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Functional and Morphological Markers of Adolescent-Onset Depression

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Functional and Morphological Markers of Adolescent-Onset Depression

By

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B.A. New York University, 2013

Advisor: Hillary R. Rodman, Ph.D.

An abstract of a thesis submitted to the faculty of the
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ABSTRACT

Morphological and Functional Markers of Adolescent-Onset Depression
By Alexander Hayim Denker

Adolescence is a time of dramatic physical, behavioral, social, mental, and brain changes. Adolescence is also a period of psychiatric vulnerability. The likelihood of a depressive episode increases dramatically post-puberty. Moreover, as suicide is one of the leading causes of death among youth, the study of depression in adolescent populations is of great public health and scientific concern. As part of a larger investigation of mechanisms and treatment of depression in adolescents, the present study aimed to address two primary questions: 1) Are there differences in white matter connectivity between regions implicated in reward processing and mood in patients diagnosed with major depressive disorder (MDD) and controls? 2) Are there different patterns of neural activity involved in reward anticipation and feedback in patients and controls? We employed diffusion tensor imaging (DTI) and functional MRI in combination with behavioral inventory data from the Beck Depression Inventory (BDI) and the Behavioral Activation for Depression Scale (BADS) to address these questions. We found a trend approaching significance for greater functional anisotropy (FA), an indicator of tract integrity, in a tract connecting the right anterior insula and the right nucleus accumbens (NAcc) in patients versus controls. The relationship between group and FA in this tract was further indicated by significant positive relationships between FA and BDI scores and between FA and the avoidance/rumination subscale of the BADS questionnaire. Using the Monetary Incentive Delay Task, we found main effects of bilateral activation of the NAcc during reward anticipation and right NAcc activation in response to reward gain feedback. Furthermore, significant relationships between bilateral NAcc activation during reward anticipation and BDI scores as well as between bilateral NAcc and BADS avoidance/rumination scores were present. Our study contributes to the understanding of the morphological markers and functional mechanisms of depression in adolescence and may have implications for the evaluation of treatment.

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INTRODUCTION

Adolescence is a time of dramatic physical, behavioral, social, mental, and brain changes. Considered to be a period of psychiatric vulnerability, adolescence is sometimes referred to as a period of "storm and stress," characterized by heightened emotionality, predisposition for anxiety and mood dysregulation (Arnett, 1999; Kessler et al., 2005; Larson, Moneta, Richards, & Wilson, 2002; Paus, Keshavan, & Giedd, 2008). The study of adolescent depression has gained attention in the developmental literature due to recent statistics on youth mortality. The likelihood of a depressive episode increases dramatically post-puberty. Prevalence of depression in youth aged 12-17 is estimated to be 5.7% by the Centers for Disease Control (CDC) and 9.8% among adults aged 40-59; rates peak at 12.3% among women aged 40-59 and the lowest rates are found in males aged 12-17 (3.4%) (Pratt & Brody, 2014). Approximately 3% of the population of all Americans aged 12 and over meet DSM-5 criteria for severe depression and it is estimated that there is a 1.5 to 3-fold higher rate of depression in females over males among all age groups (Pratt & Brody, 2014). Eleven percent of mortality among youth in the United States is due to suicide, commonly associated with depression (Miniño, 2010; Mulye et al., 2009). Thus, the importance of expanding our understanding of the mechanisms of adolescent-onset depression is evident. To accomplish this goal, researchers must examine normative behaviors impacted by depressive symptoms. The tasks examined in this study specifically engage reward-based decision-making behaviors.

Mood disorders affect reward- or incentive-based decision-making in all populations and various anatomical, chemical, behavioral, and computational neuroscience approaches have been developed to map differences in decision-making processes in disease. In a developing population, the skills involved in processing reward can be used as a predictor of cognitive

success in adolescence and into adulthood (Casey et al., 2011b; Mischel, Shoda, & Rodriguez, 1989). Behavioral findings show that sensitivity to reward and reward seeking, as defined by evaluations such as gambling tasks and sensation seeking scales, can be described by an inverted U-shaped function where sensitivity peaks between ages 14 and 16 followed by a decline through adulthood (Arnett, 1994; Roth, Schumacher, & Brähler, 2005; Steinberg et al., 2008; Zuckerman, Eysenck, & Eysenck, 1978).

As part of a larger investigation of mechanisms and treatment of depression in adolescents, the present study aimed to investigate the neural correlates of depression in adolescents through the examination of white matter connectivity and reward anticipation. The use of functional magnetic resonance imaging (fMRI) to study the interaction between brain function and behavior is increasingly common because it is a noninvasive method to observe brain activity by tracing changes in cerebral blood flow (specifically blood oxygenation). Using diffusion tensor imaging (DTI) and regionally-specific fMRI approaches in combination with targeted behavioral tasks, the study addressed two primary questions: 1) Does DTI reveal differences in white matter connectivity between regions implicated in reward processing and mood in patients and controls? 2) Are there different patterns of neural activity involved in reward anticipation and feedback in patients and controls?

