Cortical Thickness Abnormalities Within the Salience and Reward Networks in Older Depressed Adults with Apathy

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Cortical Thickness Abnormalities Within The Salience And Reward Networks In Older Depressed Adults With Apathy

by

MONIQUE A. PIMONTEL

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the City University of New York

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This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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THE CITY UNIVERSITY OF NEW YORK
ABSTRACT

Cortical Thickness Abnormalities within the Salience and Reward Networks in Older Depressed Adults with Apathy

by

Monique A. Pimontel

Advisor: Joel Sneed, Ph.D.

Background and Significance

Apathy is a common comorbidity in late-life depression. Among older depressed adults, apathy is associated with a number of adverse outcomes, including increased disability, comorbid illness, and mortality. The etiological substrates of apathy in late-life depression nonetheless remain poorly understood, and little is known about its optimal treatment. To this end, the aim of the current study was to examine cortical abnormalities within the salience (SN) and reward networks (RN), two brain systems involved in the processing of incentive salience that may underlie the syndrome of apathy in older depressed adults.

Methods

We examined the association between apathy and cortical thickness of the right insula, caudal anterior cingulate cortex (cACC), rostral anterior cingulate cortex (rACC), medial
orbitofrontal cortex (mOFC), and lateral orbitofrontal cortex (lOFC) in 49 individuals with late-life depression before and after 12 weeks of antidepressant treatment with the selective serotonin reuptake inhibitor (SSRI) escitalopram. Apathy was quantified using the Apathy Evaluation Scale (AES). Cortical thickness was computed using FreeSurfer. Regions of interest (ROIs) were parcellated using the Desikan-Killiany atlas.

Results

Within the SN, cortical thickness of the insula was significantly associated with response of apathy symptoms to escitalopram, as well as persistence of apathy symptoms after 12 weeks of treatment. Thickness of the cACC, which is involved in both salience and reward processing, was not associated with apathy at any time. Within the RN, thickness of the rACC was significantly related to apathy at baseline. Thickness of the mOFC and lOFC was not associated with apathy at any time. Exploratory analyses examining the association between cognitive functions and apathy revealed a relationship between response of apathy to treatment and several aspects of cognition, including processing speed, executive functioning (i.e., set shifting and source monitoring), and memory (i.e., retrieval of verbal information).

Conclusions

The results of this study suggest a role for abnormalities within both the SN and RN in older depressed adults with apathy. Given the interplay between structures of the SN and RN in
processing of incentive salience, older depressed adults with apathy may have a decreased ability to associate an anticipated outcome with the experience of desire, thereby decreasing motivated, goal-directed activity.
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INTRODUCTION

I. APATHY

Epidemiology

Apathy is defined as a decrease in self-motivated, goal-directed activity (Stuss et al., 2000; Levy and Dubois, 2006). Although apathy was originally viewed simply as a symptom or dimension of behavior, it is currently considered a clinical syndrome that may reflect a number of affective, cognitive, and behavioral disturbances, including emotional indifference or blunting, an inability to formulate or sequence a purposeful plan of action, and an inability to initiate behavior necessary for attaining a goal (Marin, 1991; Robert et al., 2009). Although symptoms of apathy may be experienced by individuals who are otherwise healthy (Brodaty et al., 2010), apathy more commonly occurs in the context of a wide-variety of other neuropsychiatric disorders (Marin, 1991; van Reekum et al., 2005), such as dementia (Starkstein et al., 2006), Parkinson’s disease (PD) (Starkstein et al., 1992), schizophrenia (Roth et al., 2007), and depression (Marin et al., 1993).

The prevalence of apathy increases with age (Starkstein et al., 1993; Onyike et al., 2007), and appears to be the most commonly observed behavioral disturbance in demented older adults living in nursing homes (Zuidema et al., 2007). Among non-demented, community-dwelling elderly, those with late-life depression are most susceptible to apathy (Lampe and Heeren, 2004; Onyike et al., 2007; Mehta et al., 2008; Groeneweg-Koolhoven et al., 2015). For example, in one study of 476 non-demented, community-dwelling older adults, apathy was present in 75% of
individuals with major depression, while only 25% of their non-depressed counterparts reported symptoms of apathy (Groeneweg-Koolhoven et al., 2015). Two studies examining apathy and late-life depression in inpatients have found comorbidity rates ranging from 74% to 96% (Lampe and Heeren, 2004; Wongpakaran et al., 2007), whereas studies examining the prevalence of apathy in non-depressed older adults have found apathy rates ranging from 7.5% of outpatients visiting their primary care physician (Groeneweg-Koolhoven et al., 2014) to 53% of individuals with vascular disease (Ligthart et al., 2012). Thus, although the prevalence of apathy varies, apathy nonetheless appears to occur most commonly in the context of late-life depression.

Clinical Significance

Apathy is associated with many facets of decreased quality of life. For example, a recent study of 937 community-dwelling, non-demented older adults revealed an association between apathy and increased risk of developing slow gait, frailty, and disability after adjustment for demographic characteristics, medical comorbidities, and cognitive functioning (Ayers et al., 2017). Similarly, in a sample of 1,136 community-dwelling adults aged 50 and older, apathy was associated with cognitive decline and a decrease in both instrumental and basic activities of daily life after a one-year follow up, even after accounting for age, education, race, and depression (Clarke et al., 2010). Associations have also been found between apathy, increased functional impairment, unemployment, and decreased quality of life (Starkstein et al., 1993; Onyike et al., 2007; Reyes et al., 2009; Hölttä et al., 2012; Groeneweg-Koolhoven et al., 2014). Compared to
their non-apathetic counterparts, individuals with apathy have higher frequencies of cognitive impairment, cognitive decline, and dementia, as well as other neuropsychiatric disorders and medical comorbidities (Doody et al., 1995; Levy et al., 1998; Clarke et al., 2010; Hölttä et al., 2012). Apathy is associated with high caregiver burden (Kaufer et al., 1998); in fact, in one study, caregivers of individuals with dementia rated apathy as being the most challenging behavior to manage, secondary to their decreased engagement in even basic activities of daily living (Thomas et al., 2001). In addition, apathetic individuals are less likely to be compliant with and respond to treatment for comorbid illnesses (Kopelowicz et al., 1997; Mega et al., 1999; Tattan and Creed, 2001). Finally, apathy is associated with higher frequencies of hospital admission and mortality (Levy et al., 1998; Hölttä et al., 2012).

Older adults with apathy and comorbid depression are at a particularly high risk of poor clinical outcome. For example, depression severity is higher in older adults with comorbid apathy when compared to their non-apathetic counterparts (Yuen et al., 2014). Depression is more chronic in those with comorbid apathy (Chaturvedi and Sarmukaddam, 1986), as demonstrated by a longitudinal study of 16 individuals with late-life depression that revealed an association between apathy and chronicity of depression after a 6-year follow up (Lavretsky et al., 1999). Apathetic individuals with late-life depression are also less likely to respond to antidepressant treatment than their non-apathetic counterparts (Lavretsky et al., 1999; Levkovitz et al., 2011; Yuen et al., 2014). In a study of 62 depressed individuals ages 18 to 65, apathy severity was significantly correlated with persistence of depressive symptoms following a month
of five weekly treatments with deep transcranial magnetic stimulation over the prefrontal cortex (Levkovitz et al., 2011).

Despite the wide-range of aforementioned adversities that are associated with the syndrome, apathy is frequently left undiagnosed and untreated (Chase, 2011). Apathetic individuals often lack concern and self-awareness of impairment, and may significantly underestimate the severity of their symptoms (Derouesné et al., 1999; Mograbi and Morris, 2014). For example, in a study examining apathy and awareness in Alzheimer’s disease (AD), patients’ ratings of symptom severity was equivalent to that of control participants, whereas caregiver reports revealed significantly higher apathy scores for individuals with AD when compared to controls (Robert et al., 2002). Additionally, given frequent overlap with medical illness, there is a higher likelihood that apathetic individuals will seek medical care than mental health services. Older depressed adults are at a particularly high risk of somatization, while denying mood disturbances or behavioral changes (Gallo et al., 1999; Lampe and Heeren, 2004). Physicians may mistakenly assume that apathy in late-life is an unavoidable consequence of medical illness or environmental circumstances, and as such, they may approach apathy as a benign behavioral condition (Chase, 2011). Furthermore, in these individuals, apathy may be seen as a symptom of depression, as opposed to a syndrome that requires its own targeted treatment (Yuen et al., 2014). As a result, apathy continues to pose a significant burden on older adults with late-life depression, as well as on their caregivers and society-at-large.
Apathy and Late-Life Depression

Despite the frequent co-occurrence of apathy with depression, as well as a significant overlap in symptoms, apathy and depression are nonetheless distinct entities (Marin, 1991; Marin et al., 1993; Levy et al., 1998; Reyes et al., 2009; Njomboro and Deb, 2012; Pardini et al., 2016). Studies examining apathy and depression have found that while individuals with apathy are likely to have comorbid depression, a significant number of individuals have apathy in the absence of depression. For example, in a study examining apathy and depression in PD, depressive symptoms were absent in 12% of individuals with apathy (Starkstein et al., 1992). In another study examining apathy and depression in post-stroke individuals, 30% were found to have apathy, but not depression (Okada et al., 1997). Furthermore, another study found that although apathy was present in 86% of elderly, depressed inpatients, structured clinical ratings of apathy severity were not associated with structured clinical ratings of overall depression severity (Lampe and Heeren, 2004).

Clinically, there are discrepancies between the behavioral expression of apathy and depression (Figure 1) (Levy et al., 1998; Lavretsky et al., 2007). Most notably, individuals with apathy often do not present with dysphoric symptoms such as sad mood, guilt, and hopelessness, while these symptoms are core features of major depression (Marin et al., 1993). In addition, symptoms of apathy and depression respond differently to treatment with antidepressant medication (Raskin et al., 2012; Yuen et al., 2014), such that apathy often persists despite resolution of depressive symptoms (Yuen et al., 2014). For example, in one study, 43% of non-
demented, apathetic older adults continued to have clinically significant symptoms of apathy following 12 weeks of antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI), despite improvement in depressive symptoms (Yuen et al., 2014). In another study, 32.5% of middle-aged participants with remitted depression continued to report symptoms of apathy following three months of antidepressant treatment (Fava et al., 2006).

Studies examining the neuroanatomical abnormalities underlying apathy and depression provide further evidence for a distinction between these two disorders (Marin et al., 1993; Starkstein et al., 1993; Onoda and Yamaguchi, 2015). One diffusion tensor imaging (DTI) study examining apathy and depression in middle-aged and older adults with small vessel disease found that apathy, but not depression, was related to disruptions in limbic association tracts such as the anterior cingulum, fornix and uncinate fasciculus (Hollocks et al., 2015). A magnetic resonance imaging (MRI) study of older depressed adults with apathy revealed an association between apathy severity and decreased gray matter volume of the right anterior cingulate cortex (ACC) after controlling for age and sex, while depression severity was associated with decreased gray matter volume of the bilateral orbitofrontal cortex (OFC) (Lavretsky et al., 2007). In a study of individuals with HIV, a correlation was found between apathy and decreased volume of the nucleus accumbens (NAcc), while this correlation was not found with depression (Paul et al., 2005). Finally, different neuroanatomical substrates are associated with antidepressant treatment response of apathetic and depressive symptoms. Persistence of apathy following SSRI treatment is associated with smaller left posterior subgenual cingulate volume and decreased integrity of
the left uncinate fasciculus (Yuen et al., 2014), whereas nonresponse of depressive symptoms to SSRI is associated with gray matter volume of the dorsal (dACC) and rostral anterior cingulate (rACC) (Starkstein et al., 2001), but not with subgenual cingulate volume (Gunning et al., 2009).

In conclusion, while apathy frequently co-occurs with late-life depression and was historically considered a hallmark symptom (Groeneweg-Koolhoven et al., 2015), their distinct clinical characteristics and separable neuroanatomical abnormalities suggest that apathy and late-life depression may be overlapping, albeit dissociable entities (Marin, 1991; Marin et al., 1993; Levy et al., 1998; Reyes et al., 2009; Njomboro and Deb, 2012; Pardini et al., 2016). Even so, apathy in late-life depression remains under-recognized, and the typical approach to treating apathy symptoms in older depressed adults with antidepressant medication is inadequate (van Reekum et al., 2005). Developing a better understanding of the syndrome of apathy and elucidating its specific etiological abnormalities are crucial steps toward identifying more effective treatments for the disturbances associated with apathy in older depressed adults.

Conceptual Theories

Apathy is most commonly defined as a “diminished motivation not attributable to a decreased level of consciousness, cognitive impairment, or emotional distress” (Marin et al., 1991). However, given that motivation is a subjective experience, others have advocated for a more easily measured, objective conceptualization of apathy (Levy and Czernecki, 2006). For example, apathy has been defined as “an absence of responsiveness to stimuli as demonstrated
by a lack of self-initiated action,” which may originate from changes in affective, behavioral, or cognitive functioning (Stuss et al., 2000). Others have similarly proposed that apathy be defined as “an observable behavioral syndrome consisting of a quantitative reduction in voluntary (or goal-directed) behaviors” (Levy and Czernecki, 2006).

Given the differing definitions of apathy, a task force was assembled in 2009 that combined the aforementioned conceptualizations into diagnostic criteria that could aid the diagnosis of apathy in both clinical practice and research (Robert et al., 2009; Mulin et al., 2011). As per these criteria (Figure 2), an individual must experience a decrease in motivation for at least four weeks. At least two of three objective dimensions of apathy must be present, including reduced voluntary and purposeful behavior, decreased goal-directed cognitive activity, and/or emotional indifference or blunting. Furthermore, an individual must experience identifiable functional impairment that can be attributed directly to a decline in motivation. Finally, the individual must not meet criteria for other, related diagnoses, such as abulia, akinesia and akinetic mutism, depression, dementia, delirium, and anxiety (Mann, 1990).

Neuroanatomical Abnormalities

Motivated, goal-directed behavior requires integration of sensory inputs, emotional information, and memories of prior events, as well as attribution of motivational valence to stimuli, formulation of a plan of action, and initiation of action (Haber, 2011). These functions are associated with fronto-subcortical networks, including regions within the frontal cortex and
basal ganglia (van Reekum et al., 2005; Levy and Czernecki, 2006; Levy, 2012). Consistent with its hallmark clinical features of decreased motivation and goal-directed behavior, apathy is associated with disturbances in these fronto-subcortical networks (Levy and Czernecki, 2006; Levy and Dubois, 2006; Levy, 2012; Hollocks et al., 2015; Moretti and Signori, 2016).

Furthermore, there is evidence of lateralized involvement in apathy, such that apathy is associated more strongly with disturbances in the right hemisphere, as compared to the left hemisphere. For example, an MRI study of individuals with late-life depression found decreased gray matter volume in the right, but not the left, ACC (Lavretsky et al., 2007), while another MRI found increased resting-state functional connectivity (rsFC) only between the right anterior insula (AI) and the right dorsolateral prefrontal cortex (DLPFC) in older depressed adults with apathy (Yuen et al., 2014). In addition, individuals with right-hemisphere stroke have a greater propensity toward the development of apathy than those with left-hemisphere stroke (Marin et al., 1994).

