indi/enhanced/ mri_protocol.html). Further phenotypic information may be accessed via the Nathan Kline Institute website (see http://fcon_1000.projects. nitrc.org/indi/enhanced)." In a subset of Nathan Kline Institute Rockland Sample, test-retest (< 1 month apart) and longitudinal scans (1.22 ± 0.29 years apart) demonstrated high reliability for the prediction models obtained and the ability to detect subtle differences in the longitudinal scan interval among participants (Zhao, Klein, Castellanos, & Milham, 2019).

Recently developed multiband echo planar Imaging (Moeller et al., 2010) and multiplexed echo planar imaging (Feinberg et al., 2010) approaches enable the acquisition of functional MRI and diffusion imaging data with unprecedented sampling rates for full-brain coverage through the acquisition of multiple slices simultaneously in the same time it takes to obtain a single slice image using standard echo planar imaging (see Smith et al., 2012) for initial application of multiband echo planar imaging with recent improvements (Xu et al., 2012). The Center for Magnetic Resonance Research has provided the Nathan Kline Institute effort with the latest version of the multiband echo planar imaging sequence (Xu et al., 2012) and associated image reconstruction algorithms, enabling the acquisition of state-of-the-art imaging datasets for this large-scale imaging effort. Specific parameter selections were based on initial pilot data to optimize image quality on the scanner.

The diffusion tensor imaging data were acquired using a 64-direction diffusion tensor imaging sequence implemented using generalized autocalibrating partial parallel acquisition, factor=3. A total of 76 diffusion-weighted images were acquired (axial slices = 58; repetition

time=10ms, echo time=91ms; field of view=256 mm; b-value=1000 s/mm^2; in-plane resolution = 2x2 mm^2; slice thickness=2 mm; no inter-slice gap). The acquisition time for this protocol was 13.5 minutes.

2.3. Cortical Reconstruction and Calculation of Thickness

Cortical thickness was estimated from the structural magnetic resonance images using FreeSurfer software (http://surfer. nmr.mgh.harvard.edu, Dale et al. 1999), a set of automated tools for the reconstruction of brain cortical surface (Fischl & Dale 2000). First, I used the T1-weighted images to segment cerebral white matter and to estimate the grey-white matter interface. Then topographical defects in the grey-white estimate were fixed. This grey-white matter estimate was used as the starting point of a deformable surface algorithm searching for the pial surface. The whole cortex of each individual subject was visually inspected for inaccuracies in segmentation and manually corrected if necessary. Local cortical thickness was measured based on the difference between the position of equivalent vertices in the pial and grey-white matter surfaces. The surface of the grey-white matter border was inflated and differences between subjects in the depth of gyri and sulci were normalized. Each subject's reconstructed brain was morphed and registered to an average spherical surface. In order to obtain cortical thickness difference maps the data were smoothed on the surface using a Gaussian smoothing kernel with a full-width half maximum of 10 mm. Statistical thickness difference maps were constructed using t-statistics. I used a regression approach to focus on the relationship between amygdala volume and cortical thickness, controlling for age and sex, using general linear modeling (www.surfer.nmr.mgh.harvard.edu). Only regions that survived a Monte Carlo correction ($p < 0.05$) are shown.

2.4. Tract-of-Interest Analyses

Diffusion-weighted data were processed for each participant using FreeSurfer's TRACULA (Yendiki 2011), which makes use of FSL's FMRIB's Diffusion Toolbox software for some of the preprocessing of the diffusion-weighted image. TRACULA is an automated method for reconstructing probabilistic distributions of major white-matter tracts for individual diffusion-weighted image data based on anatomical priors. It relies on an atlas of manually labeled major white matter tracts and anatomical segmentations from an independent sample of participants' data. TRACULA is able to construct 18 different major fiber tracts by using these anatomical priors in a probabilistic framework to perform tractography in novel individuals. I selected two *a priori* tracts-of-interest: The UF and CG.

TRACULA performs three processing steps. First, data is preprocessed with ball-and-stick model fitting to the diffusion-weighted image data, and tract reconstruction (Behrens et al., 2007). Preprocessing of the diffusion-weighted images included eddy current and motion correction using FMRIB's Diffusion Toolbox, intra-subject registration of diffusion-weighted images to T1 using FreeSurfer's bbregister, inter-subject registration of individual T1 images to the MNI template, the generation of white-matter and cortex masks from the FreeSurfer outputs and whole-brain masks from the diffusion-weighted and T1 images, tensor fitting using FMRIB's Diffusion Toolbox's DTIFIT, and the generation of anatomical priors for the white-matter tracts from the training data and the individual subject data. After preprocessing ball-and-stick model fitting was performed using FMRIB's Diffusion Toolbox's BEDPOSTX, which establishes a distribution of diffusion parameters at each voxel to allow for probabilistic tractography. Finally, tract reconstruction is performed by combining the anatomical priors with individual diffusion orientations and anatomical segmentations in each participant's native diffusion-weighted image

space. After reconstruction, mean functional anisotropy (i.e., a measure of white-matter integrity derived from the ration of radial and axial diffusivity) was extracted from each tract. All participants demonstrated successful tracking of both tracts-of-interest.

The UF and CG were selected a priori as they connect the limbic system to various aspects of the PFC cortex. Both regions also have an established relationship with anxious symptoms. I sought to determine if their functional anisotropy (i.e., a measure sensitive to several tissue characteristics such as myelination, axon diameter, fiber density, fiber organization) and/or their volume moderates the relationship between the amygdala volume and cortical thickness, which I would predict if the any grey-matter relationship between amygdala and frontoparietal regions were due to connectivity. Only ipsilateral analyses were examined (i.e., right amygdala to right cortical thickness; left amygdala to left cortical thickness), using the right UF/CG FA/volume and left UF/CG FA/volume, respectively.

2.5. Measures

The MASC (March, 1998) is a 45-item self-report questionnaire for symptoms of anxiety in youth. Total scores range from 0 to 120, with high scores indicating greater childhood anxiety. The four empirically derived factor index scores are Social Anxiety, Separation Anxiety, Harm Avoidance, and Physical Symptoms. The MASC has shown good internal consistency ratings from .70 to .83 and Cronbach's alpha ranging from .74 to .85 (March, 1998). Further, the MASC has demonstrated good convergent validity (Baldwin & Dadds, 2007), good concurrent validity (Rynn et al., 2006), adequate divergent validity, and good test-retest reliability (March, Parker, Sullivan, Stallings, & Conners, 1997). The total *t*-score of the MASC was used, which demonstrated high internal consistency ($\alpha = .87$).

3. Analytic Plan

3.1. Statistical Analyses

My first hypothesis was tested vertex wise across the brain surface by fitting GLMs of the effect of amygdala volume (corrected for total intracranial volume) on thickness in every vertex across the surface. Thus, I performed separate analyses for right and left amygdala to determine their independent relationships with cortical thickness across youth. Multiple linear regressions included the main effects and interactions between individual mean tract volume/tract functional anisotropy (respectively) and amygdala volume in an effort to predict cortical thickness clusters. Finally, Pearson's correlations were used to determine if cortical and subcortical grey-matter volumes would significantly correlate with self-reported anxiety.