Involvement of fronto-subcortical areas has been well documented in studies examining apathy in older adults with dementia. For example, apathy is prominent in neurodegenerative disorders with frontosubcortical involvement, such as Huntington’s disease, Lewy-Body disease (LBD), progressive supranuclear palsy, and PD (Starkstein et al., 2006; Chase, 2011; Quaranta et al., 2012). In fact, apathy is one of the most common neuropsychiatric symptoms in PD (Alzahrani et al., 2016), and in these individuals, apathy is associated with lower gray matter volume in several brain areas including the left insula, left frontal gyrus, right anterior cingulate,
and left superior temporal gyrus. Apathy is relatively uncommon in cortical dementias such AD (Paulsen et al., 1996; Hargrave et al., 2000). However, there is nonetheless evidence that individuals with AD who have neurofibrillary tangles in the ACC are more likely to suffer from apathy than individuals with AD pathology predominant in other areas (Tekin et al., 2001; Marshall et al., 2006).

Further evidence for the involvement of fronto-subcortical brain regions comes from studies examining apathy in individuals with focal lesions. Apathy is common in individuals with focal damage to the frontal lobe (Levy et al., 1998; Marsh and Hicks, 1998). However, there is conflicting evidence regarding the exact locations within the frontal lobe that are involved in apathy. For example, one study demonstrated that apathy is more common in individuals with lateral frontal lobe lesions as opposed to those with lesions in the medial frontal lobe (Paradiso et al., 1999). In contrast, another study found that individuals with ventromedial lesions of the frontal lobe were more likely to suffer from apathy than individuals with lesions in other areas of the frontal lobe (Barrash et al., 2000).

Neuroimaging studies examining the neuroanatomical abnormalities associated with apathy in various populations have also found indication of fronto-subcortical involvement. Within the frontal lobe, abnormalities have been identified in the middle and inferior frontal gyri (Yan et al., 2015). Within the basal ganglia, structural abnormalities have been found in the putamen, NAcc, internal capsule, and caudate nucleus (Starkstein et al., 1993; Bruen et al., 2008; Martinez-Horta et al., 2014; Yan et al., 2015; Kazui et al., 2017).
Imaging studies have also identified abnormalities in the ACC and in the temporal lobe in individuals with apathy. Apathy severity correlates with reduced gray matter volume and metabolic activity in both anterior and posterior areas of the ACC (Migneco et al., 2001; Apostolova et al., 2007; Lanctôt et al., 2007; Lavretsky et al., 2007; Marshall et al., 2007; Bruen et al., 2008; Starkstein et al., 2009; Tunnard et al., 2011; Stella et al., 2014; Huey et al., 2017). Within the temporal lobe, apathy is associated with abnormalities of the superior temporal sulcus and fusiform gyrus (Ott et al., 1995; Alzahrani et al., 2016; Huey et al., 2017; Kazui et al., 2017).

Several studies have identified abnormalities of the AI in individuals with apathy. In older depressed adults, apathy is associated with increased functional resting-state connectivity between the right AI and right DLPFC (Yuen et al., 2014). Apathy is also common in individuals with insular lesions in brain-damaged patients (Njomboro et al., 2012). Apathy in PD is characterized by lower gray matter volume in the left insula (Alzahrani et al., 2016), and lesion mapping in individuals with traumatic brain injuries has also revealed abnormalities in the left insula (Knutson et al., 2014). Finally, positron emission tomography (PET) imaging in AD has revealed correlations between apathy and abnormalities in the bilateral insula (Mori et al., 2014).

Evidence for the involvement of fronto-subcortical brain regions in apathy also comes from studies examining the neurocognitive functioning of individuals with apathy. Apathy is often conceptualized as a behavioral manifestation of executive dysfunction (Kuzis et al., 1999; Drijgers et al., 2011). Executive functioning refers to a broad class of mental functions necessary for adaptive and goal-directed behavior that includes planning, organization, problem-solving,
mental flexibility, and response inhibition (Miyake et al., 2000; Stuss and Alexander, 2000), and these aspects of cognition are associated with disturbances in fronto-subcortical networks (Bonelli and Cummings, 2007). Not surprisingly, studies delineating the neuropsychological profile of individuals suffering from apathy have consistently found prominent executive dysfunction (Alzahrani et al., 2016), including impaired set shifting (Kuzis et al., 1999; Feil et al., 2003; Onyike et al., 2007), cognitive inhibition (Feil et al., 2003), working memory (Zgaljardic et al., 2007), conceptualization (Zgaljardic et al., 2007), and verbal fluency (Kuzis et al., 1999; Feil et al., 2003; Onyike et al., 2007; Zgaljardic et al., 2007; Drijgers et al., 2011). In addition, impairments in executive control processes that underlie memory (Robert et al., 2006) and word retrieval (Kuzis et al., 1999) have also been reported in older adults with apathy.

Taken together, there is ample evidence for the involvement of fronto-subcortical structures in apathy. These structures primarily contribute to motor, cognitive, and behavioral functions within the brain (Bonelli and Cummings, 2007). Disruptions of fronto-subcortical circuits may result in executive dysfunction, personality changes such as disinhibition, emotional lability, and lack of empathy, and the formulation, execution, and mediation of behavior in response to physiological, emotional, and environmental cues (Bonelli and Cummings, 2007). This suggests that the decrease in volitional and goal-directed activity that defines apathy may be associated with impairments in processing internal and external stimuli, regulating emotions, and integrating these cues into goals and behavior conducive to attainment of these goals (Levy and
II. THE SALIENCE NETWORK

Function

Apathy has been associated with several focal areas in the brain (see Neuroanatomical Abnormalities). However, none of these brain areas function in isolation. Approaching complex constructs such as apathy from a network perspective allows a more dynamic and holistic approach to understanding the intricate brain mechanisms that give rise to such a phenomenon. One brain network that has been associated with motivation is the salience network (SN). The SN mediates stimulus-driven, bottom-up control of attention (Uddin, 2015) by identifying stimuli that are “infrequent in space or time, or have learned or instinctive biological importance, including those that are pleasurable and rewarding, self-relevant, or emotionally engaging” among the abundance of sensory input that is processed by the brain (Knutson and Greer, 2008; Menon, 2015; Uddin, 2015). In other words, the SN detects internal states and external stimuli that are relevant for the optimal functioning of an individual (Menon and Uddin, 2010). In turn, the SN activates other networks that adjust homeostatic states, emotional experiences, cognitive processes, and overt behaviors in order to maintain goal-directed behavior (Dosenbach et al., 2007; Menon and Uddin, 2010; Gradin et al., 2013). For example, in the right hemisphere, the SN plays a key role in disengaging the default mode network (DMN) and activating the
cognitive control network (CCN) (Menon and Uddin, 2010). Failed attribution or misattribution of salience may therefore interfere with goal-directed activity, and this may be a crucial component underlying the absence of motivation in apathy (Berridge et al., 2009).

Neuroanatomy

The SN consists of several interconnected brain structures that play a key role in integrating external sensory information with internal emotional, cognitive, and physiologic signals (Menon and Uddin, 2010), particularly in the right hemisphere (Cauda et al., 2011). The main structures associated with salience processing are the insula and dACC (Figure 3). In addition, salience processing is associated with three subcortical structures, including the amygdala, ventral striatum, and substantia nigra (Menon, 2015; Uddin, 2015).

The insula lies deep within the lateral sulcus (Cauda et al., 2011), and serves to identify stimuli that are relevant for goal-directed activity among the myriad of internal and external inputs that compete for attention at any given moment. For example, during tasks that require an individual to respond to infrequently occurring target items presented among more frequently occurring distractor items (i.e., oddball tasks), the insula consistently shows greater activation in response to target items (Uddin, 2015). In order to fulfill its function, the insula predominantly receives multimodal sensory input, for example from the primary somatosensory cortex, olfactory cortex, and superior temporal sulcus, as well as from structures that govern memory, emotion, and reward processing (Menon and Uddin, 2010). In contrast, the insula produces little
motor output, but rather has efferent connections to areas such as the dorsolateral prefrontal cortex (DLPFC) and OFC (Menon and Uddin, 2010).

The insula is cytoarchitectonically divided into three regions (Cauda et al., 2011; Stephani et al., 2011). Specifically, the insula consists of an anterior, agranular region, which is connected both functionally and anatomically to a posterior granular area via a transitional dysgranual area (Cauda et al., 2011). The posterior insula (PI) receives interoceptive input such as pain, itch, touch, and the sensation of warm and cold, which it uses to inform other areas of the brain that serve to maintain physiological homeostasis. While the AI is also involved in maintaining physiological homeostasis, it has an added role of processing external and affective input. Specifically, the AI receives communications regarding interoceptive states from the PI and other sensory areas, and consolidates this input with information regarding the external environment, emotional states, and memories (Craig, 2002; Critchley et al., 2004; Singer et al., 2009; Lamm et al., 2011). As an example, while the PI is only activated when an individual receives a painful stimulus, the AI is also activated when an individual witnesses another person in pain (Singer et al., 2004).

The functional distinctions between the AI and PI suggest a more prominent role for the AI in functions subsumed by the SN. The AI is activated by a wide variety of tasks involving the subjective awareness of external events that may have a positive or negative effect on goal attainment (Craig, 2002). For example, the AI is activated by prosocial cues that elicit experiences such as love and trust, as well as by situations that involve social error, such as when
there is a sudden change in the emotional state of another individual in the environment (Allman et al., 2010). In mothers, the AI is activated in response to the sound of a crying infant (Allman et al., 2010). The AI is also activated during experiences of resentment, embarrassment, and guilt (Allman et al., 2010). Furthermore, the AI is activated during tasks that require social judgment, such as when an individual is asked to describe a person’s intentions based on facial expressions (Baron-Cohen et al., 1999), when empathy is elicited (Singer, 2006), and when an individual is exposed to another’s malevolent intentions, such as dishonesty or deceit (Baumgartner et al., 2009; Baumgartner et al., 2013). Finally, the AI is activated in response to negative feedback signaling the need for behavioral regulation (Ullsperger et al., 2010), for example, when a loss is anticipated or experienced during a gambling task (Preuschoff et al., 2008; Jones et al., 2011).

The dACC consists of Brodmann area 32, and comprises a section of the cingulate cortex that surrounds the anterior aspect of the corpus callosum (Cauda et al., 2011). In contrast to the AI, the dACC receives little sensory input, and instead has strong connections to areas that subsume executive control of cognition, emotion, and motor function, including the DLFC and premotor cortex (Mansouri et al., 2009). This allows it to fulfill its primary function of conflict monitoring and response selection (Ide et al., 2013). In the context of the SN, the dACC monitors for salient stimuli that conflict with goal-directed action (Posner and DiGirolamo, 1998; Bush et al., 2000; Paus, 2001; Walton et al., 2003; Vogt, 2005). Upon detection of information that signals a conflict, the dACC evaluates the potential rewards and losses associated with that conflict, and initiates the most favorable solution by activating other brain networks, such as the
CCN and motor system. The dACC monitors for conflict in both internal states and external events. For example, the dACC is activated when an individual is exposed to competing stimuli that require cognitive inhibition of a preponderant response (Braver et al., 2001; Albert et al., 2012), such as during signal tasks in which a prepotent response must be inhibited to allow response with a less intuitive response (Manza et al., 2016).

The AI and dACC are connected by specialized neurons present only in these brain structures (Allman et al., 2010). These neurons, known as spindle cells or von Economo neurons (VENs) (Sarter et al., 2001), are found only in humans, gorillas, chimpanzees, and bonobos. VENs are morphologically distinct, with large cell bodies, prominent axons, a simplified dendritic tree, and a spindled appearance. This morphology facilitates their function, such that VENs are able to rapidly integrate and transmit small amounts of specific information to distant parts of the brain through dopaminergic and serotonergic transmission (Butti et al., 2013; Allman et al., 2010). In contrast, neighboring pyramidal neurons are responsible for sending more detailed information, and transmission of information from these neurons occurs at a slower pace (Butti et al., 2013). In infants, the number of VENs is equal in both hemispheres. While a hemispheric balance remains into adulthood in the ACC, the number of VENs in adults is higher in the right than the left AI (Allman et al., 2010).
The Role of the SN in Apathy

Evidence for the involvement of the SN in apathy comes from both human and animal studies. First, neuroanatomical abnormalities within the AI and ACC are associated with apathy (Migneco et al., 2001; Benoit et al., 2002; Alzahrani et al., 2016). A recent resting-state fMRI study of older depressed adults with apathy revealed an association between apathy and decreased connectivity within the SN, including the right AI and dACC (Yuen et al., 2014). In an fMRI study with a partially overlapping sample, apathy in late-life depression was associated with changes in resting-state connectivity between the insula, dACC, and a variety of subcortical structures (Alexopoulos et al., 2013). In addition, electrical brain stimulation of areas within the SN elicits a sense of motivation and “the expectation of an imminent challenge coupled with a determined attitude to overcome it” (Parvizi et al., 2013). Finally, in animal studies, rodents with lesions in the SN give up more easily when required to climb over a barrier in order to reach a food pellet (Rudebeck et al., 2006).

In sum, given the role of the SN in processing and responding to motivationally relevant stimuli, as well as findings associating apathy with the brain areas involved in salience processing, it is possible that the SN is associated with the motivational deficits that underlie apathy. As such, apathy might be the consequence of decreased awareness of salient events that are relevant for goal-directed behavior.
III. THE REWARD NETWORK

Function

In addition to salience processing, brain regions commonly associated with apathy are also involved in reward processing. As such, another network that may be disrupted in individuals with apathy is the reward network (RN). Indeed, a key component to self-motivated behavior is the attribution of a potential reward to a future goal (Haber, 2011). The role of the RN can be separated into three steps (Haber, 2011). First, the RN integrates incoming sensory information with emotional valence and memories of prior outcomes in order to determine the value of current or anticipated rewards and losses. Second, the RN activates cognitive networks to determine potential responses and select the most optimal option. Finally, the RN activates networks that subsume control of cognition, motor function, emotions, and homeostasis in order to implement the selected response (Haber, 2011).

Neuroanatomy

The RN consists of a complex network of cortical and subcortical structures. At the center of the RN are the OFC, ACC, thalamus, and basal ganglia (Haber, 2011; Liu et al., 2011). While subcortical structures are involved in attaining goals that satisfy basic needs, cortical structures are more strongly associated with abstract motivators such as money, power, or challenge (Haber, 2011). The ACC and OFC mediate different aspects of reward-based behaviors, including error prediction, value attribution, and the choice between short- and long-
term gains. Specifically, the OFC attributes value and reward potential to incoming stimuli, while the ACC is responsible for computing possible methods for attaining a goal, comparing these methods for their success potential, and evaluating outcome after an action has been implemented (Posner and DiGirolamo, 1998; Bush et al., 2000; Ochsner and Gross, 2005; Etkin et al., 2006; Rudebeck et al., 2008).

The OFC is activated by stimuli such as touch, taste, and smell, as well as more abstract reinforcers such as monetary gains and losses. It then integrates this information in order to create models of reward-based cause and effect (Kringelbach and Rolls, 2004; Rolls, 2004). Damage to the OFC impairs the learning and forgetting of associations between stimuli and rewards or losses. Thus, individuals with lesions to the OFC are unable to adjust their actions according to changes in the environment that influence goal attainment (Kringelbach and Rolls, 2004; Rolls, 2004). Furthermore, individuals with damage to the OFC are less emotionally reactive to rewarding stimuli, have difficulty evaluating whether their choices have positive or negative outcomes, and demonstrate a decrease in self-motivated, goal-directed behavior (Bechara et al., 2000; Bechara, 2004).

The OFC is located in the ventromedial region of the frontal lobe. It can be divided into two distinct areas based on function and connectivity, namely the medial OFC (mOFC) and lateral OFC (lOFC). These areas are roughly equivalent to Brodmann areas 11 and 47, respectively. The mOFC has strong connections to the hippocampus, retrosplenial cortex, entorhinal cortex, and anterior thalamus (Morecraft et al., 1992; Carmichael and Price, 1995;
Cavada et al., 2000), and serves to monitor novel reward-based associations between stimuli, for example when a reinforcer is paired with a stimulus that was previously unrewarding (Mar et al., 2011). The lOFC has strong connections with the amygdala, midline thalamus, DLPFC, and temporal pole (Barbas and De Olmos, 1990; Fuster, 2001), and is implicated in inhibiting behavior when a conditioned response no longer results in the expected reward (Mar et al., 2011). As such, the mOFC and lOFC have differing roles in evaluating rewards and punishments (Kringelbach and Rolls, 2004). Specifically, stimuli associated with rewards are more prominently processed by the mOFC, whereas the lOFC is more strongly associated with processing stimuli associated with loss or punishment (Kringelbach and Rolls, 2004).

The role of the ACC within the RN is similar to the function it serves within the SN. Specifically, the ACC detects conflicts that may impede attainment of a goal, evaluates the potential rewards and losses associated with that conflict, initiates the most favorable solution by activating other brain networks (e.g., the CCN and motor system), and monitors the outcome of goal-directed actions (Bush et al., 2000). The ACC is associated with event-related potentials (ERPs) that follow negative or unintended outcomes of actions, including error-related negativity (ERN) and feedback-related negativity (FRN) (Miltner et al., 2003; Stemmer et al., 2004; Brázdil et al., 2005; Hogan et al., 2006; San Martín et al., 2010). Additionally, activation of the ACC occurs when a monetary loss is experienced on gambling tasks, and when an error is made on a decision-making task (Bush et al., 2002; Marsh et al., 2007).
The ACC can be divided into a dorsal and a rostral area based on differences in connectivity and function. The dACC includes Brodmann area 32, while the Brodmann areas included in the rACC are the subgenual area 25 and pregenual area 33 (Starkstein et al., 2001; Haber, 2011; Menon, 2015). Functionally, the dACC is more involved in reward-based decision making, while the rACC is more involved with the experience and regulation of affective responses to feedback, for example when an individual experiences frustration associated with a loss (Taylor et al., 2006).

The dACC receives little sensory input, and instead has strong connections with areas that subsume executive control of cognition, emotion, and motor function, including the DLFC and premotor cortex (Mansouri et al., 2009). This allows it to fulfill its primary function of conflict monitoring and response selection (Ide et al., 2013). In the context of the RN, the dACC monitors for task-irrelevant stimuli that conflict with goal-directed action (Posner and DiGirolamo, 1998; Bush et al., 2000; Paus, 2001; Walton et al., 2003; Vogt, 2005). Upon detection of information that signals a conflict, the dACC evaluates the potential rewards and losses associated with a conflict, and initiates the most favorable solution by activating other brain networks, such as the CCN and motor system. The dACC monitors for conflict in both internal states and external events. For example, the dACC is activated when an individual is exposed to competing stimuli that require cognitive inhibition of a preponderant response (Braver et al., 2001; Albert et al., 2012), such as during stop signal tasks, in which a prepotent
response must be inhibited to instead allow response with a less intuitive response (Manza et al., 2016).

The rACC has strong connections to structures that underlie emotional processes, such as the amygdala and hypothalamus. As such, the rACC is activated in the context of emotionally-salient distracters (Whalen et al., 1998; Shin et al., 2001; Vuilleumier et al., 2001; Bishop et al., 2004; Etkin et al., 2006). The rACC is activated during affect labeling (Kopelowicz et al., 1997; Burklund et al., 2007) and when individuals are required to distract themselves from fear-inducing stimuli (Delgado et al., 2008). Furthermore, activation of the rACC inhibits amygdala activity, which allows regulation of emotional responses and serves to decrease interference of emotional distracters during goal-directed tasks (Etkin et al., 2006; Egner, 2008).

The OFC and ACC are connected to the AI, and these connections are of crucial importance to the functions they serve within the RN. The OFC receives multimodal sensory information from the AI, which the OFC then integrates to distinguish between reinforcing and aversive stimuli (Morecraft et al., 1992). The AI also signals information regarding unfavorable, interoceptive events, such as negative emotions and pain, to the ACC, thereby allowing the ACC to determine when an action fails to result in a desired outcome (Ibanez et al., 2010; Ichikawa et al., 2011; Couto et al., 2013).
The Role of the RN in Apathy

Apathy may be associated with an inability to perceive rewards and losses, resulting in a lack of motivation to initiate goal-directed action (Levy and Dubois, 2006; Schmidt et al., 2008). Indeed, several studies have implicated the RN in apathy. For example, SPECT studies examining apathy in individuals with AD have consistently found a decrease in blood perfusion to the OFC and ACC (Craig et al., 1996; Migneco et al., 2001; Benoit et al., 2002; Robert et al., 2002; Rudebeck et al., 2006; Lanctôt et al., 2007). Furthermore, apathy is associated with disturbances in the dopaminergic mesolimbic and mesocortical pathways, which connect structures involved in reward processing. In rats, blockade of dopamine receptors inhibits the behavioral effects of rewarding and aversive stimuli (Chase, 2011). Primates with lesions in the dopaminergic mesolimbic pathway demonstrate apathetic behavior (Brown et al., 2012). In humans, depletion of dopamine in this pathway results in a decreased motivation to obtain a reward, while anticipation of a potential reward increases the firing rate of neurons within this pathway (Salamone et al., 2015). In individuals with dementia, apathy is associated with decreased dopamine uptake in the putamen and caudate nuclei, which are key subcortical structures associated with reward processing (Chase, 2011). Finally, clinical trials suggest the possible efficacy of dopaminergic agents for the treatment of apathy, which is attributed to an increase in dopamine within the mesolimbic pathway (Mann et al., 1995).
IV. INCENTIVE SALIENCE

Together, the different functions carried out by the SN and RN allow processing of incentive salience, which is required to determine which goals should be pursued and what the best strategy is to attain those goals (Delgado, 2007; Pool et al., 2016). Incentive salience involves the coupling of a desired incentive to a previously neutral stimulus, and as such, it describes the process by which an individual associates a future event with a positive valence and becomes motivated to obtain that specific goal. Incentive salience is synonymous to the action-inducing experience of “wanting”, which can be contrasted to the immediate, passive experience of hedonistic “liking” (Berridge et al., 2009; Zhang et al., 2009; Berridge and Kringelbach, 2015; Pool et al., 2016).

Incentive salience requires the integration of functions subsumed by the AI, OFC, and ACC. Specifically, within the context of incentive salience processing, the AI integrates salient sensory information, emotional experiences, and memories, and transfers this information to the OFC, where it is transformed into a conditioned stimulus with a motivational pull. The ACC then selects, initiates, and evaluates behavior that is most likely to result in attainment of the desired goal (Zhang et al., 2009; Pool et al., 2016).

Given that incentive salience requires participation of structures involved in both the SN and RN, it is possible that the processing of incentive salience is impaired in apathetic individuals, and underlies the decrease in motivation and goal-directed behavior in these individuals (Levy and Dubois, 2006; Schmidt et al., 2008). Indeed, abnormalities have been
identified in the connections between the SN and RN in individuals with apathy (Alexopoulos et al., 2013). For example, rsFC between the ACC and AI is increased in individuals with apathy, as is rsFC between the ACC and OFC (Alexopoulos et al., 2013). Another study found not only an association between apathy and poor sensitivity to reward, but also identified key involvement of the AI and prefrontal cortex, including the OFC, in reward insensitivity in apathetic individuals (Rochat et al., 2013). Finally, dopaminergic abnormalities within the mesolimbic network are associated with both apathy and the “wanting” aspect of incentive salience, as opposed to the more general “liking” aspect of the broader construct of reward (Berridge et al., 2009; Berridge and Kringelbach, 2015).

Taken together, there is evidence of impaired incentive salience in apathy, as well as abnormalities within key structures underlying incentive salience. Thus, disturbances in the assignment of incentive salience, which can result from disruptions within both the salience and reward networks, may result in the emotional indifference and decreased goal-directed behavior that characterize apathy.

V. CORTICAL THICKNESS

The Cerebral Cortex

Changes of the cerebral cortex, such as thinning and volume loss, are common in older adults and may be associated with the high prevalence of apathy in late life. The cerebral cortex is comprised of gray matter, which consists mostly of neuronal cell bodies. The gray matter
forms a folded sheet at the surface of the cerebral hemispheres and cerebellum, of which the thickness varies between 1 and 4.5 millimeters. In addition, several gray matter structures are located below the cerebellum, including the thalamus, hypothalamus and basal ganglia, and in the brainstem, including the substantia nigra, red nucleus, olivary nucleus and cranial nerve nuclei.

Substantial decreases in gray matter volume and thickness occur with age (Jernigan et al., 1991). These decreases occur secondary to morphological changes of neurons, such as a decreased neuronal size, loss of presynaptic terminals, and loss of the complexity of dendritic arborizations (Shipp, 2007). There are no specific age-related differences between left and right hemispheres changes. However, there appears to be a slightly faster decline in men than in women (Good et al., 2002). Brain areas involved in salience and reward processing appear to be particularly susceptible to cortical changes in older adults. Specifically, the prefrontal, entorhinal, and temporal cortices undergo the most prominent changes with aging (Raz et al., 1997). In contrast, the primary visual and primary somatosensory cortices appear to be more resilient to age-related processes (Raz et al., 1997). One study examined longitudinal changes in 127 non-demented individuals aged 20 to 77 over five years (Raz et al., 2005), and found the greatest decrease in volume in the lateral prefrontal cortex. In this area, there was a change in volume of 0.91% yearly, corresponding with a total mean decrease of 7.83 cm$^3$ over five years. In contrast, the smallest change was found in the primary visual cortex. This area showed a
0.05% decrease in volume per year, corresponding with a total mean change in volume of 1.51 cm³ over five years.

Measuring Cortical Thickness

Identification of changes of the gray matter is often labor intensive, and the highly folded nature of the cortex makes accurate estimation difficult. Automated methods have been developed, of which the two most widely used are measures of gray matter volume and cortical thickness (Ashburner and Friston, 2000; Fischl and Dale, 2000). Gray matter volume is measured using voxel-based morphometry, which is a procedure that requires division of gray matter into voxels, followed by a comparison of the concentration of voxels between two brain areas (Ashburner and Friston, 2000). This procedure involves spatial normalization of neuroimaging data, smoothing of gray-matter segments, and application of voxel-wise parametric statistical tests. Analysis of cortical thickness follows a similar method, including spatial normalization of neuroimaging data and smoothing of gray-matter segments. However, the final step involves estimating the distance between white matter and the pial surface at different regions in the brain.

The extent to which there is a correlation between measures of cortical volume and thickness is unclear. However, cortical thickness is less susceptible to bias caused by gray matter folding, and may therefore be considered a more valid method for measuring gray matter changes in late-life (Hutton et al., 2009; Winkler et al., 2010; Pereira et al., 2012).
VI. AIMS AND HYPOTHESES

Despite the wide-range of adversities associated with apathy in late-life depression, apathy is often left undiagnosed and untreated in these individuals (Chase, 2011). Apathy and late-life depression have distinct clinical characteristics and separable neuroanatomical abnormalities that indicate that these disorders are dissociable entities that require separate approaches to treatment (Marin, 1991; Marin et al., 1993; Levy et al., 1998; Reyes et al., 2009; Njomboro and Deb, 2012; Pardini et al., 2016). Developing a better understanding of the syndrome of apathy and elucidating its specific etiological abnormalities are crucial steps toward identifying more effective treatments for the disturbances associated with apathy in older depressed adults.

Given evidence for the involvement of fronto-subcortical structures in the apathy of late-life depression, and especially for those areas involved in the processing of incentive salience, the aim of the current study was to examine the association between apathy and gray matter abnormalities in the SN and RN. Specifically, we examined cortical thickness of the right AI, ACC and OFC in older depressed adults with and without apathy. In addition, we examined the association between these areas and persistence of apathy symptoms following 12 weeks of antidepressant treatment with the SSRI escitalopram.

We focused on cortical thickness of the right hemisphere for various reasons. First, abnormalities (e.g., focal lesions) in the right hemisphere are more commonly associated with apathy than abnormalities in the left hemisphere. Second, there is hemispheric lateralization of
the SN, such that the right AI is more strongly involved in salience processing than the left AI. Finally, VENs connecting structures within the SN occur with more abundance in the right than the left hemisphere.

Relative to non-psychiatric comparison participants, we expected there to be a high rate of apathy among individuals with late-life depression. We further hypothesized that the cortical thickness within key areas of the SN and RN (i.e., right AI, OFC, and ACC) would be less in apathetic older, depressed adults than in their non-apathetic counterparts, and that decreased cortical thickness within these areas would predict non-response of apathy symptoms to 12-weeks of escitalopram treatment.

We also performed exploratory analyses examining the cognitive profile of apathetic individuals with late-life depression in order to further characterize apathy in late-life depression. Compared to non-apathetic individuals, we expected that older, depressed adults with apathy would show impairment in executive functions, including cognitive inhibition, set shifting, and executive control aspects of memory.
METHODS

I. PARTICIPANTS

Participants were depressed or psychiatrically healthy older adults (>60 years) without dementia or mild cognitive impairment (MCI) who were recruited through radio and print advertisement in community media outlets. The patient group consisted of 50 older adults with a DSM-IV diagnosis of major depressive disorder without psychotic features. Diagnostic evaluation was conducted by clinical psychologists using the Structured Clinical Interview for DSM-IV Axis I, clinical trial version (SCID-CT) (First et al., 1995), and by study psychiatrists through clinical interview. Trained research assistants assessed eligibility using the 24-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Hamilton, 1980), and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Depressed individuals were included in the study if they met DSM-IV criteria for major depressive disorder, scored 18 or higher on the HDRS (i.e., moderate depression), and scored 25 or higher on the MMSE (i.e., cognitively intact). Depressed patients were excluded if they met any of the following criteria:

- High suicide risk with plan or intent, as determined by a study psychiatrist through clinical interview.
- Past or present axis I psychiatric disorder or substance abuse. Patients with a history of depression were not excluded. Given the high comorbidity between late-life depression and generalized anxiety disorder (GAD), patients with a history of GAD were also not excluded.
• Acute or severe medical illness within the three months preceding entry to the study.