As previously mentioned, because age is negatively associated with cortical thickness (Gee et al., 2013; Fjell et al., 2009; Salat et al., 2004; Westlye et al., 2009) and girls tend to have elevated levels of anxiety compared to boys (Kessler et al., 2012), I included age and sex as covariates in all statistical models. To reduce the probability of Type I errors, all cortical thickness analyses were corrected for multiple comparisons using cluster size inference by means of Z MCS as implemented in FreeSurfer (Hayasaka & Nichols, 2003; Hagler et al., 2006). All clusters were tested against an empirical null distribution of maximum cluster size built using synthesized Z-distributed data across 10,000 permutations. These analyses yielded clusters fully corrected for multiple comparisons across the surface. The initial cluster-forming threshold employed will be $p < 0.05$. Surface-based t-statistics for each corrected cluster, representing raw effect-sizes across the brain, will also be presented ($p < 0.05$). I also present surface-based t-statistics for each corrected cluster, representing raw effect-sizes across the brain.

In sum, I first determined the independent associations between right/left amygdala volume (corrected for total intracranial volume) and cortical thickness in youth (respectively). Following, I completed an interaction analysis to determine whether white matter structural connectivity moderates the relationship between the amygdala volume and correlated cortical regions. Next, the relationship between cortical/subcortical grey matter and anxiety symptoms was explored. Finally, I explored whether PFC cortical thickness clusters have an indirect effect on the relationship between youths' amygdala volume and youth's self-reported anxiety.

4. Results

4.1. Demographics

Youths' demographic, psychometric, and neurocognitive data are reported in Table 4.1. All subjects had a Full-Scale Intelligence Quotient over 80 (see mean and minimum/maximum values in Table 4.1 using the Wechsler Abbreviated Scale of Intelligence, second edition). At the time of data acquisition from the Nathan Kline Institute Rockland Sample database, T1-weighted MRI scans were available for 46 children and adolescents. Four youth were excluded from the analysis because their MRI scan did not survive quality control inspection. Seven participants were excluded because of missing MASC scores. One participant was excluded because they were younger than 10 years-old. Thus, the final sample, on which the analyses were performed, included 34 youth.

Table 4.1. Demographics and psychometric scales.

Demographics (n = 34)	N (%) or mean ±SD (range)
Males	17 (50.0%)
Age (years)	13.91±2.21 (10-17)
Right Handedness	30 (88.2%)
Race	
White	24 (70.6%)
Black	6 (17.6%)
Asian	4 (11.8%)
Ethnicity-Non-Hispanic/Spanish	24 (70.6%)
Psychometric Scales (n = 34)	
MASC-Total T-Score	46.19±9.15 (26-68)
WASI-FSIQ	108.82±12.05 (83-129)

4.2. Amygdala Volume and Cortical Thickness: Ipsilateral Analyses

Figure 4.1 shows MCS corrected maps from a GLM testing the relationship between amygdala volume and ipsilateral cortical thickness in a cluster-wise manner, corrected to $p < .05$. Full results can be found in Table 4.2, which shows significant zMCS corrected clusters resulting from a significant relationship between amygdala volume and ipsilateral cortical thickness with age and sex as covariates. All clusters showed a negative effect, consistent with previous literature (e.g., Ducharme et al., 2014).

Table 4.2. Ipsilateral relationships between cortical thickness and right/left amygdala. Note. Z-value based on voxel of peak effect size; *p*-value calculated from the Z-value; Cluster size is mm^2.

Variable/Location	L/R	X	Y	Z	Cluster Size	Z-value	*p*
Right Amygdala							
Negative Effects							
RMF; vlPFC	R	27.6	56.1	-11.0	4896.21	-4.725	<.0001
SPL	R	10.3	-49.5	69.4	2119.75	-4.501	<.0001
SFG; dPFC	R	21.5	6.2	57.5	1315.67	-3.093	<.0001
Cuneus	R	19.4	-66.2	13.8	3733.19	-2.658	<.01
Left Amygdala							
Negative Effects							
lOFC; vlPFC; rACC	L	-12.2	53.8	-17.5	4409.42	-6.475	<.0001

4.2.1. Right Amygdala Volume and Right Hemisphere Cortical Thickness

Most notably, in the right hemisphere, significant clusters were observed in the RMF extending down to the vlPFC and parts of the lOFC ($p < .0001$). In addition, a significant cluster was observed in the SFG and dPFC ($p < .0001$) and in the SPL ($p < 0001$).

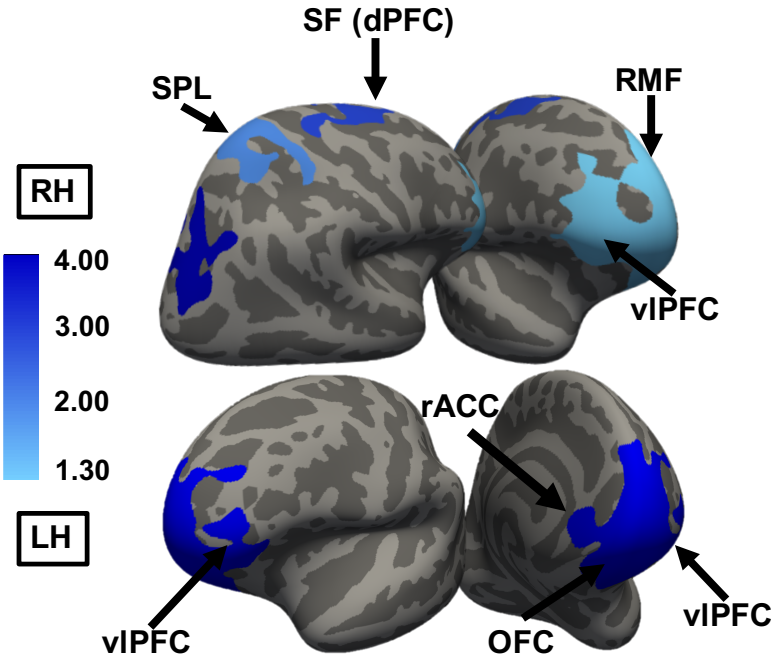


Figure 4.1. Ipsilateral relationships between cortical thickness and right/left amygdala. The light blue-dark blue scale represents the effect-size in Freesurfer's -log10(*p*) format.

4.2.2. Left Amygdala Volume and Left Hemisphere Cortical Thickness

The relationship between left amygdala volume and cortical thickness in the left hemisphere indicated one larger, robust cluster in the LOFC extending into the vlPFC and back into the rACC ($z = 6.475$; $p < .00001$).

4.3. Amygdala Volume and Cortical Thickness: Contralateral Analyses

Figure 4.2 shows MCS corrected maps from a GLM testing the relationship between amygdala volume and contralateral cortical thickness in a cluster-wise manner, correct to $p < .05$. Full results can be found in Table 4.3.

Table 4.3. Contralateral relationships between cortical thickness and right/left amygdala. Note. Z-value based on voxel of peak effect size; *p*-value calculated from the Z-value; Cluster size is mm^2

Variable/Location	L/R	X	Y	Z	Cluster Size	Z-value	*p*
Right Amygdala							
Negative Effects							
RMF; vlPFC; dlPFC	L	-36.9	28.7	32.7	8121.95	-4.062	<.0001
PCL	L	-15.6	-42.3	65.1	2865.01	-3.969	<.0001
FG	L	-28.9	-46.6	-18.6	4014.20	-3.934	<.0001
SFG; dmPFC	L	-7.0	26.2	45.9	1890.96	-3.259	<.001
PCS /Post-CG	L	-20.3	-70.9	19.2	3479.10	-2.977	<.01
Pre-CG	L	-57.1	-3.6	15.2	1307.37	-2.265	<.01
MTG	L	-62.1	-41.8	-6.2	1181.93	-2.245	<.01
Left Amygdala							
Negative Effects							
RMF; vlPFC	R	28.5	54.9	-10.9	4027.26	-4.795	<.0001
SPL 1	R	11.0	-51.5	67.5	1624.84	-3.427	<.001
SPL 2	R	18.0	-86.1	22.2	1277.79	-2.277	<.01

4.3.1. Right Amygdala Volume and Left Hemisphere Cortical Thickness

There were seven significant clusters observed. Most notably, there was a large cluster detected in the RMF extending down to the vlPFC, parts of the lOFC, and over to the superior and MTG ($p < .0001$). Additionally, a significant cluster was observed in the SFG and dmPFC ($p < .0001$) and in the SPL ($p < .0001$).