• Current involvement in psychotherapy, given that this would bias outcome measures of response to pharmacological treatment.

The comparison group consisted of 40 non-demented participants without past or present psychiatric disorder or treatment, without acute or severe medical illness within the past three months preceding entry to the study, and with an MMSE score of 25 or higher.

Patients and controls were screened by phone, prior to being invited for an in-person visit to further assess eligibility. Participants were provided with small monetary compensations, as well as 12-weeks of free treatment with escitalopram. The Institutional Review Boards of the Weill Cornell Medical College and Rockland Psychiatric Center/Nathan S. Kline Institute for Psychiatric Research approved all procedures. All participants received a complete description of the study and signed written informed consent statements prior to participation.

II. ASSESSMENT

• Depression Severity: The 24-item HDRS was used to quantify depression severity. The HDRS is a clinician-rated, interview-based scale that evaluates a variety of symptoms commonly associated with depression during the week prior to the assessment, such as low mood, feelings of guilt, suicidal ideation, insomnia, reduced appetite, agitation/retardation, anxiety, and somatic complaints. The HDRS consists of 24 items that are scored on either a three or five point Likert scale. A total score of 0-7 is considered normal, while 18 or
higher indicates moderate depression, and a score of 30 or more suggests severe depression. The HDRS is considered by many to be the “gold standard” for assessing depression severity in clinical trials, and is the most commonly used measure of depression in clinical practice (Williams, 2001; Demyttenaere et al., 2003).

• Diagnostic Evaluation: The SCID-CT is a semi-structured diagnostic interview used to determine DSM-IV Axis I disorders. It is designed to carefully assess inclusion/exclusion criteria for clinical trials. It provides customizable indication-specific configurations of the modules. The version used for the current study was designed to provide full evaluation of mood symptoms, and screening of other DSM diagnoses.

• Apathy Severity: The clinician-rated version of the Apathy Evaluation Scale (AES) (Marin et al., 1991) was used to quantify symptoms of apathy. The AES is an 18-item scale that evaluates three dimensions of apathy within one month prior to the assessment, including behavioral apathy (e.g., “I get things done every day”), cognitive apathy (e.g., “I am interested in learning new things”), and emotional apathy (e.g., “When something good happens, I get excited”). The measure uses a four-point Likert scale that requires individuals to rate each item as "not at all,” "slightly,” "somewhat,” or "a lot.” A score of 36.5 or higher is considered an indication of clinically significant apathy (Clarke et al., 2007). The AES is among the most widely used measures of apathy severity in both research and clinical practice (Clarke et al., 2010). It includes seven items that lack correlation with the HDRS, and as such, the AES is able to reliably differentiate between
apathy symptoms and depression (Marin et al., 1991). In addition, reliability and validity of the AES has been demonstrated in adults with major depressive disorder through examination of interrater reliability, and convergent, divergent, and internal validity (Marin et al., 1991). Although informant-rated and self-report versions of the AES exist, this study utilized the clinician-rated version, given that older depressed adults with apathy may underreport psychiatric symptoms (Derouesné et al., 1999; Mograbi and Morris, 2014), and informants were not always available.

- Cognitive Functioning
  - Mini-Mental Status Examination (MMSE): The MMSE is brief screening measure that assesses cognitive impairment. Items examine a broad range of cognitive functions, including attention, working memory, orientation, language, memory, and visuomotor functioning. The maximum score of 30 can be obtained on this measure. A score lower than 25 suggests cognitive impairment. Scores ranging from 19 to 24 are considered indicative of mild cognitive impairment, while scores in the 10 to 18 point range are considered to be indicative of moderate cognitive impairment, and scores below 10 are considered indicative of severe cognitive impairment.
  - Hopkins Verbal Learning Test-revised version (HVLT): This measure evaluates learning and memory of rote information (i.e., a word list) (Benedict et al., 1998). The examiner reads a list of 12 nouns to the examinee, after which the examinee is asked to recall as many words as possible. This is repeated three times. Following a
20- to 25-minute delay, the individual is asked to again recall as many words as possible. A recognition trial is also administered, during which the examiner reads 24 words (12 target items and 12 distractor words), and the individual must indicate whether a word was on the original list. The HVLT allows the examination of several cognitive processes involved in learning, recall, recognition, and the executive control processes involved in memory (e.g., retrieval and source monitoring). As such, the HVLT taxes several brain areas, most notably in the frontal and temporal lobes.

- **Stroop Color and Word Test**: The Stroop color and Word Test (Stroop, 1935; Golden and Freshwater, 1978) was used as a measure of processing speed and cognitive inhibition. The measure consists of three trials. The first two trials evaluate processing speed, and require an individual to read the names of colors printed in black ink (“word reading”), and to name colors of rows of X’s printed in either green, red, or blue (“color naming”). The third trial consists of the words from the first trial, printed in mismatched colors from the second trial (“color/word”). An individual is required to name the color of the ink in which each item is printed, while ignoring the word that is printed. Because the meaning of the written word is a more salient aspect of each item than the color of the ink, examinees are required to inhibit the tendency to read the word in order to fulfill the task’s requirement. The score for each trial consists of the number of correct responses within a 45 second
period, such that higher scores represent stronger performance. This results in a score for all three trials, from which a fourth score is derived that quantifies an individual’s ability to inhibit salient responses. The interference score is calculated with the following formula:

\[ cw' = cw - \frac{w \times c}{w + c} \]

In this equation, “cw’” represents the interference score, “cw” is the score obtained on the color/word trial, “w” represents the score on the word trial, and “c” represents the score on the color trial.

Different trials of the Stroop Color and Word Test are associated with abnormalities in different brain areas. Left hemisphere or diffuse injuries attenuate all scores, while reduced performance on the color-naming and color/word trials are associated with right-hemisphere injuries (Golden and Freshwater, 1978), and abnormalities in the frontal lobe are associated with impaired cognitive inhibition (Perret, 1974; Golden and Freshwater, 1978; Vendrell et al., 1995). Specifically, cognitive inhibition predominantly taxes two areas of the brain, including the ACC and the DLPFC (Milham et al., 2003).

- Trail Making Test (TMT): The TMT (Army, 1944) is a measure of psychomotor speed, scanning, and rapid set shifting. The measure consists of two trials. On the first trial (trial “A”) individuals are required to connect 25 numbers scattered on a
page in sequential order. On the second trial (trial “B”), individuals are required to connect 25 numbers and letters in sequential order, alternating between numbers and letters. Two scores are derived consisting of the time taken to complete a trial. The score for trial A is considered a measure of psychomotor speed, while the score for trial B is reflective of set shifting ability. The neural networks underlying set shifting ability are complex, and involve both cortical and subcortical areas (Kramer et al., 2007; Mukhopadhyay et al., 2007). Nonetheless, set shifting is considered predominantly an aspect of cognitive control, which is mediated by the ACC and DLPFC (Nakahara et al., 2002; Ravizza and Ciranni, 2002; Brass et al., 2005).

- Wisconsin Card Sorting Test-64 item computer-version (WCST): The WCST is a measure of conceptualization, cognitive flexibility, and novel problem solving (Grant and Berg, 1948). Individuals are presented with four key cards on which different shapes are printed. Each card differs in the number of shapes, the type of the shapes, and the color of the shapes. The individual is then presented with 64 cards that also contain shapes differing in type, color, and number. Individuals are asked to match each card with a key card, and receive feedback on whether or not a match is correct or incorrect, requiring the individual to deduce matching rules from the feedback provided. The tasks allows calculation of a number of different scores, including the number of categories completed, the number of perseverative errors made, and the number of times an individual deviates from a category after several
correct responses (“failure to maintain set”). While this measure requires integration of several brain functions, it includes a prominent component of cognitive flexibility, which is subsumed by the ACC and DLPFC (Kleinman et al., 2013).

- Cortical Thickness: Cortical thickness is a brain morphometric measure used to quantify the thickness of cerebral cortex. It is measured by determining the distance between white matter and pial surfaces using semi-automated methods (see MRI procedures).

III. TREATMENT

Depressed participants entering the study underwent a two-week single-blind placebo lead-in/wash-out phase. Participants who continued to meet eligibility criteria after the first two weeks were treated with an SSRI (i.e., escitalopram) at a daily target dose of 10mg for 12 weeks, as recommended by the FDA. Depressed participants received weekly assessments throughout the treatment trial. These assessments consisted of a brief meeting with a research psychiatrist, and administration of rating scales by trained research assistants. Assessments focused on the evaluation of psychiatric symptoms and side effects; participants did not receive psychotherapy.

IV. MRI PROCEDURES

- Image Acquisition: Scans were acquired on a Siemens 1.5T Vision MR system (Erlangen, Germany) at Nathan Kline Institute’s Center for Advanced Brain Imaging.
Control participants received a scan following their baseline evaluation. Depressed participants were scanned at the end of a 2-week single-blind placebo lead-in/drug washout phase. Participants received a magnetization prepared rapidly acquired gradient echo (MPRAGE) T1-weighted scan (TR = 11.6 ms, TE = 4.9 ms, TI = 1017.6 ms, matrix = 256 × 256, FOV = 320 mm, NEX = 1, slice thickness = 1.25 mm, 172 slices, no gap), as well as a turbo dual spin echo scan (TR = 5000 ms, TE = 22/90 ms, matrix = 256 × 256, FOV = 240 mm, slice thickness = 5, 26 slices, no gap).

• Image Processing: MPRAGE images for each participant were processed using an automated segmentation method (Fischl and Dale, 2000; Fischl, 2012), which constructs boundaries between white matter and pial surface. This segmentation process consists of the following serial processing steps. First, motion corrections and intensity normalizations are applied. This is followed by an affine registration to MNI305 space (Collins et al., 1994). Next, skull stripping is performed, after which white matter, gray matter, and pial surface are identified based on intensity and neighbor constraints. Error analyses and corrections are applied throughout the segmentation process. Cortical thickness is then measured by calculating the distance between white matter and pial surface. Finally, an automated labeling system is used to identify different regions of interest (ROIs). For this final step, we used a gyral-based atlas (Desikan et al., 2006). This atlas, referred to as the Desikan-Killiany atlas, was developed based on gyral morphology, and consists of 34 cortical areas (Figure 8). The atlas was developed...
using MRI scans of 40 subjects who varied widely in age and clinical status, in order to account for variability in studies of aging and dementia. ROIs were manually delineated by tracing from the depth of one sulcus to another, thereby including both gyri and banks of adjacent sulci. The final automated cortical atlas was generated by using a probabilistic registration procedure across all 40 manually labeled brains. The current study utilized only right hemisphere structures, given evidence of right-hemisphere dominant involvement in apathy and salience processing. Because the Desikan-Killiany atlas is based on morphologically distinct regions, whereas the delineation of structures associated with the SN and RN is based on functional and connective distinctions, not all ROIs corresponded exactly with those available in the atlas. Thus, ROIs were chosen that had the greatest topographical overlap. For the AI, the atlas ROI labeled “insula” was used, which includes both the AI and PI. For the dACC, the atlas ROI labeled “caudal anterior cingulate” (cACC) was selected. This area includes the dACC (Brodmann area 32), as well as Brodmann area 24, which is a small section of the ACC that lies ventral to the dACC. For the rACC, an atlas ROI was used that is equivalent in both name and topography. This area encompasses the subgenual Brodmann area 25 and the pregenual Brodmann are 33. Atlas ROIs equivalent in both name and topography were also used for the mOFC and IOFC. These areas roughly correspond to Brodmann areas 11 and 47, respectively.
V. DATA ANALYSIS

• Statistical analyses were performed with SPSS 24.0 (Corp, 2013), G*Power (Faul and Erdfelder, 1992), and STATA (Stata, 2009).

• Data Cleaning: Missing data analyses were conducted for all variables included in the study. Adjustments to the data set were made as needed. A score was considered an outlier if it differed from either Q1 or Q3 by more than double the interquartile range. After visual inspection of any identified outlier, adjustments to the data set were made if a score was considered erroneous.

• Assumptions: The data was examined to ensure that all requirements were met before conducting any statistical analyses.
  o Normality was determined with the Shapiro-Wilk test. In addition, Q-Q plots were visually inspected.
  o Equality of variances was determined using Levene’s test.
  o Independence of observations was determined using the Durbin-Watson test. The absence of a correlation between residuals was assumed if this test resulted in a value of approximately two.
  o To test for linearity, partial regression plots for each independent and dependent variable in a model were inspected.
  o Homoscedasticity was assessed by visual inspection of scatterplots of studentized residuals and unstandardized predicted values.
o Tolerance and VIF values were used to inspect multicollinearity. If a variable had a
tolerance value of more then 0.7 and a corresponding VIF of 10 or greater,
collinearity was assumed.
o Histograms and P-P Plots were used to examine normal distribution of residuals.

- Demographics: T-tests and Fisher’s exact tests were used to compare the demographic
and clinical characteristics of controls and depressed older adults. For the t-tests,
student’s t-tests were used if Levene’s tests indicated equal variances. In all other
instances, Welch’s test was used. Demographic and clinical characteristics were also
contrasted between controls, depressed individuals with apathy, and depressed
individuals without apathy. For these analyses, one-way ANOVAs were used in
combination with Tukey’s HSD post hoc tests if Levene’s tests indicated equal
variances. In all other instances, Welch’s ANOVA and Games-Howell post hoc tests
were used.

- Treatment response: Change in apathy severity following antidepressant treatment was
calculated by subtracting week 12 AES scores from baseline AES scores. Thus, higher
AES change scores indicated a more favorable response to antidepressant treatment. T-
tests and Welch’s tests were used to examine change in symptoms of apathy and
depression following 12 weeks of antidepressant treatment. Student’s t-tests were used if
Levene’s tests indicated equal variances. In all other instances, Welch’s test was used.
• Regressions: Hierarchical linear regressions were conducted to examine the relationship between specific ROIs and AES score within the depressed group of participants. Covariates were entered at level one of each model to control for their effect on apathy severity (see Covariates). Cortical thickness of ROIs within the SN and RN was included in the second level of the analyses. The third level included interaction terms, which were calculated by multiplying the thickness of different ROIs. All analyses were conducted at an alpha level of .05.

• Covariates: Covariates were chosen based on their expected mediating properties between independent and dependent variables. Given the high correlation between depression severity and apathy, and the possible involvement of ROIs within the SN and RN in the clinical expression of both apathy and depression, HDRS scores were included at level one of hierarchical regressions examining associations between ROIs and AES scores. Modified HDRS scores were calculated by omitting items that assess apathy symptomatology in order to ensure that relevant variance was not removed from the model, including diminished work/interests, psychomotor retardation, anergia, and lack of insight (Marin et al., 1993; Yuen et al., 2014). Because individuals with higher scores on the AES and HDRS at baseline have more opportunity to decrease their scores upon receiving treatment, regression models examining change in AES score over time included both baseline AES scores and modified baseline HDRS scores. Mean cortical thickness was also included at level one of regression models examining cortical
thickness of ROIs, in order to control for inherent individual variability. Other
covariates, including age, gender, and education, were also considered. However, given
weak evidence of mediating properties for these variables, as well as non-significant
correlations between these covariates and other variables in this study’s models, these
covariates were not included.

- Exploratory analyses: For the exploratory analyses, hierarchical linear regressions were
carried out to examine the relationship between cognitive functioning and AES score
within the depressed group of participants. A modified HDRS score, as previously
described, was included in the first level of each regression model to control for the
influence of this variable. Performance on different measures of cognitive functioning
was included in the second level of the analysis. Hierarchical linear regressions were
also conducted to examine the relationship between cognitive functioning and change in
AES score following 12 weeks of antidepressant treatment. Given the high correlation
between baseline apathy and depression, and change in apathy and depression, variables
to control for these effects were included in the model at levels one and two.
Performance on different measures of cognitive functioning was included in the third
level of the analysis. All analyses were conducted at an alpha level of .05.
RESULTS

I. MISSING DATA

Among the sample of 50 older depressed adults, 92% had baseline AES data (n=46; M=36.7, SD=10.36), and 64% had week 12 AES data (n=32; M=27.63, SD=7.81). Twenty-nine participants had both baseline and week 12 AES data (Baseline AES: M=35.55, SD=11.44; Week 12 AES: M=27.07, SD=7.95). Three participants did not have baseline AES data. There was no significant difference between the week 12 AES scores of participants who did and did not have baseline AES data (t(4.4)= -2.3, p=.07). Seventeen participants did not have week 12 AES data. There was no significant difference between the baseline AES score of participants who did and did not have week 12 AES data (t(42.2)= -1.1, p=.29). One participant had neither baseline nor week 12 AES data. This participant was excluded from further analyses, resulting in a total sample size of 49 individuals with late-life depression.

Among the remaining 49 participants, all had baseline HDRS data (M=22.2, SD=3.74). Of these individuals, 69.4% also had week 12 HDRS data (n=34; M=6.91, SD=5.47). There was no difference in baseline HDRS score between participants who did and did not have week 12 data (t(23.3)= -1.2, p=.25). Baseline scores for individual items on the HDRS were available for all participants, and therefore adjusted baseline HDRS scores, which excluded apathy items, could be calculated for all participants. Seven participants with week 12 HDRS data did not have scores available for individual items on the HDRS. Therefore, adjusted HDRS scores could be calculated for 27 participants (MD=5.26, SD=5.3). There was no difference between the week 12...
HDRS scores of those who did and did not have data available for individual items (t(32)=.43, p=.67).

MRI data was complete for all 49 participants.

II. OUTLIER ANALYSES

Among the complete sample of 49 older depressed adults, none of the participants had extreme scores on the AES at either baseline or week 12. Two participants had outlying scores on the HDRS at baseline (i.e., 33 and 34). However, when compared only to individuals with apathy at baseline, these scores were not considered outliers. Therefore, these participants were not excluded from further analyses. There were no outlying scores on the HDRS at week 12. One participant had an extremely low value on IOFC thickness (i.e., 1.61). Because this score is not outside the range of what is considered typical for cortical thickness (Fischl and Dale 2000), this individual was not removed from further analysis. No outliers were identified for the cortical thickness of other ROIs. There were also no outliers in mean cortical thickness. Among cognitive measures, one individual had an extremely high number of false positive errors on the HVLT at baseline (i.e., five), and this participant was therefore excluded from the analysis. One individual had an extreme score on the TMTB at baseline (i.e., 300). This score indicates that this individual was unable to complete this task within the maximum allowed time, and this participant was therefore excluded from the analysis. No outliers were identified on any other cognitive measure.
Of the twenty-five older depressed adults who did not have clinically significant apathy at baseline, one individual had an extreme score on the TMTA at week 12 (i.e., 87). Although this score is indicative of impairment, it is not uncommon in clinical practice (Tombaugh 2004). In addition, when compared to the complete sample of 49 participants, this score did not constitute an extreme value. This individual was therefore not excluded from further analysis. There were no other outliers on measures of symptom severity, cortical thickness, or cognitive ability within the sample of non-apathetic, depressed older adults.

Other than the aforementioned extreme score of five false positive errors on the HVLT at baseline, there were no other outliers on measures of symptom severity, cortical thickness, or cognitive ability within the sample of depressed older adults who were apathetic at baseline.

III. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The entire sample included in the analyses consisted of 89 older adults. Of these, 49 participants met inclusion criteria for depression, and 40 participants were non-depressed controls (Table 1). There were no significant differences in age, gender, education, and MMSE between depressed and control participants. At baseline, depressed participants had significantly higher HDRS and AES scores than their non-depressed counterparts. There was no longer a significant difference between the AES scores of depressed participants and controls after 12 weeks of escitalopram treatment. In contrast, depressed participants continued to have significantly higher HDRS scores than controls after 12 weeks of escitalopram treatment.
Within the group of depressed older adults, 21 had a score above 36.5 on the AES at baseline, indicating clinically significant apathy (Table 2). There were no significant differences in age, gender, education, and MMSE between controls, depressed individuals without apathy at baseline, and depressed individuals with apathy at baseline. At baseline, AES scores differed significantly between controls, depressed individuals without apathy at baseline, and depressed individuals with apathy. Baseline scores on the HDRS were significantly different between controls and the samples of both apathetic and non-apathetic depressed participants, but not between depressed individuals without apathy at baseline and depressed individuals with apathy. HDRS scores at week 12 were significantly different only between controls and depressed individuals without apathy at baseline.

IV. ANTIDEPRESSANT TREATMENT RESPONSE

Among the complete sample of 49 depressed older adults, depressive symptoms were significantly more responsive to antidepressant treatment than symptoms of apathy ($t(28)=-4.53$, $p=<.01$). Participants improved an average of 15 points ($SD=7.35$) on the HDRS after 12 weeks of antidepressant treatment, which represented a 68% decrease from baseline. In contrast, the mean change in AES score following 12 weeks of antidepressant treatment was 8.48 points ($SD=10.14$), which represented a 23% decrease from baseline.

Following 12 weeks of escitalopram treatment, 55.6% of depressed older adults ($n=25$) remitted from depression. There was no difference between the remission rates of those with and
without apathy at baseline (p=.35; Fisher’s exact test). Participants with apathy at baseline experienced an average improvement of 15.77 points (SD=9.9) on the HDRS, which represented a 68% decrease from baseline. Those without apathy at baseline improved an average of 14.83 points (SD=4.58), which also represented a 68% decrease from baseline.

Within the sample of participants who were apathetic at baseline, 72.7% (n=8) no longer met apathy criteria after 12 weeks of treatment with escitalopram. The average improvement in AES score amongst those who were apathetic at baseline was 16.18 points (SD=12.42), which is a 36% improvement from baseline. There was no significant difference between change in apathetic and depressive symptoms following treatment in this sample (t(10)=.54, p=.6).

V. STRUCTURAL ABNORMALITIES WITHIN THE SN

Baseline

A three-level hierarchical linear regression was constructed to examine the association between cortical thickness within ROIs of the SN and apathy in older depressed adults (Table 3; Graph 1). Baseline AES score was included as the dependent variable. Two covariates were added at level one of the model to control for mediating effect between cortical thickness of ROIs and apathy severity, including mean cortical thickness and a modified baseline HDRS score that excluded items previously shown to be sensitive to apathy. Cortical thickness of ROIs within the SN (insula and cACC) was entered at level two of the regression. Finally, an interaction term between the insula and the cACC was added at level three. However,
examination of assumptions revealed significant multicollinearity between ROIs and this interaction term, which was not resolved by centering the variables. As such, the interaction term was omitted from the final model.

All remaining assumptions were met. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.07. Visual inspection of a plot of studentized residuals and unstandardized predicted values revealed adequate homoscedasticity. There were no studentized deleted residuals greater than ±3 standard deviations from the mean. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.

At level one of the hierarchical linear regression, depression severity was a statistically significant predictor of baseline AES score, whereas mean cortical thickness was not. Introducing the ROIs into the model at level two resulted in a non-significant increase in explained variance of 2% (F(2,41)=.37, p=.69). Within this final model, only the modified HDRS score significantly predicted baseline apathy severity on the AES.

Week 12

A three-level hierarchical linear regression was conducted to examine whether cortical thickness of ROIs within the SN were predictive of apathy severity following 12 weeks of antidepressant treatment with escitalopram (Table 4; Graph 2). In this model, week 12 AES score
was included as the dependent variable. Mean cortical thickness and a modified HDRS score at week 12 that excluded items assessing symptoms of apathy were added at level one of the model to control for their mediating effect on the dependent variable. Cortical thickness of ROIs within the SN (insula and cACC) was entered at level two of the regression. An interaction term between the insula and the cACC was added at level three. However, this again resulted in significant multicollinearity, and as such, the interaction was removed from the final model.

All remaining assumptions were met. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.57. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals and unstandardized predicted values. There were no studentized deleted residuals greater than ±3 standard deviations from the mean. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.

At level one of the hierarchical linear regression, modified week 12 HDRS score was significantly predictive of week 12 AES score, whereas mean cortical thickness was not. Adding ROIs at level two of the model resulted in an insignificant increase in explained variance of 13% (F(2,21)=3.22, p=.06). Within this model, modified week 12 HDRS score remained significantly predictive of week 12 AES score. In addition, insular thickness also significantly predicted week 12 AES score; specifically, insular thickness was decreased in individuals with higher AES scores at week 12 (B=-17.66, SE=6.97).
A three-level hierarchical linear regression was conducted to examine the extent to which cortical thickness of ROIs within the SN could predict change in apathy severity following antidepressant treatment (Table 5; Graph 3). In this model, change in AES score between baseline and week 12 was included as the dependent variable. Given the association between symptom severity at baseline and symptom improvement following antidepressant treatment, baseline AES score and modified baseline HDRS score were both included at level one of the model. In addition, mean cortical thickness was included at this level of the model to account for its mediating effect between ROI thickness and apathy severity. At level two, ROIs within the SN (i.e., insula and cACC) were added to the model. A third level consisting of an interaction term between the insula and the cACC was omitted, secondary to multicollinearity.

All remaining assumptions were met. Partial regression plots and a plot of studentized residuals against the predicted values were examined to ensure linearity. A Durbin-Watson statistic of 2.18 provided indication of independence between residuals. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals and unstandardized predicted values. There were no studentized deleted residuals greater than ±3 standard deviations from the mean. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.

At level one of the model, modified baseline HDRS score and baseline AES score were both significantly predictive of improvement in apathy following antidepressant treatment with
escitalopram. Adding cortical thickness of ROIs at level two of the model resulted in a statistically significant increase in variance explained of 8.9% ($F(2,23)=4.74, p=.02$). At level two of the model, modified baseline HDRS score and baseline AES score continued to be predictive of change in AES score. Within the SN, thickness of the insula was also significantly predictive of improvement in AES score; specifically, individuals with greater insular thickness demonstrated a greater decrease in AES score following antidepressant treatment ($B=20.12$, $SE=6.63$).

VI. STRUCTURAL ABNORMALITIES WITHIN THE RN

Baseline

A three-level hierarchical linear regression was conducted to examine the extent to which cortical thickness within ROIs of the RN predicted baseline apathy severity (Table 6; Graph 4). In this model, baseline AES score was included as the dependent variable. Modified baseline HDRS score and mean cortical thickness were entered at level one of the model to account for their mediating effect between cortical thickness of the ROIs and AES score. At level two, cortical thickness of ROIs within the RN (rACC, cACC, IOFC and mOFC) was entered. Interaction terms between orbitofrontal areas and areas within the ACC were added at level three. However, inclusion of these interaction terms resulted in significant multicollinearity, and as such, the interactions were removed from the final model.
All remaining assumptions were met. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.1. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals and unstandardized predicted values. There were no studentized deleted residuals greater than ±3 standard deviations. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.

Level one of the hierarchical regression revealed that the modified baseline HDRS score significantly predicted baseline AES score, whereas mean cortical thickness did not. A 10% change in explained variance occurred after introducing the ROIs into the model, but this change was not significant (F(4,39)=1.3, p=.29). Within this model, modified baseline HDRS score was predictive of baseline apathy severity. In addition, thickness of the rACC significantly predicted baseline apathy severity; specifically, rACC thickness was decreased in individuals with higher AES scores at baseline (B=-14.48, SE=6.56).

Week 12

A three-level hierarchical linear regression was conducted to examine the whether cortical thickness within ROIs of the RN predicted apathy following 12 weeks of antidepressant treatment (Table 7; Graph 5). In this model, week 12 AES score was included as the dependent variable. A modified HDRS score at week 12 that excluded items assessing apathy was entered
to the regression as a covariate at level one. Mean cortical thickness was also included in the model as a covariate at level one. At level two, cortical thickness of ROIs within the RN (rACC, cACC, lOFC and mOFC) was entered. Interaction terms between orbitofrontal areas and areas within the ACC were added at level three of the model. However, these again resulted in significant multicollinearity, and as such, the interactions were removed from the final model.

All remaining assumptions were met. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.54. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals and unstandardized predicted values. There were no studentized deleted residuals greater than ±3 standard deviations. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.

Level one of the hierarchical regression revealed that the modified week 12 HDRS score significantly predicted week 12 AES score, whereas mean cortical thickness did not. A 2%, non-significant change in explained variance occurred after introducing the ROIs into the model (F(4,19)=.21, p=.93). In this model, only the modified week 12 HDRS score significantly predicted week 12 AES score.
Change in Apathy Severity

A three-level hierarchical linear regression was conducted to examine the association between cortical thickness within ROIs of the RN and change in apathy following 12 weeks of antidepressant treatment (Table 8; Graph 6). In this model, a variable reflecting the difference between AES score at baseline and week 12 was included as the dependent variable. Given the association between symptom severity at baseline and symptom improvement following antidepressant treatment, baseline AES score and a modified baseline HDRS score were both included at level one of the model. In addition, mean cortical thickness was included at this level of the model to account for its mediating effect between ROI thickness and apathy severity. Cortical thickness of ROIs within the RN (rACC, cACC, lOFC, and mOFC) was entered at level three of the regression. Interaction terms between orbitofrontal areas and areas within the ACC were added at level three. However, inclusion of these interaction terms resulted in significant multicollinearity, and as such, the interactions were removed for the final model.

All remaining assumptions for this analysis were met. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.96. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals and unstandardized predicted values. There were no studentized deleted residuals greater than ±3 standard deviations. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.
At level of one of the model, modified baseline HDRS score and baseline AES score significantly predicted change in apathy severity. The amount of variance explained by the model increased by 11% following introduction of the ROIs (F(4,21)=.2, p=.94). At level two of the model, only modified baseline HDRS score and baseline AES score were significantly predictive of change in apathy severity with escitalopram treatment.