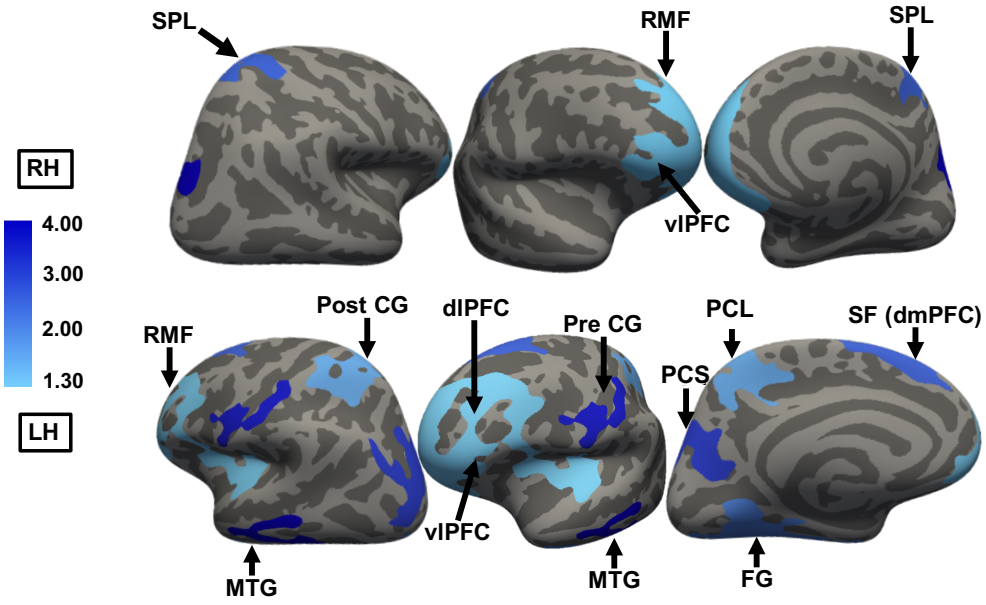


Figure 4.2. Contralateral relationships between cortical thickness and right/left amygdala. The light blue-dark blue scale represents the effect-size in Freesurfer's -log10(p) format.

4.3.2. Left Amygdala Volume and Right Hemisphere Cortical Thickness

The relationship between left amygdala volume and cortical thickness in the right hemisphere had three significant clusters. The largest and most robust cluster was located in the RMF extending down to the vlPFC and over into the vmPFC ($p < .0001$). An additional two clusters were observed in the SPL ($p < .01$).

4.4. Interaction Between Amygdala and Functional Connectivity

Multiple regressions were used to test the hypotheses that the ipsilateral relationships between amygdala volume and cortical thickness were moderated by UF and/or CG volume and fractional anisotropy with age and sex as covariates. Figure 4.3 demonstrate the significant interaction effect, all of which were found utilizing tract volume.

4.4.1. Right Amygdala Volume by Right UF Volume Predicting Ipsilateral Cortical Thickness

Results indicated that the volume of the right UF tract significantly moderated the relationship between right amygdala volume and cortical thickness in the right SPL. In the model with right amygdala volume and right UF volume as predictors of right SPL cortical thickness, only right amygdala volume ($\beta = -.630$, $t(31) = -4.493$, $p > .001$) significantly predicted right SPL cortical thickness, $F(3, 29) = 9.228$, $p < .001$; Adjusted $R^2 = .488$. The addition of the interaction of right amygdala volume and right UF volume was statistically significant ($\beta = -.303$, $t(31) = -1.987$, $p = .05$).

Right UF volume significantly moderated the relationship between right amygdala volume and cortical thickness in the right cuneus. In the model with right amygdala volume and right UF volume as predictors of right cuneus thickness, right amygdala volume ($\beta = -.498$, $t(31) = -3.66$, $p = .001$) and right UF volume ($\beta = -.371$, $t(31) = -2.481$, $p < .05$) significantly predicted cuneus thickness, $F(3, 29) = 10.463$, $p < .00001$; Adjusted $R^2 = .469$. The addition of the interaction of right amygdala volume and right UF volume was also statistically significant ($\beta = -.542$, $t(31) = -3.662$, $p = .001$).

The relationship between right amygdala volume and cortical thickness in the right RMF/vlPFC was only trending towards significance ($\beta = -.266$, $t(31) = -1.743$, $p = .092$), with only right amygdala volume ($\beta = -.676$, $t(31) = -4.669$, $p < .001$) and right UF volume ($\beta = -.314$, $t(31) = -2.013$, $p = .05$) significantly predicting right RMF/vlPFC cortical thickness, $F(3, 29) = 9.239$, $p < .001$; Adjusted $R^2 = .436$.

In the model with right amygdala volume and right UF volume predicting right SFG/dPFC cortical thickness, only right amygdala volume was significant ($\beta = -.531$, $t(31) = -3256$, $p < .01$).

4.4.2. Right Amygdala Volume by Right CG Volume Predicting Ipsilateral Cortical Thickness

The volume of the right CG significantly moderated the relationship between right amygdala volume and right RMF/vlPFC cortical thickness. In the model with right amygdala volume and right CG volume as predictors of right RMF/vlPFC thickness, right amygdala volume ($\beta = -.807$, $t(31) = -6.752$, $p < .00001$) and right CG volume ($\beta = -.463$, $t(31) = -3.829$, $p < .001$) significantly predicted right RMF/vlPFC thickness, $F(3, 29) = 16.895$, $p < .00001$; Adjusted $R^2 = .598$. The addition of the interaction of right amygdala volume and right CG volume was statistically significant ($\beta = -.322$, $t(31) = -2.798$, $p < .01$).

The remaining models testing the hypotheses that the relationship between right amygdala volume and the remaining three right hemisphere cortical thickness clusters (i.e., SPL, SFG/dPFC, and cuneus) would be moderated by CG volume were not significant.

4.4.3. Left Amygdala Volume by Left UF Volume Predicting Ipsilateral Cortical Thickness

The left UF volume significantly moderates the relationship between left amygdala volume and left lOFC/vlPFC cortical thickness. In the model with left amygdala volume and left UF volume as predictors of left lOFC/vlPFC cortical thickness, only left amygdala volume ($\beta = -.692$, $t(31) = -5.344$, $p < .0001$) significantly predicted left lOFC/vlPFC thickness, $F(3, 29) = 11.361$, $p < .00001$; Adjusted $R^2 = .493$. The addition of the interaction of left amygdala volume and left UF volume was statistically significant ($\beta = -.343$, $t(31) = -2.444$, $p < .05$).

4.4.4. Left Amygdala Volume by Left CG Volume Predicting Ipsilateral Cortical Thickness

The volume of the left CG tract significantly moderated the relationship between left amygdala volume and left lOFC/vlPFC cortical thickness. In the model with left amygdala volume and left

CG volume as predictors of left lOFC/vlPFC cortical thickness, only left amygdala volume (β = -.739, t(31) = -5.564, $p < .0001$) significantly predicted left lOFC/vlPFC thickness, F(3, 29) = 10.856, $p < .00001$; Adjusted $R^2 = .480$. The addition of the interaction of left amygdala volume and left CG volume was statistically significant (β = -.299, t(31) = -2.256, $p < .05$).