VII. COGNITIVE FUNCTIONING

Baseline

A two-level hierarchical linear regression was conducted to examine the association between measures of cognitive functioning and apathy in late-life depression (Table 9). Baseline AES score was included as the dependent variable in this model. Modified baseline HDRS score was added at level one of the model to control for the mediating effect of depression severity on apathy. Measures of cognitive functioning were added at level two of the model. The word-reading, color-naming, and color/word trials of the Stroop Color and Word test were omitted to reduce multicollinearity.

All remaining assumptions were met. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.87. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals and unstandardized predicted values. There were no studentized deleted residuals greater than ±3
standard deviations. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.

Level one of the hierarchical regression revealed that baseline HDRS score accounted for 5% of the variance in baseline AES score, which was not statistically significant (F(1,31)=1.54, p=.23). A 30% change in explained variance occurred after introducing measures of cognitive functioning into the model; however, this change was also non-significant (F(12,19)=.74, p=.7). None of the individual variables were significantly predictive of baseline AES score at any level of the model.

Week 12

A two-level hierarchical linear regression was conducted to examine the association between measures of cognitive functioning and apathy in late-life depression following 12 weeks of antidepressant treatment (Table 10). Week 12 AES score was included as the dependent variable in this model. Modified week 12 HDRS score was added at level one of the model to control for the effect of depression on apathy severity. Measures of cognitive functioning were added at level two of the model. Because the word-reading, color-naming, and color/word trials of the Stroop Color and Word test were found to have collinearity, these were omitted from the final model.

All remaining assumptions were met. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was
independence of residuals, as assessed by a Durbin-Watson statistic of 1.63. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals and unstandardized predicted values. There were no studentized deleted residuals greater than ±3 standard deviations. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.

Level one of the hierarchical regression revealed that modified week 12 HDRS score accounted for a significant 46% of the variance in week 12 AES score (F(1,18)=15.23, p<.01). A 32% increase in explained variance occurred after introducing measures of cognitive functioning into the model, which was a non-significant change (F(12,6)=.75, p=.69). Only modified week 12 HDRS score significantly predicted week 12 AES score in this model.

Change in apathy severity

Two hierarchical linear regressions were conducted to examine the association between cognitive functioning and improvement in apathy following antidepressant treatment. The first included performance on cognitive measures at baseline (Table 11), and the second included performance on cognitive measures at week 12 (Table 12). In both models, a variable reflecting change in AES score between baseline and week 12 was included as the dependent variable. Given the association between symptom severity at baseline and symptom improvement following antidepressant treatment, baseline AES score and a modified baseline HDRS score were both included at the first level of the models. Measures of cognitive functioning were added
at level two of the models. The word-reading, color-naming, and color/word trials of the Stroop Color and Word test were omitted to reduce multicollinearity.

All remaining assumptions for this analysis were met. There was linearity, as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.46 for the baseline model and 1.55 for the week 12 model. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals and unstandardized predicted values. There were no studentized deleted residuals greater than ±3 standard deviations. The assumption of normality of residuals was met, as assessed by inspection of P-P Plots.

Regarding cognitive functioning at baseline, the hierarchical regression revealed that at level one, both modified HDRS score at baseline and AES score at baseline significantly predicted change in AES score. Introducing cognitive measures into the model at level two resulted in a statistically significant increase in variance explained of 43% (F(12,5)=7.0, p=.02). Within this model, modified baseline HDRS score was significantly predictive of change in AES score, whereas baseline AES score was not. Several measures of cognition at baseline also significantly predicted change in apathy severity following antidepressant treatment. Individuals who demonstrated a greater decrease in AES score had higher baseline scores on HVLT immediate recall (B=2.08, SE=.81), lower baseline scores on HVLT delayed recall (B=-2.89, SE=.85), an increased number of HVLT false positive errors at baseline (B=-5.28, SE=2.0),
slower performance on TMT A (\(B=.45, SE=.11\)), and faster performance on TMT B (\(B=-.15, SE=.02\)).

Regarding cognitive functioning at week 12, both modified HDRS score at baseline and AES score at baseline significantly predicted change in AES score. Introducing cognitive measures into the model at level two resulted in a statistically insignificant increase in variance explained of 14% (\(F(12,9)=.77, p=.67\)). Within this model, modified baseline HDRS score remained significantly predictive of change in AES score, whereas baseline AES score did not. None of the measures of cognition at week 12 were significantly predictive of change in apathy severity.
DISCUSSION

I. MAIN FINDINGS

Apathy is a common comorbidity in late-life depression (Yuen et al., 2014). Amongst older depressed adults, apathy is associated with a number of adverse outcomes above and beyond those associated with the depressive illness, such as decreased quality of life, increased disability, exacerbation of comorbid illness, and higher rates of mortality (Starkstein et al., 1993; Onyike et al., 2007; Reyes et al., 2009; Hölttä et al., 2012; Groeneweg-Koolhoven et al., 2014). Apathy nonetheless remains broadly overlooked and undertreated in these individuals (van Reekum et al., 2005). Indeed, the etiological substrates of apathy in late-life depression remain poorly understood, and little is known about its optimal treatment. To this end, the aim of the current study was to examine cortical abnormalities within the SN and RN, two brain networks that have a plausible association with the syndrome of apathy in older depressed adults.

Specifically, we examined the association between AES score and cortical thickness of the right insula, cACC, rACC, mOFC, and lOFC in 49 individuals with late-life depression before and after antidepressant treatment with escitalopram. Within the SN, cortical thickness of the insula was significantly associated with response of apathy symptoms to escitalopram, as well as severity of apathy symptoms after 12 weeks of treatment. Within the RN, thickness of the rACC was significantly related to apathy severity before treatment was initiated. Thickness of the mOFC and lOFC was not associated with apathy at any time. Thickness of the cACC, which is involved in both salience and reward processing, was also not associated with apathy at any time.
Exploratory analyses examining the association between cognitive functioning and apathy revealed a relationship between the extents to which apathy symptoms improved with escitalopram treatment and several aspects of cognition, including processing speed, executive functioning (i.e., set shifting and source monitoring), and memory (i.e., encoding and retention of verbal information).

II. APATHY AND LATE-LIFE DEPRESSION

The current results support previous reports of high comorbidity between apathy and depression in late-life. The prevalence of apathy in this study of older depressed adults was 46%. This is consistent with other studies, which have found prevalence rates of apathy in elderly depressed individuals of 35.5% (Yuen et al., 2014), 43% (Groeneweg-Koolhoven et al., 2015), and 53% (Marin et al., 1994). In contrast to other studies (Okada et al., 1997; Kant et al., 1998), the current results revealed a strong association between apathy and depression severity. This contradicts the premise that apathy is a clinically distinct entity that should be considered in isolation from depression (Yuen et al., 2014). However, depressive symptoms were found to be significantly more responsive to antidepressant treatment than symptoms of apathy. In fact, the response of apathetic participants to antidepressant medication in the current study was less than reported in previous studies (Bolling and Kohlenberg, 2004; Yuen et al., 2014). Apathy persisted in 27.3% of older depressed adults following treatment with escitalopram. In contrast, another study documented persistence of apathy in 18.6% of older depressed adults (Bolling and
Kohlenberg, 2004), and in a study with a smaller sample of older depressed adults that overlapped partially with the sample included in the current study, apathy persisted in 15.6% of older depressed adults (Yuen et al., 2014). This differential response of apathetic and depressive symptoms to antidepressant treatment suggests that apathy has neurobiological underpinnings that are distinct from depression, and may not be adequately targeted with SSRI treatment.

III. CORTICAL THICKNESS

The current findings suggest a role for salience processing in the clinical expression of apathy. Results indicated that a decrease in cortical thickness of the insula is associated with poor response of apathy symptoms to antidepressant treatment, as well as with the severity of apathy symptoms following treatment. Baseline apathy severity was not associated with cortical thickness of the insula, which suggests that the SN may be involved specifically in the mechanism by which antidepressant medication alleviates apathy symptoms, but not in the expression of apathy symptoms per se.

These findings are consistent with prior studies that used a partially overlapping sample (Alexopoulos et al., 2013; Yuen et al., 2014). In one study, depressed older adults with apathy had an abnormal pattern of rsFC between the insula, dACC, NAcc, and several other subcortical structures (Alexopoulos et al., 2013). In another study, apathetic individuals with late-life depression showed a decrease in rsFC within the SN, and an increase in rsFC between the right AI and right DLPFC compared to their non-apathetic counterparts (Yuen et al., 2014).
Other studies provide further support for the involvement of neuroanatomical abnormalities of the AI and SN in apathy (Benoit et al., 2004; Alzahrani et al., 2016). For example, electrical brain stimulation of areas within the SN has been reported to elicit a sense of motivation and determination (Greicius et al., 2004; Parvizi et al., 2013). Rodents with lesions in the SN give up more easily when required to climb over a barrier in order to reach a food pellet, which suggests that these animal may experience the equivalent of apathy symptoms in humans (Rudebeck et al., 2006). Finally, a graph theory study examining apathy and depression in middle-aged and older adults found that while depression was characterized by increased processing within the SN, apathy was associated with decreased processing within the SN (Onoda and Yamaguchi, 2015).

The right AI plays a prominent role in identifying internal and external stimuli that may facilitate or interfere with goal-directed activity. Upon detection of such cues, it activates other networks that adjust homeostatic states, emotional experiences, cognitive processes, and overt behaviors in order to stay on task (Gehring et al., 1993; Dehaene et al., 1994; Klein et al., 2007; Lamm and Singer, 2010). To this end, the AI receives communications regarding interoceptive states from the PI and other sensory areas, consolidates this information with information regarding the external environment, memories, and internal states, and activates brain areas involved in emotion, higher order cognition, and complex behavior, such as the amygdala and ventral striatum (Craig, 2002; Critchley et al., 2004). As such, apathy might be the consequence of decreased identification of events that are relevant for maintaining goal-directed behavior.
The finding that rACC thickness is associated with apathy severity in untreated patients with late-life depression is indicative of a role for the RN in the clinical expression of apathy symptoms. Of note, although thickness of the right rACC was not associated with treatment response or persistence in this study, a prior study using a partially overlapping sample revealed that response of apathy symptoms to SSRI treatment was associated with larger left posterior subgenual cingulate volume (Yuen et al., 2014).

The rACC is activated in the context of emotionally-salient distracters (Whalen et al., 1998; Shin et al., 2001; Vuilleumier et al., 2001; Bishop et al., 2004; Etkin et al., 2006), and plays a crucial role in the affective evaluation of experienced and anticipated rewards and losses (Bush et al., 2000; Etkin et al., 2011; Toda et al., 2012). In addition, the rACC is involved with the regulation of affective responses to feedback, for example when an individual interprets a loss as a frustrating event (Taylor et al., 2006). Thus, the current results suggest that impairment in an individual’s ability to attribute emotional valence to rewards and losses may contribute to the decline in motivation that characterizes apathy.

Interestingly, abnormalities of the rACC are also implicated in depression. The rACC plays a role in the resolution of emotional conflict, as well as the inhibition of task-irrelevant emotional experiences, through top-down, inhibitory modulation of the amygdala and other limbic regions (Devinsky et al., 1995; Whalen et al., 1998; Bush et al., 2000; Phan et al., 2002). Depression is associated with hypoactivation of the rACC and hyperactivity of the amygdala (Hull, 2002). Hypoactivity of the rACC is predictive of poor response to antidepressant treatment.
(Kumari et al., 2003), and higher rACC activation is associated with a more favorable response (Etkin et al., 2006). Thus, it is possible that deficient limbic inhibition by the rACC may result in a preponderance of negative experiences, which may interfere with the association of positive valence with potential future rewards, thereby depleting an individual of the motivation to dedicate resources to the attainment of those rewards. This may play a role in the development of both depression and apathy (Etkin et al., 2006), and may explain the frequent co-occurrence of apathy and depression in older adults.

The rACC has strong connections to the AI (Whalen et al., 1998; Shin et al., 2001; Vuilleumier et al., 2001; Bishop et al., 2004; Etkin et al., 2006). Together, these structures contribute to the attribution of incentive salience to stimuli. Thus, abnormalities in the processing of incentive salience may contribute to the clinical expression of apathy. Individuals with apathy may not experience the motivational drive and behavioral activation that is associated with reward anticipation in non-apathetic individuals. However, from this perspective it is noteworthy that the cACC was not predictive of apathy in the current study. Compared to the cACC, the rACC is more prominently implicated in affect regulation and has strong connections to areas that underlie emotional processes, such as the amygdala and hypothalamus (Mansouri et al., 2009), whereas the cACC plays a bigger role in cognition and has strong connections with brain regions that mediate cognitive control processes, such as the DLPFC. This suggests that while incentive salience may be impaired in older depressed adults with apathy, the lack of motivation in these individuals is likely to be specific to an inability to associate desire with a reinforcing
stimulus, as opposed to an impairment in the formulation and execution of activity required to attain a reinforced goal.

Neither the medial nor the lateral areas of the OFC were associated with apathy severity at baseline, week 12, or response to treatment. The OFC is activated by stimuli such as touch, taste, smell, and more abstract reinforcements such monetary gains and losses, and integrates this information in order to create predictions of losses and rewards (Kringelbach and Rolls, 2004; Rolls, 2004). Damage to the OFC impairs the learning and forgetting of associations between stimuli and their potentially reinforcing or aversive qualities. Furthermore, individuals with damage to the OFC are less emotionally reactive to rewarding stimuli and have difficulty evaluating whether choices made have positive or negative outcomes (Bechara et al., 2000; Bechara, 2004). Thus, individuals with lesions to the OFC are unable to adjust their actions to task-related changes in the environment that may effect the attainment of rewards (Kringelbach and Rolls, 2004; Rolls, 2004). Given these functions of the OFC, combined with the current non-significant findings, it appears that learning of reward associations may not be required for the lack of motivation that is associated with apathy.

IV. COGNITIVE FUNCTIONING

Regarding exploratory analyses, several aspects of baseline cognition were related to improvement in apathy severity following escitalopram treatment, including processing speed, executive functioning (i.e., set shifting and source monitoring), and memory (i.e., encoding and
retention of verbal information). These associations with apathy were specific to change in symptom severity with antidepressant treatment, and were not present either before or after antidepressant treatment. Thus, it is possible that the structural abnormalities underlying impairment in these cognitive domains interfere with the mechanism by which serotonergic antidepressant medication alleviates apathy symptoms in older depressed adults, but are not directly associated with the clinical expression of apathy.

In the current study, decreased processing speed was associated with a weaker response of apathy symptoms to antidepressant treatment. Other studies have found similar associations between processing speed and apathy. One study examining processing speed in apathetic individuals with depression found an additive, detrimental effect of apathy on processing speed (Cohen et al., 2015). Another study examining apathy in individuals with HIV demonstrated that apathy attenuated age-related declines in processing speed (Shapiro et al., 2013). Finally, a case study of an individual with apathy secondary to radiation necrosis of the bilateral mesial frontal lobe reported reduced processing speed in the context of otherwise intact functioning of the cognitive processes typically associated with the frontal lobe (Kirsch-Darrow et al., 2006).

Processing speed is often considered a fundamental aspect of cognition. Although processing speed is typically associated with overall white matter integrity (Penke et al., 2010), decreased processing speed may also be associated with more focal white matter abnormalities. For example, a study that applied VBM to diffusion tensor images from 39 healthy, adult participants found an association between processing speed and structural integrity of white
matter tracts in only the parietal cortex, temporal cortex, and left middle frontal gyrus (Turken et al., 2008). Decreased processing speed may interfere with many other cognitive processes, including those found to be associated with apathy in the current study. However, controlling for processing speed in the current study did not remove the relation between other cognitive difficulties and apathy. These associations therefore likely exist independent of changes in processing speed.

The current findings revealed a relationship between set shifting and the response of apathy symptoms to antidepressant treatment. However, contrary to expectations, the results revealed that individuals with better set-shifting ability had a weaker response of apathy symptoms to antidepressant treatment, which is in contrast to prior to studies. For example, several studies examining set shifting in individuals with apathy and comorbid depression have found that set shifting impairments are specific to apathy, and are unrelated to depression (Varanese et al., 2011; Klaasen et al., 2017). Set shifting is typically associated with activation of the DLPFC (Yochim et al., 2007). For example, in a study of 101 participants with various types of dementia, set shifting was associated with bilateral frontal lobe volumes, but not with cortical volume in any other brain region (Kramer et al., 2007). An fMRI study of set shifting in 12 healthy adults found activation in favor of the left hemisphere, most notably in regions of the frontal lobe, and in the middle temporal and superior temporal gyrus (Zakzanis et al., 2005). Associations between set shifting and areas of the left, as opposed to the right, hemisphere were also found in another, similar study (Moll et al., 2002). In this study, set shifting was specifically
associated with the left DLPFC and medial prefrontal cortex. Thus, the current results, taken
together with other findings of the neuroanatomical localization of set shifting abilities, suggest
a possible role for the left hemisphere in apathy of late-life depression, particularly in treatment
response to antidepressant medication.

Interestingly, there was no association between cognitive flexibility, perseveration, and
apathy improvement in response to antidepressant treatment in the current study, even though
these aspects of cognition are often considered synonymous with set shifting. Similar to set
shifting, cognitive flexibility and perseveration are subsumed primarily by areas in the prefrontal
cortex, particularly the DLPFC (Mukhopadhyay et al., 2007; Head et al., 2009; Konishi et al.,
1998; Lombardi et al., 1999; Kleinman et al., 2013). The DLPFC is one of the key nodes of the
CCN (Langenecker et al., 2007). Within the CCN, the ACC monitors for the presence of conflict,
and activates the DLPFC to resolve the conflict using adjustment processes, for example when
there is a need for switching attentional focus based on task requirements (Milham et al., 2003;
Erickson et al., 2004). Although the CCN has been implicated in treatment non-response in older
depressed adults (Pimontel et al., 2012), the current results provide inconclusive results
regarding the involvement of the CCN in the persistence of apathy in older depressed adults.

Source monitoring was associated with decreased improvement in apathy severity
following antidepressant treatment in the current study. Impaired source monitoring is associated
with a disturbance in the process of conjoining knowledge of information with details about the
source of that information (Johnson and Raye, 1981; Johnson et al., 1993; Johnson, 1997).
Source monitoring is considered an executive control process that underlies memory, as opposed to a primary memory function, given that it is more prominently associated with activation in areas of the brain that are responsible for frontally-mediated, “higher order” cognition, rather than with areas of the temporal lobe that are typically involved in primary memory processes such as learning and retention of information. For example, while amnestic individuals with lesions in the mesial temporal lobe demonstrate impairment in encoding, consolidation, and retrieval, they do not necessarily have difficulty with source monitoring (Kopelman et al., 1997). In contrast, individuals with frontal lobe lesions demonstrate impaired source monitoring, including extremely high rates of false positive errors (Buckner et al., 1995; Parkin et al., 1995; Schacter et al., 1996; Kopelman et al., 1997; Schacter and Coyle, 1997). Individuals with lesions to the right OFC and anterior prefrontal cortex are particularly susceptible to source monitoring errors (Buckner et al., 1995; Parkin et al., 1995; Schacter et al., 1996; Schacter and Coyle, 1997).

Give the lack of an association between the OFC and apathy in the current study, these results do not fully explain the association between source monitoring and change in apathy severity with antidepressant treatment.

Several primary memory processes were also associated with response of apathy symptoms to antidepressant treatment, namely encoding and retention of verbal information. Interestingly, a stronger response of apathy symptoms to antidepressant treatment was associated with better encoding of verbal information, while individuals whose apathy symptoms responded to antidepressant medication demonstrated weaker retention of information. Other studies have
also found associations between these memory processes and apathy. In one study of 38 individuals with schizophrenia and comorbid apathy, apathy severity was associated with performance on a measure of verbal learning and recall (Roth et al., 2007). In a study of 48 individuals with PD, apathy was more strongly associated with performance on a measure of immediate recall than with performance on a wide variety of other neuropsychological tasks, including processing speed, attention, working memory, and executive functioning (Varanese et al., 2011). Interestingly, in a study of 53 individuals with severe TBI, only the cognitive dimension of apathy was associated with weak information encoding, whereas no such association was found for the behavioral and emotional dimensions of apathy (Andersson and Bergedalen, 2002).

Deficits in an individual’s ability to retrieve information may mimic difficulties with retention (Stuss and Knight, 2013). In these cases, individuals are unable to access information that was nonetheless learned and retained over time. Individuals may perform poorly on spontaneous recall tasks, while their recall will improve when provided with recognition cues that decrease the need for self-guided retrieval. Similar to the aforementioned source monitoring, retrieval is considered an executive control process that underlies memory, as opposed to a primary memory function, given that retrieval of information is subsumed by prefrontal areas of the brain that are responsible for executive processes, as opposed to the areas of the temporal lobe that are primarily involved in encoding and retention (Stuss and Knight, 2013). For example, in a study examining individuals with frontal lobe lesions, lesions located in the left
posterior DLPFC and the posterior medial frontal lobe demonstrated impairment in both learning and retention, but this was secondary to retrieval difficulties (Alexander et al., 2003). Given that true positive responses on a recognition task were not associated with treatment response of apathy symptoms in the current study, it is possible that frontally-mediated retrieval deficits underlie the association between retention and apathy in older depressed adults.

Contrary to expectation, there was no significant association between apathy and cognitive inhibition on the Stroop Color and Word task. Cognitive inhibition requires activation of the CCN, which involves both conflict detection and response regulation. The ACC is commonly regarded as the main structure involved in conflict detection, and abnormalities within the ACC may therefore result in impairment in cognitive inhibition. Within this context, the rostral and caudal regions of the ACC play different roles, such that the rACC is involved in processing emotional conflicts, whereas the cACC is involved in processing non-emotional conflicts. These distinctions are evident on tasks assessing cognitive inhibition. While the need for cognitive inhibition on the Stroop Color and Word task activates the cACC, the rACC is activated when there is a demand for inhibition of an emotional response. Two studies found greater activation of the rACC than the cACC during a task that required individuals to categorize images of faces based on their emotional expression (e.g., happy or sad), while ignoring words describing congruent or incongruent emotions (e.g., “HAPPY” or “SAD”) (Etkin et al., 2006; Egner, 2008). Thus, the lack of an association between cortical thickness of the
cACC and apathy in the current study may explain the additional absence of a correlation with performance on the Stroop Color and Word task.

V. CLINICAL IMPLICATIONS

The current findings have important clinical implications. First, the findings support the clinical and etiologic distinction between apathy and depression in older adults. The current results also add to the literature suggesting that SSRI treatment does not adequately target apathy symptoms in older depressed adults. Indeed, other studies demonstrate that treatment of older depressed adults with SSRIs may, in fact, exacerbate symptoms of apathy (Barnhart et al., 2004; Wongpakaran et al., 2007; Leontjevas et al., 2013; Lanctôt et al., 2017). Thus, taken together with prior research, the current results support the need for an alternative approach to the treatment of apathy in late-life depression.

The finding that apathy in older depressed adults may be associated with impaired incentive salience suggests a role for dopamine abnormalities in the clinical expression of apathy. While dopamine is historically considered to be associated with reward processing in general, more recent studies suggest that dopamine is specifically involved in the processing of incentive salience, such that dopaminergic transmission in the mesolimbic pathway modulates reward attribution and anticipation (i.e., “wanting”), as opposed to hedonistic experiences (i.e., “liking”) (Berridge and Robinson, 1998; Berridge, 2007). Dopaminergic abnormalities in the mesolimbic pathway may therefore be associated with an impaired experience of motivational
value, which, in turn, may underlie the clinical expression of apathy symptoms in older adults with late-life depression.

The possible involvement of dopaminergic abnormalities may also explain the poor response of apathy symptoms to SSRI treatment. There is an intricate balance between monoaminergic neurotransmitters, such that serotonin has an inhibitory effect on dopaminergic activity in the frontal lobe and striatum. Thus, the increase in serotonin that results from SSRI treatment may lead to a decrease in dopamine transmission (Kapur and Remington, 1996), thereby preventing remission of apathy symptoms, or even exacerbating these symptoms.

Studies examining the role of dopamine in apathy have consistently found associations between decreased activity in dopaminergic systems and increased apathy. For example, a comprehensive review examining the association between dopamine and symptoms of apathy in individuals with AD concluded that dopaminergic abnormalities are associated with the clinical expression of apathy in these individuals (Mitchell et al., 2010). A study examining apathy severity and striatal dopamine uptake in individuals with AD and LBD found a relationship between apathy and dopamine transporter levels, suggesting that apathy may be associated with loss of dopaminergic neurons in the striatum (David et al., 2007). Similar results were found in another study examining the association between apathy and dopamine transporter levels. In this study, apathetic individuals with PD had less dopamine uptake in the striatum than their non-apathetic counterparts, most notably in the right caudate (Santangelo et al., 2015).
Despite evidence of dopaminergic abnormalities in apathy, there are limited clinical trials examining the use of dopamine agonists for the treatment of apathy. In a case study examining the use of ropinirole in an individual who developed apathy after a cerebral infarction in the prefrontal cortex, improvement was seen in “verbal output and spontaneity in daily life” following treatment, and this was associated with an increase in blood flow in the prefrontal cortex and basal ganglia (Kohno et al., 2009). In a 12-week randomized controlled trial examining piribedil for the treatment of apathy in individuals with PD, quantitative ratings of apathy symptoms on the Starkstein Apathy Scale improved by 46.6% in those treated with piribedil, whereas ratings of apathy symptoms on this scale worsened by 2.3% in those treated with placebo (Thobois et al., 2013). Modafinil has been shown to effectively decrease apathy symptoms in AD (Frakey et al., 2012). Bromocriptine and amantadine have been studied primarily in individuals with TBI, stroke, and PD. Results indicate decreased apathy, and increased motivation, initiative, and spontaneity following treatment with this medication (van Reekum et al., 2005). Methylphenidate and d-amphetamine have been examined in a wide range of neurologic disorders, including AD, stroke, Wilson’s disease, and HIV-related dementia, and have been shown to decrease apathy and social withdrawal, and increase motivation, physical activity, attention to personal hygiene, and independence in activities of daily life (Herrmann et al., 2008; Padala et al., 2010; Martin et al., 1995; Bonelli and Cummings, 2007).

In addition to dopaminergic agents, the use of acetylcholinesterase inhibitors is also of interest for the treatment of apathy in older depressed adults, given that dopamine depletion may
be alleviated by an increase in acetylcholine (Martorana et al., 2009). Indeed, several studies examining the use of acetylcholinesterase inhibitors for the treatment of cognitive decline in individuals with neurodegenerative disorders have found a response of apathy symptoms to treatment (Bonelli and Cummings, 2007; Cummings and Back, 1998; Kaufer et al., 1998). A meta-analysis of randomized controlled trials concluded that metrifonate was useful for the decrease of apathy severity in individuals with AD (Lopez-Arrieta and Scheider, 2006). Studies have also demonstrated beneficial effects of tacrine (Kaufer et al., 1996) and donepezil (Waldemar et al., 2011) on apathy symptoms in individuals with AD. Finally, apathy is effectively treated with rivastigmine in individuals with PD (Moretti et al., 2017) and LBD (McKeith et al., 2010).

In summary, there is strong, albeit limited data suggesting a crucial role of dopaminergic abnormalities in the clinical expression of apathy symptoms, as well the utility of dopamine-enhancing agents for the treatment of apathy. These agents include not only medications that directly increase dopaminergic activity, but also agents that indirectly effect dopamine transmission, such as acetylcholinesterase inhibitors.

VI. LIMITATIONS

The results of the current study should be interpreted in the context of several limitations. First and foremost, the number of participants was relatively small, particularly in the group of apathetic individuals at week 12. This limitation is further complicated by the large number of
variables in the regression analyses, which may have resulted in overfitting. Regarding the neuroanatomical regions included in the analyses, use of a preexisting atlas with parcellations based on morphology, as opposed to functional or connectivity properties, may have decreased the accuracy of the ROIs included in the analyses. For example, the literature clearly stipulates a more pronounced role for the AI in salience processing, as opposed to the PI. However, the Desikan-Killiany atlas does not distinguish between anterior and posterior areas of the insula, and as such, the ROI used in the current study included the entire insular region. It should also be noted that cortical thickness is merely an indirect measure of a presumed disease-related process, as is the case with all imaging-based modalities. Specifically, a decrease in cortical thickness is considered unfavorable, in that it presumably reflects a detrimental decline of healthy cerebral tissue. However, cortical thickness is not a direct measure of cerebral health, and as such, it may in fact not be a valid indice of pathology. Finally, although all participants in the current study were screened for dementia, it cannot be ruled out that some individuals may have been in a prodromal phase of dementia. Thus, it cannot be ruled out that all individuals with apathy were affected by the same disease processes.

VII. FUTURE DIRECTIONS

The current finding of an association between apathy and cortical thickness within the SN and RN in older depressed adults contributes to the literature aiming to extricate the
neuroanatomical mechanisms underlying apathy. However, there is still a grave need for further examination of causal factors underlying apathy, as well as of potential treatment modalities.

Further exploration of the neuroanatomical abnormalities associated with apathy in late-life depression is warranted. First and foremost, long-term follow-up studies with a larger number of participants will allow the relationship between apathy and abnormalities within the SN and RN to be explored with more confidence. In addition, there is a need for examination of the role of the left hemisphere in the clinical expression of apathy. The current results revealed an association between set shifting and apathy, which, taken together with other findings of the neuroanatomical localization of set shifting abilities, suggests that there may be a possible role for the left hemisphere in the apathy of late-life depression. In addition, although the right insula is more commonly associated with salience processing than the left insula, there is also evidence of specialized hemispheric involvement. While the right insula is associated with processing of sympathetic arousal and aversive stimuli, such as disgust and anxiety, the left insula may be involved in parasympathetic nervous functions and processing of positive emotions (Cauda et al., 2011). Finally, although thickness of the right rACC was not associated with treatment response or persistence in this study, a prior study using a partially overlapping sample revealed that response of apathy symptoms to SSRI treatment was associated with larger left posterior subgenual cingulate volume (Yuen et al., 2014).