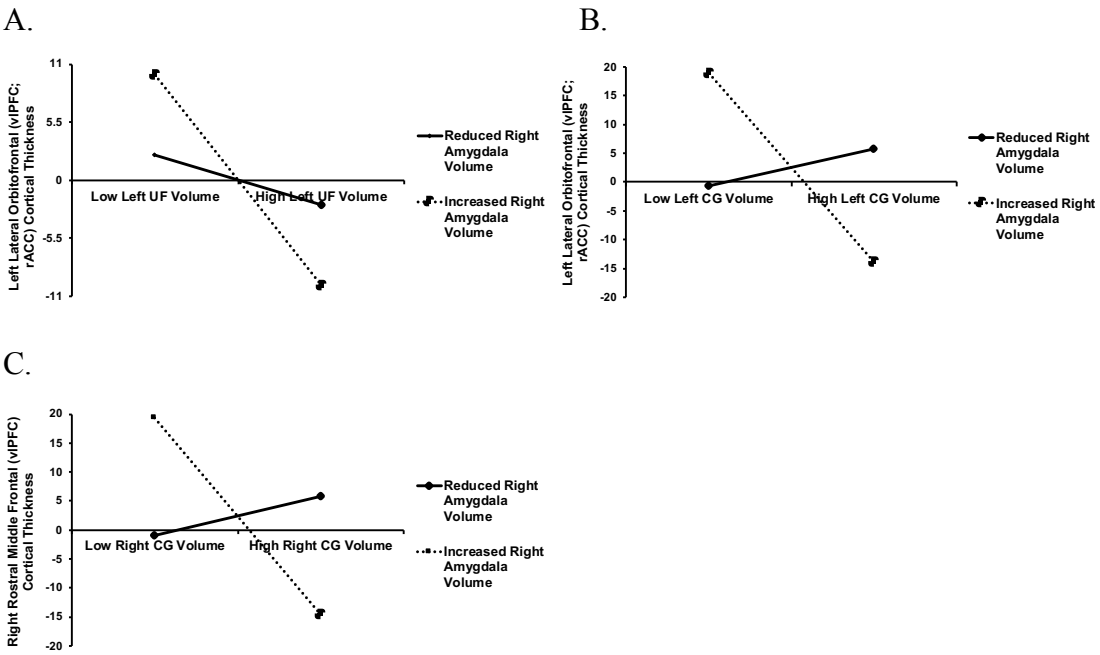


Figure 4.3. (A) Volume of the left uncinate fasciculus moderates the relationship between left amygdala volume and left OFC/rACC cortical thickness. (B) Volume of the left CG moderates the relationship between left amygdala volume and left lOFC/vlPFC/rACC) cortical thickness. (C) Volume of the right CG moderates the relationship between right amygdala volume and right RMF/vlPFC cortical thickness.

4.5. Correlations Among Amygdala, Cortical Thickness, and Anxiety Symptoms

Full results of the correlations among brain volume (i.e., right/left amygdala volume), significant ipsilateral cortical thickness clusters (i.e., right RMF/vlPFC, right SPL, right SFG/dPFC, right cuneus, and left lOFC/vlPFC), anxiety symptoms (i.e., MASC total T-Score) are located in Table 4.4.

Right and left amygdala volume did not significantly correlate with self-reported anxiety. As shown in Figure 4.4, cortical thickness in the right SPL (r = .344, p < .05). Similarly, right RMF/vlPFC cortical thickness significantly correlated with youth's anxiety symptoms (r = .489, p < .01), as did cortical thickness in the left lOFC/vlPFC (r = .494, p < .01). Cortical thickness in the right SFG/dPFC (r = .314, p < .10) and right cuneus (r = .30, p < .10) trended towards significance.

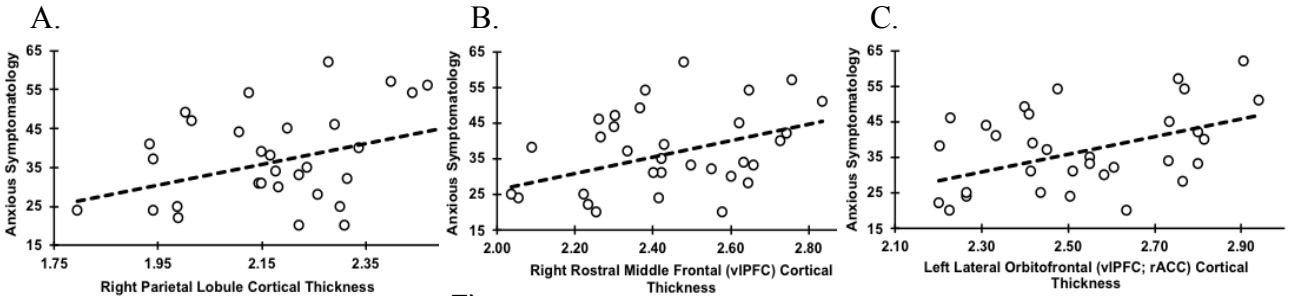


Figure 4.4. (A) The relationship between right SPL cortical thickness and anxiety symptoms (B) The relationship between right RMF/vlPFC cortical thickness and anxiety symptoms. (C) The relationship between left lOFC/vlPFC/rACC cortical thickness and anxiety symptoms.

4.6. Correlations Among UF Volume, CG Volume, and Anxiety Symptoms

Table 4.4 shows the full results of the correlations among UF volume, CG volume, and anxiety symptoms (i.e., MASC total T-Score). CG volume significantly correlated with anxiety symptoms (r = -.41, p < .05). In addition, UF volume demonstrated a trend toward significance (r = -.29, p < .10). All other correlations were either not significant.

Table 4.4. Pearson's correlations among right/left amygdala, ipsilateral cortical thickness, and anxiety symptoms (top); Pearson's correlations among right/left UF, right/left CG, and anxiety symptoms (bottom). Note: * = $p < .05$; † = $p < .10$.

Subcortical and Cortical Volumes	Anxiety symptoms
Right Amygdala	-.23
Left Amygdala	-.14
OFC / vlPFC / rACC	.49*
RMF / vlPFC	.44*
SPL	.34*
SF / dPFC	.31†
Cuneus	.30†
Tracts-of-Interest	
Right Hemisphere	
UF Volume	-.09
UF Functional Anisotropy	-.27
CG Volume	-.41*
CG Functional Anisotropy	-.22
Left Hemisphere	
UF Functional Anisotropy	-.29†
UF Volume	-.29†
CG Volume	-.19
CG Functional Anisotropy	-.28

4.7. Tests of Indirect Effects: Two-System Framework of Emotion Regulation

Despite finding no relationship between amygdala volume and anxiety symptoms, given previous literature, I conducted a test of indirect effects given the finding that clusters in the PFC associated with amygdala volume have a robust relationship with anxiety symptoms. Specifically, a suppression effect was suspected during the post-hoc examination of the Pearson's correlations between right/left amygdala volume and anxious symptomatology (r = -14, $p > .05$; r = -23, $p > .05$), as well as the strong positive relationship between the right RMF/vlPFC and left OFC/vlPFC/rACC and anxious symptomatology (respectively) (r = 49, $p < .05$; r = 44, $p < .05$; See Table 4.4).