Studies examining white matter abnormalities in older depressed adults with apathy will also be important. It is possible that apathy may be caused by disturbances in the connections
within and between structures of the SN and RN, while the actual structures may be unaffected. This is suggested by the current finding of decreased processing speed in apathy, which is often associated with diffuse disturbances of white matter integrity. Finally, the possible involvement of subcortical areas in apathy should be explored. For example, the ventral striatum is involved in both salience and reward processing (Haber, 2011; Menon, 2015), and may therefore contribute to the clinical expression of apathy in late-life depression.

Future studies examining neuroanatomical abnormalities associated with apathy should distinguish between the different dimensions of the syndrome, given that different dimensions of apathy may be associated with distinct neuroanatomical abnormalities. For example, there is evidence that emotional apathy may be associated with abnormalities in the orbital and medial prefrontal cortex, while cognitive apathy may be associated with abnormalities in the basal ganglia (i.e., caudate nucleus, globus pallidus, substantia nigra) and anterior thalamic nuclei, and behavioral apathy may be associated with abnormalities in the caudate nucleus, globus pallidus, medial dorsal thalamus, and dorsal and ventral ACC (Levy and Dubois, 2006). In addition, one study found that cognitive apathy was associated with weak performance on information encoding, whereas no such association was found for the behavioral and emotional dimensions of apathy (Andersson and Bergedalen, 2002). This further supports differing etiologies for the different dimensions of apathy. Given current findings indicating a role for the rACC in apathy, but not the cACC, a more fine-tuned perspective on the involvement of these cortical structures may be provided by contrasting the emotional and cognitive dimensions of apathy.
Regarding treatment, future research should focus on examining the role of dopamine deficiency in the clinical expression of apathy. For example, clinical trials should examine the efficacy of dopaminergic agents in older depressed adults whose apathy symptoms do not respond to SSRI medication, as well as the association between abnormalities within the SN and RN and response to dopaminergic medications.

Finally, regarding the cognitive characteristics of apathy in late-life depression, there are several additional measures that may be of interest. Future studies should examine performance of apathetic individuals on emotion-based interference tasks. Given the results of the current study demonstrating abnormalities of the rACC in individuals with apathy, it is expected that these individuals will perform more poorly on such a task than their non-apathetic counterparts. Another task of interest is the Iowa Gambling Task (Ligthart et al., 2012; Bechara et al., 1997). The IGT is a face-valid measure that evaluates reward-based decision-making. This task requires individuals to select cards from four decks, each resulting in a monitory reward, loss, or both. Two decks contain cards that with smaller monetary rewards but also fewer losses, which will result in a net gain over time. The other two decks contain cards with larger monetary gains and greater losses, resulting in a net loss over time. While healthy individuals often choose disadvantage decks initially, most will eventually switch to the more advantageous decks. However, apathetic individuals consistently select cards from the less advantageous decks, suggesting impaired incentive salience processing in these individuals (Njomboro et al., 2012; Bayard et al., 2014). Furthermore, apathy and impaired performance on the IGT are both
associated with abnormalities in the dopaminergic mesolimbic pathway, which subsumes incentive salience processing. Specifically, dopamine depletion impairs performance on the IGT, while increased dopamine improves IGT performance (Bechara et al., 2001). Thus, examination of IGT performance in older depressed adults with apathy will not only aid in characterizing the clinical presentation of apathy, but may also provide further insight into the underlying etiology of this syndrome.

VIII. CONCLUSION

In summary, the results of this study support the premises that apathy is a commonly occurring syndrome in late-life depression that is nonetheless etiologically distinct, and that may not be adequately targeted with SSRI treatment. Indeed, the neuroanatomical involvement of the AI and rACC in apathy, as well as a possible role for impaired processing of emotionally-based incentive salience, suggest that dopaminergic agents may be more effective for the treatment of apathy. To this end, future research examining apathy in individuals with late-life depression should focus on exploring deficits in connectivity within and between the SN and RN, as well as on associations between apathy, emotionally-based tasks, and possible pathophysiological abnormalities. Given the broad-ranging detrimental effects of apathy in older depressed adults on both an individual and a societal level, further examination of clinical and neuropathological characteristics, as well as of treatment and prevention modalities, is warranted.
APPENDIX A - TABLES AND GRAPHS

I. DEMOGRAPHICS

Table 1. Key study variable for all study participants

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<thead>
<tr>
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<th>All</th>
<th>Controls</th>
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<th>p-value</th>
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<td>49</td>
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<tr>
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<td>70.7 (6.3)</td>
<td>70.22 (6.04)</td>
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<td>Gender (% female)</td>
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<td>55</td>
<td>.64a</td>
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<tr>
<td>Education</td>
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<td>16.08 (3.37)</td>
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Note. All data presented as mean (SD) unless otherwise specified; *Fisher’s exact test; *Welch’s t-test; all other p-values are student’s t-test results; AES=Apathy Evaluation Scale; HDRS=Hamilton Depression Rating Scale; MMSE=Mini Mental Status Exam; rACC=Rostral Anterior Cingulate Cortex; cACC=Caudal Anterior Cingulate; lOFC=Lateral Orbitofrontal Cortex, mOFC=Medial Orbitofrontal Cortex
Table 2. Key study variables at baseline

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Note. All data presented as mean (SD) unless otherwise specified; aWelch’S ANOVA and Games-Howell Post Hoc test; all other p-values are one-way ANOVA results with Tukey’s HSD Post Hoc test; aSignificant differences between all three comparison groups; bSignificant difference between controls and depressed older adults with no apathy at baseline; cSignificant difference between controls and older depressed adults with apathy at baseline; AES=Apathy Evaluation Scale; HDRS=Hamilton Depression Rating Scale; MMSE=Mini Mental Status Exam;
rACC=Rostral Anterior Cingulate Cortex; cACC=Caudal Anterior Cingulate Cortex; lOFC=Lateral Orbitofrontal Cortex, mOFC=Medial Orbitofrontal Cortex

II. SALIENCE NETWORK

Table 3. Hierarchical linear regression predicting baseline apathy severity

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Note. N=46; *p<.05, **p<0.01; mHDRS=Modified Hamilton Depression Rating Scale; cACC=Caudal Anterior Cingulate Cortex
Graph 1. Scatterplot of Salience Network and AES Baseline

Note. N=46; AES=Apathy Evaluation Scale; cACC=Caudal Anterior Cingulate Cortex
Table 4. Hierarchical linear regression predicting week 12 apathy severity

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Note. N=26; *p<.05, **p<0.01; mHDRS=Modified Hamilton Depression Rating Scale; cACC=Caudal Anterior Cingulate Cortex
Graph 2. Scatterplot of Salience Network ROIs and AES Week 12

Note. N=26; AES=Apathy Evaluation Scale; cACC=Caudal Anterior Cingulate Cortex
Table 5. Hierarchical linear regression predicting change in apathy severity

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Note. N=29; *p<.05, **p<0.01; mHDRS=Modified Hamilton Depression Rating Scale; AES=Apathy Evaluation Scale; cACC=Caudal Anterior Cingulate Cortex
Graph 3. Scatterplot of SN ROIs and AES Change

Note. N=29; AES=Apathy Evaluation Scale; Insula=Anterior Insula; cACC=Caudal Anterior Cingulate Cortex
### III. REWARD NETWORK

Table 6. Hierarchical linear regression predicting baseline apathy severity

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Note. N=46; *p<.05, **p<0.01; mHDRS=Modified Hamilton Depression Rating Scale; lOFC=Lateral Orbitofrontal Cortex, mOFC=Medial Orbitofrontal Cortex, rACC=Rostral Anterior Cingulate Cortex, cACC=Caudal Anterior Cingulate Cortex
Graph 4. Scatterplot of RN ROIs and AES Baseline

Note. N=46; AES=Apathy Evaluation Scale; lOFC=Lateral Orbitofrontal Cortex, mOFC=Medial Orbitofrontal Cortex, rACC=Rostral Anterior Cingulate Cortex, cACC=Caudal Anterior Cingulate Cortex
Table 7. Hierarchical linear regression predicting week 12 apathy severity

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Note. N=26; *p<.05, **p<0.01; mHDRS=Modified Hamilton Depression Rating Scale; lOFC=Lateral Orbitofrontal Cortex, mOFC=Medial Orbitofrontal Cortex, rACC=Rostral Anterior Cingulate Cortex, cACC=Caudal Anterior Cingulate Cortex
Graph 5. Scatterplot of RN ROIs and AES Week 12

Note. N=26; AES=Apathy Evaluation Scale; lOFC=Lateral Orbitofrontal Cortex, mOFC=Medial Orbitofrontal Cortex, rACC=Rostral Anterior Cingulate Cortex, cACC=Caudal Anterior Cingulate Cortex
Table 8. Hierarchical linear regression predicting change in apathy severity

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Note. N=29; *p<.05, **p<0.01; AES= Apathy Evaluation Scale; mHDRS=Hamilton Depression Rating Scale; IOFC=Lateral Orbitofrontal Cortex, mOFC=Medial Orbitofrontal Cortex, rACC=Rostral Anterior Cingulate Cortex, cACC=Caudal Anterior Cingulate Cortex
Graph 6. Scatterplot of RN ROIs and AES Change

Note. N=29; AES=Apathy Evaluation Scale; lOFC=Lateral Orbitofrontal Cortex, mOFC=Medial Orbitofrontal Cortex, rACC=Rostral Anterior Cingulate Cortex, cACC=Caudal Anterior Cingulate Cortex
IV. COGNITIVE FUNCTIONING

Table 9. Hierarchical linear regression predicting baseline apathy severity

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Note. N=33; *p<.05, **p<0.01; mHDRS=Modified Hamilton Depression Rating Scale; HVLT=Hopkins Verbal Learning Test; IR=Immediate Recall; DR=Delayed Recall; Persev=Perseverative Errors; Intru=Intrusion Errors; TP=True Positives; FP=False Positives; Inter=Interference Score; WCST=Wisconsin Card Sorting Test; PersErr=Perseverative Errors; Cat=Categories Completed; FMS=Failure to Maintain Set
Table 10. Hierarchical linear regression predicting week 12 apathy severity

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<th>R</th>
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Note. N=20; *p<.05, **p<0.01; mHDRS=Modified Hamilton Depression Rating Scale; HVLT=Hopkins Verbal Learning Test; IR=Immediate Recall; DR=Delayed Recall; Persev=Perseverative Errors; Intru=Intrusion Errors; TP=True Positives; FP= False Positives; Inter=Interference Score; WCST=Wisconsin Card Sorting Test; PersErr=Perseverative Errors; Cat=Categories Completed; FMS=Failure to Maintain Set
Table 11. Hierarchical linear regression predicting change in apathy severity

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<td>WCST Cat baseline</td>
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<td>WCST FMS baseline</td>
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Note. N=20; *p<.05, **p<0.01; mHDRS=Modified Hamilton Depression Rating Scale; HVLT=Hopkins Verbal Learning Test; IR=Immediate Recall; DR=Delayed Recall; Persev=Perseverative Errors; Intru=Intrusion Errors; TP=True Positives; FP=False Positives; Inter=Interference Score; WCST=Wisconsin Card Sorting Test; PersErr=Perseverative Errors; Cat=Categories Completed; FMS=Failure to Maintain Set
Table 12. Hierarchical linear regression predicting change in apathy severity

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<th>Step</th>
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<th>ΔR²</th>
<th>F</th>
<th>β</th>
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Note. N=24; *p<.05, **p<0.01; AES= Apathy Evaluation Scale; mHDRS= Modified Hamilton Depression Rating Scale; HVLT= Hopkins Verbal Learning Test; IR= Immediate Recall; DR= Delayed Recall; Persev= Perseverative Errors; Intru= Intrusion Errors; TP= True Positives; FP= False Positives; Inter= Interference Score; WCST= Wisconsin Card Sorting Test; PersErr= Perseverative Errors; Cat= Categories Completed; FMS= Failure to Maintain Set.
## APPENDIX B - FIGURES

Figure 1. Differences and similarities between symptoms of apathy and depression

<table>
<thead>
<tr>
<th>Apathy</th>
<th>Apathy and Depression</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased motivation</td>
<td>Decreased interest or pleasure</td>
<td>Sad or depressed mood</td>
</tr>
<tr>
<td>Reduced emotional</td>
<td>Psychomotor retardation</td>
<td>Irritability</td>
</tr>
<tr>
<td>reactivity</td>
<td></td>
<td>Guilt</td>
</tr>
<tr>
<td>Blunted affect</td>
<td>Anergia</td>
<td>Feelings of worthlessness</td>
</tr>
<tr>
<td>Poor initiation</td>
<td>Social withdrawal</td>
<td>Hopelessness</td>
</tr>
<tr>
<td>Lack of insight</td>
<td></td>
<td>Helplessness</td>
</tr>
<tr>
<td>Indifference</td>
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<td>Indecisiveness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suicidality</td>
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</table>

Adapted from Marin 1991
For a diagnosis of apathy, criteria A, B, C, and D should be fulfilled.

**A.** Loss or diminished motivation in comparison to the patient’s previous level of functioning, either by self-report or observation.

**B.** Presence of at least one symptom in at least two of the following three domains most of the time for at least four weeks:

- **Behavior**
  - Initiation: loss of self-initiated behavior
  - Responsiveness: loss of environment-stimulated behavior
- **Cognition**
  - Initiation: loss of spontaneous ideas and curiosity for routine and new events
  - Responsiveness: loss of environment-stimulated ideas and curiosity for routine and new events
- **Emotion**
  - Initiation: loss of spontaneous emotion, observed or self-report
  - Responsiveness: loss of emotional responsiveness to positive or negative stimuli or event

**C.** These symptoms cause clinically significant impairment in personal, social, occupational and/or other important areas of functioning.

**D.** These symptoms are not exclusively explained by physical disabilities, motor disabilities, diminished level of consciousness, or the direct physiological effects of a substance.

Adapted from Mulin et al., 2010
Figure 3. Key nodes in the Salience Network

Coronal View

Axial View

Note. ACC = Anterior Cingulate Cortex
Figure 4. The Salience Network

Note. AI = Anterior Insula; dACC = Dorsal Anterior Cingulate Cortex

Adapted from Menon 2015
Figure 5. Key nodes in the Reward Network

Sagittal View

Note. ACC = Anterior Cingulate Cortex; OFC = Orbitofrontal Cortex

Adapted from Klein and Tourville 2012
Figure 6. The Reward Network

Note. OFC = Orbitofrontal Cortex; ACC = Anterior Cingulate Cortex
Figure 7. Incentive Salience Processing

Note. AI = Anterior Insular; OFC = Orbitofrontal Cortex; ACC = Anterior Cingulate Cortex
Figure 8. Cortical ROI parcellations in the Desikan-Killiany atlas

From Klein and Tourville 2012
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rewards modulate the feedback error-related negativity associated with wins but not
losses in a monetarily rewarded gambling task." Neuroimage 51(3): 1194-1204.