As noted in the introduction, the literature is equivocal on the association between amygdala volume and anxious symptomatology (e.g., De Bellis et al., 2000; Milham et al., 2005), with more recent research on cortical regions involved while youth regulate their emotional responses (Wager, Davidson, Hughes, & Lindquist, 2008; Buhle et al. 2014; Silvers et al., 2015; Silvers et al., 2016). Therefore, it was hypothesized that the relationship between right amygdala volume and self-reported anxiety would be indirectly affected by right RMF/vlPFC, whereas the OFC/vlPFC/rACC will have an indirect effect on the relationship between left amygdala volume and self-reported anxiety.

Put differently, I first explored whether the relationship between right/left amygdala volume and self-reported anxiety would strengthen once the restricted variance of associated cortical thickness regions is considered. First, right amygdala volume's relationship with anxiety symptoms was examined controlling for individual variance in the right RMF/vlPFC. In the left hemisphere, the left OFC/vlPFC/rACC was examined as potentially restricting the variance of the model, allowing for a more robust relationship between left amygdala volume and self-reported anxiety to emerge.

The test of indirect effects was run using the Preacher and Hayes model (2004). These clusters, which were previously identified via GLM analyses, (see Figure 4.1), were evaluated for total effect of amygdala volume on anxiety symptoms, which was divided into direct and indirect effects that vary as a function of the explanation of variance provided by the presence of the respective cortical thickness PFC clusters. A bootstrapping method with 10,000 iterations was used to test the 95% confidence intervals of the indirect effect (Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013). All analyses included age and sex as covariates. Variables used

include right amygdala volume controlled for intracranial volume, MASC total T-Score, and mean PFC cluster thickness generated from the previously ran GLMs.

4.7.1. The Indirect Effect of Cortical Thickness in the Right Hemisphere

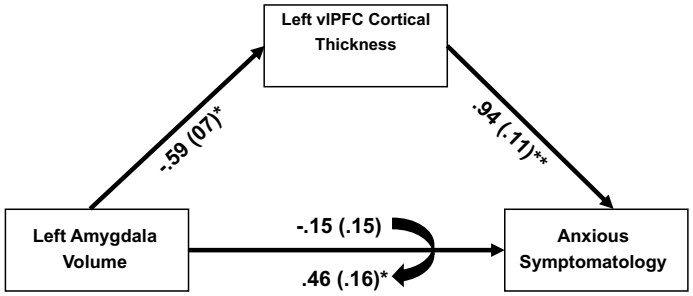
Results of this analysis indicated a reduction in gray matter volume in the vlPFC indirectly affected the relationship between right amygdala volume and differences in anxiety symptoms. The test of indirect effect model for vlPFC cortical thickness ($R^2 = 0.53$; $F[4, 29] = 11.39$, $p < .00001$; total effect coefficient = 0.0262) had significant fit. However, right amygdala volume had a non-significant direct effect on anxiety symptoms ($t(33) = .85$ $p > .05$) and a nonsignificant indirect effect ($t(33) = -1.31$, $p = .19$). However, mean gray matter volume in the vlPFC had a significant direct effect on anxiety symptoms ($t(33) = 2.95$, $p < .01$), 95% confidence limits from bootstrap test (11.62 – 64.19) and a significant indirect effect (completely standardized coefficient (SD) = -.42 (.14), $p < .05$), 95% confidence limits from bootstrap test (-.74 – -.17).

4.7.2. The Indirect Effect of Cortical Thickness in the Left Hemisphere

Results of this analysis indicated that left amygdala related differences in anxiety symptoms was indirectly affected by reduced gray matter thickness in the vlPFC. The test of indirect effect model for vlPFC cortical thickness ($R^2 = 0.56$; $F[4, 29] = 12.60$, $p < .00001$; total effect coefficient = 0.027) had significant fit. Left amygdala volume had a significant direct effect on anxiety symptoms ($t(33) = 2.33$, $p < .05$) and a non-significant indirect effect ($t(33) = -.82$, $p > .05$). Mean gray matter thickness in the vlPFC had a significant direct effect on anxiety symptoms ($t(33) = 4.39$, $p < .01$), 95% confidence limits from bootstrap testing (26.80 – 73.56) and a significant indirect effect, completely standardized coefficient (SD) = -.61 (.17), $p < .05$,

95% confidence limits from bootstrap test (-.95 – -.30). There was a large effect, where the partial correlations between left amygdala volume and anxiety symptoms (with age and sex as covariates) increased (r = -.08, p > .05) when the left vlPFC grey matter volume was added as a covariate (r = .50, p < .01). See Figure 4.5.

A.



B.

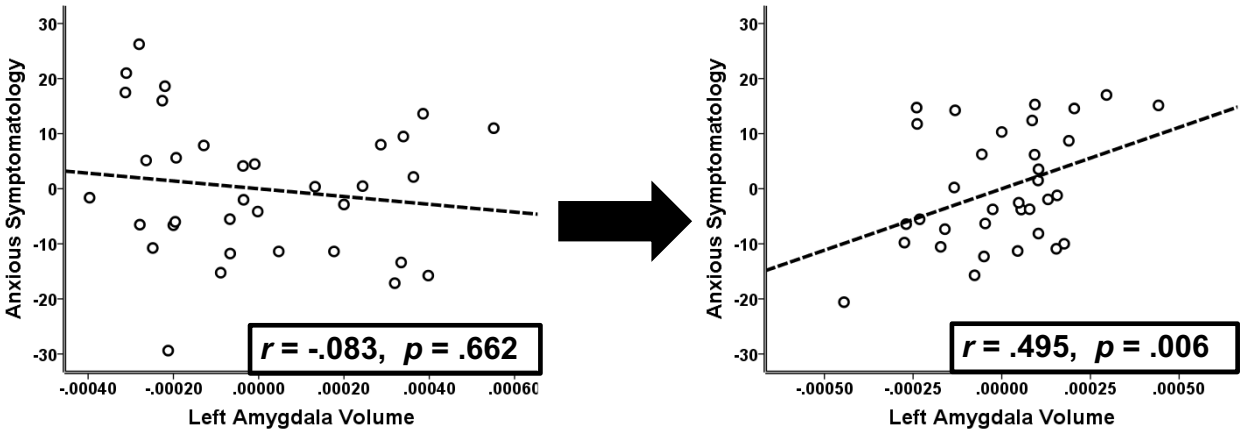


Figure 4.5. (A)Left vlPFC cortical thickness has an indirect effect on the relationship between left amygdala volume (controlled for intracranial volume) and anxiety symptoms; * = p < .01, ** = p < .0001; standardized betas (standard error); anxiety symptoms as measured by the MASC T-score; covariates included sex and age. (B) Scatterplot illustrating no relationship between left amygdala volume and anxiety symptoms with only sex as a covariate (left; p > .05); Scatter plot of the partial correlation between left amygdala volume and anxiety symptoms with left vlPFC cortical thickness, sex, and age as covariates (p < .0001). All measures were centered prior to analysis (hence negative values).

4.8. Follow-up Analyses: Right/Left Amygdala Volume by Right/Left vlPFC Thickness as Respective Predictors of Self-Reported Anxiety

Follow-up analyses were conducted on the variables included in the two tests of indirect effect analyses in an effort to provide further support for the independence of these two systems. To this end, I utilized two linear multiple regressions to examine whether right/left amygdala volume is moderated by gray matter volume in the right/left vlPFC. Results are congruent with the above findings of the independence of these neural systems.

The main effects of right amygdala volume and right vlPFC, along with their interaction, were examined as predictors of self-reported anxiety. The overall model, $F(5, 26) = 1.58$, $p > .05$; $R^2 = .233$, was not significant. Examining the test of higher order unconditional interactions was also not a significant predictor of youths' self-reported anxiety, $F(1, 26) = 1.67$, $p > .05$; $\Delta R^2 = .049$, $p > .05$.

The main effects of left amygdala volume and left vlPFC, along with their interaction, were examined as predictors of self-reported anxiety. The overall model, $F(5, 26) = 2.28$, , $p > .05$; $R^2 = .305$, was not significant. Examining the test of higher order unconditional interactions was also not a significant predictor of youths' self-reported anxiety, $F(1, 26) = 2.26$, $p > .05$; $\Delta R^2 = .060$, $p > .05$.

5. Discussion

The purpose of this study was three-fold. First, I aimed to 1) determine regions of cortical thickness that relate to amygdala volume in a sample of typically functioning youth, with the goal of identifying cortical regions implicated in emotion regulation, 2) I looked to establish if this relationship was moderated by their structural connectivity, and 3) then link grey-matter thickness (i.e., regions that correlated amygdala volume) and subcortical volume (i.e., amygdala), and anxiety symptoms.

I hypothesized that amygdala volume in older youth (i.e., >10 years old) would be negatively correlated with regions involved in the top-down regulation of amygdala activity (i.e., ventral and dorsal PFC, lOFC, and mOFC, and the parietal lobe; See Gee et al., 2013; Silvers et al., 2016). Additionally, I posited that the volumetric and functional anisotropy differences in the UF and CG tracts would moderate the relationship between the amygdala and predicted gray-matter thickness (i.e., regions that correlated amygdala volume). Next, I hypothesized that cortical and subcortical grey-matter volume would significantly correlate with anxiety symptoms in youth. Finally, in an exploratory nature, I examined whether the relationship between amygdala volume and anxiety symptoms would strengthen once the restrictive variance of associated cortical regions is considered.

5.1. General Linear Model: Amygdala Volume and Cortical Thickness

I found support for my first hypothesis that older youths' amygdala volume would be negatively correlated with regions involved in the top-down regulation of amygdala activity; the ventral and dorsal PFC, lOFC, mOFC, and pPL were correlated with youths' amygdala volume (while controlling for intracranial volume) and survived the MCS to reduce the likelihood of

type-one errors. The negative relationship between amygdala volume and PFC thickness is congruent with the functional cross-sectional research done on amygdala-PFC connectivity throughout development (e.g., Ducharme et al., 2014; Gee et al., 2013).

The findings are also in line with structural studies examining the relationship between reported anxiety and cortical thickness. Specifically, Ducharme and colleagues (2014) demonstrated that cortical thickness in portions of the vmPFC/mOFC are positively correlated with anxiety in childhood (i.e., < 9 years), but negatively correlated in adolescents and young adults. Similarly, Newman and colleagues (2015) found that anxiety was negatively correlated with vmPFC cortical thickness, but the relationship diminished with age. Furthermore, this positive-negative connectivity switch has also been found functionally by Gee et al. (2013) as well. Specifically, there is evidence that there is a developmental reversal of function in amygdala-PFC connectivity where positive amygdala-PFC connectivity, found in early childhood, becomes negative during the transition to adolescence. Although I did not have a sample of young children large enough to demonstrate positive relationships earlier in development (cross-sectionally), the negative relationships among the amygdala and regions involved in the top-down regulation in older youth is congruent with past literature (e.g., Ducharme et al., 2014; Newman et al., 2015).

The PFC clusters found to be associated with amygdala volume overlap with the functional literature on emotion regulation as well. For instance, functional literature has consistently found that activity in the PFC, along with the pPL, are associated with emotion regulation (e.g., Ochsner & Gross, 2005). More specifically, the vmPFC, vlPFC, dlPFC, and dmPFC cortices have been found to be associated with cognitive control of negative emotion (Wager, et al., 2008; Buhle et al. 2014; Silvers et al., 2015; 2016). It has been suggested that the

emotion regulation network includes the ventral PFC, dorsal PFC, lOFC, and mOFC, as well as the pPL (Buhle et al. 2014; Ducharme, 2014; Gee et al., 2013; Newman et al., 2015; Silvers et al., 2015; 2016; Wager et al. 2008). The structural PFC cortical thickness clusters I found had significant overlap with the aforementioned functional emotion regulation network. To my knowledge, this is the first study to demonstrate that correlating subcortical grey matter structural volume (e.g., amygdala) with cortical thickness may be a parsimonious and useful method for exploring potential cortical regions related to emotion regulation.

The contralateral analyses were more robust which was unexpected. These results were difficult to interpret given the dearth of literature examining the relationship between contralateral cortical areas that are associated with the amygdala and, presumably, related to emotion regulation. Despite these analyses being exploratory, the results were largely congruent with the ipsilateral analyses, as well as the larger emotion regulation literature. While this may be partially explained by the large correlation between an individual's right/left amygdala volumes; however, if multicollinearity solely explained the contralateral effects it would be surprising for the results of the contralateral analyses to be more robust (i.e., larger effect size and more cortical regions identified). More research is needed on ipsilateral and contralateral cortical areas and their structural/functional connectivity with the amygdala as it relates to an individual being able to appropriately regulate his or her emotions.

Consistent with some of the previous literature in pediatric samples examining the relationship between amygdala volume and self-reported anxiety (De Bellis et al., 2000), neither the right nor left amygdala were correlated with anxiety. When examining the correlation between mean cortical thickness in clusters found to be related to amygdala volume in the GLMs, the lOFC/vlPFC/rACC, right RMF/vlPFC, and right SPL (in the ipsilateral analyses)

were significantly related to self-reported anxiety symptoms in youth. These findings provide support for the clusters related to amygdala volume as being important in emotion regulation. To my knowledge, this is the first study to demonstrate evidence that subcortical grey-matter volume correlates with regions of the cortex that are associated with emotion regulation.

5.2. Interaction Analyses: Amygdala Volume and White Matter

The current study attempted to provide further support for the notion that the amygdala and associated cortical structures were related to due to their connectivity, and therefore, important for the regulation of emotion. To this end, I provided partial support for my hypothesis that the relationship between amygdala volume and correlated individual cortical thickness clusters would be moderated by their structural connectivity. I decided a priori the UF and CG would serve as the tracts-of-interest, as they have been found to be perturbed in anxious samples (Abe et al., 2006; Bremner et al., 2004; Cannistraro et al., 2007; Chiu et al., 2011; Gilbertson et al., 2001; Phan et a., 2009; Vasterling et al., 1998; Vasterling et al., 2002; Yehuda et al., 1995; Han et al., 2008; Yu et al., 2013) and play a role in fear extinction processes (Fani et al., 2014). My hypothesis that reduced volume and/or poor CG tract integrity may disrupt cognition and emotion regulation was only partially supported.

In the right hemisphere, the volume of the UF significantly moderated the relationship between amygdala volume and cortical thickness of the SFG, SPL, and cuneus. CG volume was only found to moderate the relationship between amygdala volume and cortical thickness in the RMF/vlPFC. Interestingly, the most robust moderations were those with regions that are most consistently linked with emotion regulation in youth (Silvers et al., 2015, 2016). For instance, the moderation analyses predicting lOFC/vlPFC/rACC cortical thickness and right RMF/vlPFC

cortical thickness were found to demonstrate the most robust moderating effects, consistent with a wealth of functional literature on regions important for emotion regulation (Buhle et al. 2014; Ducharme, 2014; Gee et al., 2013; Newman et al., 2015; Silvers et al., 2015; 2016; Wager et al. 2008). The CG volume was the only tract variable that was significantly (negatively) related to anxiety symptoms. Counter to my hypothesis, neither UF volume nor the functional anisotropy were correlated with anxiety symptoms.

In the left hemisphere, ipsilateral analyses indicated that both the CG and UF volumes significantly moderated the relationship between amygdala volume and the OFC/vlPFC cortical thickness cluster, providing further support that the ipsilateral GLM analyses reflected that the amygdala volume (controlled for intracranial volume) was predicting cortical thickness clusters potentially due to their structural connectivity.

The findings also indicate that tract volume, but not FA, may have a stronger effect on the relationship between amygdala volume and the PFC, as well as self-reported anxiety in youth. Models including tract volume, but not FA, were the only significant models. Additionally, only the mean volume of the CG was significantly (negatively) related to anxiety symptoms. However, these findings should be interpreted with caution as it may reflect that both variables of the interaction term are structural volumes (i.e., tract and amygdala volumes). Future research should continue to explore both the functional anisotropy and volume of the UF and CG tracts as my findings indicate that their volumes have a differential effect on the relationship between amygdala volume and PFC cortical thickness clusters.

5.3. Test of Indirect Effects

A combination of previous inconsistent past literature, and the *post-hoc* suppression effect observed, I conducted an exploratory test of indirect effects. As noted in the introduction, the literature is equivocal on the association between amygdala volume and anxious symptomatology (De Bellis et al., 2000; Milham et al., 2005), with more recent research on cortical regions involved while youth regulate their emotional responses (Wager, Davidson, Hughes, & Lindquist, 2008; Buhle et al. 2014; Silvers et al., 2015; Silvers et al., 2016). Therefore, it was hypothesized that the relationship between right amygdala volume and self-reported anxiety would be indirectly affected by right RMF/vlPFC, whereas the OFC/vlPFC/ rACC will have an indirect effect on the relationship between left amygdala volume and self-reported anxiety.

The exploratory analyses were conducted based on past research not taking into consideration the role of individual differences in top-down regulation may have one the relationship between amygdala volume and anxiety (De Bellis et al., 2000; Milham et al., 2005). I conducted these analyses because it was suspected that the relationship between amygdala volume and anxiety would strengthen due to the restricted variance of associated cortical thickness regions. I found partial support for this hypothesis: the left amygdala was indirectly related to self-reported anxiety through the mean thickness of the left lOFC/vlPFC. Specifically, the indirect effect of cortical thickness in the vlPFC significantly strengthened the correlation between left amygdala volume self-reported anxiety; while there was not a direct effect of amygdala volume and anxiety, as would be expected from the Pearson correlations (r = -.08), the inclusion of mean cortical thickness in the vlPFC led to a robust relationship between left amygdala volume and anxiety (r = .50).

Neurologically, the amygdala is a collection of nuclei, which is all captured by the single volume variable used to quantify the amygdala (Kim et al., 2011). It is well known that different nuclei of the amygdala serve various functions (e.g., sensory input and memory input), and it is not a unitary structure. Since the current study used the entire amygdala volume, capturing all nuclei, this may explain a portion of the results extending to many areas related, functionally, with emotion regulation. Studies parsing the neural correlates of certain aspects of the amygdala (i.e., lateral nucleus) would be particularly interesting.

These results have important implications for future research. From a practical standpoint, conducting an MRI is much easier (especially with youth) and cheaper than functional imagining. The results of this dissertation suggest that volumetric cortical and subcortical grey-matter can be related to behavioral reports of anxiety. Moreover, many regions found to be related to emotion regulation are similar to those found in task-based functional neuroimaging studies. This method is much more parsimonious and efficient than other methods of examining the neural correlates of emotion regulation in youth. Additionally, many regions found in the current study overlap with a study using similar methodology; relating distinct facets of anxiety (i.e., apprehension and arousal) to cortical thickness in youth (Castagna et al., 2017). The results also have particular relevance given the switch in positive-to-negative connectivity between the PFC and amygdala during development (e.g., Gee et al., 2013). There are many challenges to conducting a functional neuroimaging scan with a young child (e.g., excessive head movement, longer scan times, and low motivation to engage in the task). These findings suggest that research may benefit from examining individual differences in young children's cortical and subcortical volumes, how they relate to emotion regulation, and how this cortical-subcortical relationship changes over development. These findings partially support the

overall exploratory hypothesis that the incongruent past research relating amygdala volume and anxiety may be due to not taking into consideration the restricted variance provided by individual differences in cortical regions that are found to be important for successful emotion regulation.

In contrast to my hypothesis, the other models of indirect effects with clusters found to be related to right/left amygdala volume in the ipsilateral analyses were not significant, such as the cortical areas that are within the emotion regulation network: ventral PFC, dorsal PFC, lOFC, mOFC, and the pPL (Buhle et al. 2014; Ducharme, 2014; Gee et al., 2013; Newman et al., 2015; Silvers et al., 2015; 2016; Wager et al. 2008).

5.4. Interaction Analyses: Amygdala Volume and Cortical Thickness

In my follow-up analyses, I looked to provide more evidence that regions involved in emotion regulation have an indirect effect on the relationship between amygdala volume and anxiety by demonstrating that the interaction between amygdala volume and associated cortical regions were not predictive of self-reported anxiety. The overall aim was to demonstrate that it is unlikely that amygdala volume has a differential effect with emotion regulation as a function of individual differences (variance) in cortical thickness in significant areas of the PFC. I found support for my hypotheses that these models would not be significant, which indicated that the relationship between amygdala volume and emotion regulation did not become stronger or weaker as a function of youth's variability in PFC cortical thickness. Congruent with my hypotheses, the relationship between amygdala volume and anxiety symptoms was indirectly affected by the variance explained by cortical thickness, where the regions appear to work as a third variable that modulates the amygdala volume and amount of anxiety reported by healthy youth.

5.5. Evidence for a Two-System Framework of Emotion Regulation

The overall findings were directed at exploring whether there is evidence for a two-system framework of emotion regulation that scaffolds off of two similar theories of emotional consciousness (LeDoux & Brown, 2017) and popular frameworks of fear/anxiety (LeDoux & Pine, 2016). The central theoretical hypothesis was that emotional consciousness – being self-aware that you are currently in a particular emotional state (i.e., you are aware you are in a certain emotional state) – and emotion regulation share the same underlying brain mechanisms. In addition, it was hypothesized that the more appropriate dichotomy between non-adaptive and adaptive emotion regulation is better captured by whether a particular emotion regulation strategy is unconscious (type-one) and conscious (type-two), respectively. It was posited that the differences between emotional consciousness and emotion regulation function as differences in the recruitment of lower-order, subcortical networks and their interpretation by higher-order structures (e.g., PFC cortical thickness).

I provide partial evidence for this hypothesis that suggest an extension of LeDoux and Pine's (2016) two-system framework of fear/anxiety to one of emotion regulation is feasible. I found support for the specific circuits within the network as being type-one emotion regulation – often called emotion reactivity/responsivity/sensitivity – and type-two emotion regulation (i.e., effortful strategies). The purpose of exploring LeDoux and Pine's (2016) two-system framework of fear/anxiety and LeDoux and Brown's (2017) higher-order theory of consciousness was to scaffold off dominate theories of emotional processing (i.e., LeDoux & Brown, 2017; LeDoux & Pine, 2016) in an effort to integrate and orient these two overlapping fields.

5.6. Results of the Theoretical Hypotheses

Although broad structures are mentioned by LeDoux et al. (2016; 2017), as shown in Figure 1.2B, the theorized neural circuits or substructures which comprise the general network of cognitions (type one and two) are not fundamentally different than those involved in type-two (and type-one) emotion regulation was largely supported. Briefly, a review of the literature was congruent with my findings, supporting the notion that the GNC-2 and type-two emotion regulation strategies heavily rely on the dlPFC, vlPFC, dmPFC cortices, as well as the dACC, aIN, and portions of the OFC. On the other hand, I provide preliminary evidence that the GNC-1 and type-one emotion regulation may be supported by the vmPFC, portions of the OFC, amygdala nuclei, and pIN.

5.7. The General Network of Cognition and Emotion Regulation

Hypotheses were driven by neuroimaging studies of these emotion regulation strategies (e.g., Otto, Misra, Prasad, & McRae 2014; Zilverstand, Parvaz, & Goldstein, 2017) map on to the GNC outlined by Ledoux and Brown (2017), where the various strategies differ only on lower-order, subcortical input. As seen in Figure 1.2AB, my results largely support the broader literature, implicating the pPL, IN, ACC, and a number of areas in the PFC (i.e., ventral-lateral, dorsal-lateral, orbital-lateral, orbital-medial, dorsal-medial, and ventral-medial). In terms of functional neuroimaging, these same regions are involved in type-two emotion regulation strategies such as, cognitive reappraisal (Zilverstand et al., 2017), active suppression (Goldin et al., 2008; Wyland et al., 2003), as well as type-one regulatory processes such as the initiation of defensive behaviors (e.g., Mogenson, Jones, & Yim, 1980), rumination (Cooney, Joormann, Eugène Dennis, & Gotlib, 2010), and worry (Paulesu et al., 2010).

Further evidence comes from the structural (i.e., cortical thickness, subcortical volumes) differences (and overlap) found between self-reported anxious apprehension (largely mapping on to type-two emotion regulation strategies such as worry) and anxious arousal (capturing type-one defensive behaviors/changes in physiology). In line with structures comprising the GNC, anxious apprehension, but not anxious arousal, correlated with clusters in the dlPFC, dmPFC and vlPFC, whereas anxious arousal, but not anxious apprehension, produced clusters in the aIN and the amygdala (Castagna et al., 2017), again, congruent with the two-system framework of fear/anxiety (LeDoux & Pine, 2016). Interestingly, a conjunction analysis revealed the importance of a number of frontoparietal regions with strong relationships to both systems (Castagna et al., 2017). The overlap among the GNC and regions involved in emotion regulation, broadly, is fairly evident; however, my aim is to extend LeDoux and Brown's (2017) distinction between GNC-1 and GNC-2. Support for the first hypothesis was partially provided by demonstrating that the neural regions or substructures which comprise GNC-2 (and GNC-1) may not fundamentally different than those involved in type-two (and type-one) emotion regulation, given their relationship within the test of indirect effects and relationship to anxiety symptoms

5.8. The Two-System Neuroscience Framework of Fear

In brief, the two-system neuroscience framework of fear provides evidence for the distinction and independence between the two threat systems. The first-system is thought to be primarily subcortical (e.g., sensory system, amygdala, bed nucleus of the stria terminalis, and striatum), leading to behavioral responses (i.e., the nucleus accumbens facilitating escape and avoidance behaviors; Delgado, Jou, LeDoux, & Phelps, 2009; Schlund, Hudgins, Magee, &

Dymond, 2013) and accompany physiological changes in the brain and body – type-one, automatic, and non-effortful, termed defensive behaviors (i.e., DFN).

The second system is posited to be an independent, higher-order cortical system that facilitates the subjective experience of emotion depending on the subcortical input (e.g., DFN). Specifically, they suggest that the general network of cognition (GNC), which gives rise to perceptual (non-emotional) conscious experience (Craig, 2009; Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Frith & Dolan, 1996; Frifth, Perry, & Lumer, 1999; Lau & Passingham, 2006; Naccache et al., 2002; Rees & Frith, 2007), is not fundamentally different than the network that facilitates emotionally conscious experience; differing on lower-order, subcortical input (e.g., DFN). The current study extends the reach of the GNC by providing evidence of its overlap with regions important in emotion regulation (see Figure 1.2A). The evidence I provide for the independence of the two-systems (e.g., DFN and GNC) framework comes from a number of areas of research and parallels the distinction between type-one (unconscious) and type-two (consciousness) emotion regulation.

5.9. The Higher-Order Theory of Consciousness (LeDoux & Brown, 2017)

LeDoux and Brown's (2017) higher-order theory of emotional consciousness suggests that the subcortical regions that receive primary sensory signals from the body (Damasio, 1999), memory systems (Squire & Zola-Morgan, 1991), and the visual system (Van Essen, Anderson, & Felleman, 1992) are all involved in the first-order representations that indirectly influence higher-order assembly of conscious feelings by a GNC. Thus, the subjective experience of fear, within this framework, is modulated by the DFN, along with the subcortical body sensing network, memory, and visual systems, but directly arises from other independent higher-order

frontoparietal networks integrating the information (i.e., the GNC). Consistent with the central hypothesis, I found support for the same regions LeDoux and Brown (2017) posit as being important for the two respective GNCs: a first GNC is thought to integrate subcortical input outside of an individuals' conscious awareness, and a second GNC that receives this input and gives rise to the conscious experience of fear.

Taken together, the current findings largely support the notion that perceptual (non-emotional) and emotional consciousness both require the incorporation of higher-order representation (i.e., involving cortical regions of the PFC) of lower, subcortical information (i.e., involving individual differences in amygdala volume) by the GNC; differences in consciousness (non-emotional and emotional) arise from the subcortical input and higher-order representation. Extendedly, this would suggest that LeDoux and Brown (2016) are may be correct in hypothesizing that one can report having an emotional experience when asked (i.e., self-report being scared), when a higher-order representation of the first higher-order representation is created. They posit that the higher-order representations are integrated by the GNC, which fits directly with the finding that the test of indirect effects, but not the interaction, significantly predicted youth's self-reported anxiety.

5.10. Limitations and Future Considerations

The sample includes a broad age range, and although age and sex were used as covariates in all analyses, these results cannot extend to certain developmental periods. Independent-samples t-test did not indicate significant differences in younger youth (i.e., aged 10-13) and older youth (i.e., aged 14-17) on their reporting of their anxiety symptoms, $t(33) = -1.02$, $p > .05$; nevertheless, younger youth may still have differences in their reporting of anxiety symptoms,

along with different cognitive and self-reflective capacity, compared to older youth, and is a limitation of the current study. Moreover, the study was also cross-sectional, which does not allow for a developmental course of events to be examined. The results are also derived from typically developing youth, thus, it is unclear how this relationship might look in clinical populations of youth. Nevertheless, the study demonstrates that amygdala grey matter volume predicts clusters of cortical thickness grey-matter, where most clusters demonstrated significant relationships with self-reported anxiety and significantly overlap with the larger literature on regions important for successful emotion regulation in youth. While I attempted to control for multiple comparisons with MCS, a limitation of the current study involves the number of analyses conducted.

The current study has a number of strengths as well. Evidence for relating subcortical amygdala volume with cortical thickness, while providing preliminary evidence that they are associated due to their connectivity, is novel. Structural imaging is less burdensome than collecting functional data, and therefore, the methodology may be beneficial to future researchers to replicate and extend the results to younger children and adults. As previously mentioned, functional studies may benefit from a better understanding of contralateral top-down emotion regulation, as the results tentatively suggest that contralateral cortical regulation may be important during the emotion generative process. This study presents a foundation in a potentially convenient method of examine emotion regulation with structural imaging relating cortical and subcortical grey matter, as well as proving preliminary evidence potentially extending two major theories in the field of emotional processing (LeDoux & Brown, 2016; LeDoux & Pine, 2017).

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