Studying the neural markers of reward-based decisions in adolescents

Identifying the neural correlates of expectation and evaluation of potential reward is central to understanding changes to reward-based decisions in adolescent depression. Adolescence is marked by vulnerability to thrill-seeking and rewarding risk-taking behavior (Liston et al., 2006). The coupling of mature subcortical structures with immature prefrontal control may create a state whereby weak control of reward systems explains adolescents' mostly

emotional and incentive-based behavior (Somerville, Jones, & Casey, 2010). Healthy adolescents may also be more attracted to reward outcomes while giving much less consideration to negative outcomes than adults. For instance, gambling tasks reveal that adolescents are less avoidant after receiving negative feedback than adults and significantly more likely to respond positively to positive feedback that may result in making riskier gambling choice (Cauffman, Shulman, Steinberg, Claus, Banich, Graham, & Woolard, 2010a; Figner, Mackinlay, Wilkening, & Weber, 2009). However, avoidant behavior is commonly observed in depressed individuals. Diminished reward responses are also consistent with one of the hallmark symptoms of depression, anhedonia. Anhedonia is defined by "deficits in the capacity to feel pleasure and take interest in things; a lack of enjoyment from, engagement in, or energy from life's experiences" along with diminished interest in daily activities (American Psychological Association, 2013). In general, the type of positive response to reward anticipation lacking in anhedonic individuals is exaggerated in the healthy adolescent brain, especially in the dorsal and ventral striatum (J. R. Cohen et al., 2010; Ernst et al., 2005; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010). Such exaggerated reactivity along with the aforementioned developmental changes in reward processing may, in part, be due to failed recruitment of the ventromedial prefrontal cortex (VMPFC), which, in adults, has been linked to clinical depression, poor emotion regulation, decision-making deficits, and cognitive control limitations (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Ochsner & Gross, 2005). Additionally, in adults, reward magnitude affects activity in the nucleus accumbens (NAcc), the thalamus, and the orbital frontal cortex (OFC) during prediction and anticipation of reward (Galvan et al., 2005). Ventral striatal/nucleus accumbens (VS/NAcc), vmPFC, and posterior cingulate cortex activity increases with objective reward as indicated by temporal discounting, a measurement of the ability to delay gratification; this activity increases as objective reward increases (Kable & Glimcher, 2007).

However, whether these patterns of neural activity are also found in adolescents is not well established. It is therefore particularly important to employ behavioral tasks with established findings in adults by which to examine reward processes in a developing population. Using the knowledge of these types of neural markers of reward perception, this study presents data using a monetary incentive delay (MID) task that is specifically used to probe activity in a key part of reward circuitry, the NAcc (Knutson, Westdorp, Kaiser, & Hommer, 2000).

Using the Monetary Incentive Delay (MID) task to probe the neural mechanisms of reward anticipation

In normal development, reward systems in the brain such as the ventral striatum/nucleus accumbens (NAcc) mature more quickly than the cognitive control mechanisms of the pre-frontal cortex (Steinberg, 2010). Neurotypical adolescents are thus expected to exhibit exaggerated reward-seeking behaviors (Casey, Jones, & Somerville, 2011a). Furthermore, heightened NAcc activity relative to prefrontal activity in adolescents has been observed when contrasted to the pattern seen in adults (Forbes et al., 2010). We therefore expected that the MID task (described below) would reliably recruit NAcc activity and reveal activational differences between adolescent patients and controls.

The MID task is an established measure of response to anticipation of monetary reward and loss (Knutson et al., 2000). The participants' objective is to hit a button as soon as a red square flashes on a screen and before it disappears to win or avoid losing money. In adults, the task reliably recruits activity in the NAcc, an area commonly associated with reward. Knutson and colleagues examined the neural correlates of monetary incentive processing in unmedicated depressed adult patients and controls. Despite finding group differences in anterior cingulate cortex (ACC) activity, no differences in NAcc recruitment were found in anticipation of gain and

loss (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008b). However, we questioned whether the lack of group difference in NAcc activity holds up in adolescence, a developmental period when depression is likely to first emerge.

We therefore examined what group differences might emerge in an adolescent population. Moreover, we were interested in any differences in activation between patients and controls. Previous research indicates that NAcc activity is markedly different in a developing population. For example, in depressed pediatric patients (9-17), Forbes and colleagues observed reduced NAcc responses during reward conditions when compared to pediatric controls (Forbes et al., 2006). Based on developmental differences from adults, Galvan and colleagues posit that adolescents are predisposed to prefer immediate gains due to a disproportionate activation in the NAcc relative to areas crucial for cognitive control (Galvan et al., 2006). Finally, depressed adolescents may also exhibit less striatal (associated with reward processing) but more dorsolateral and medial prefrontal cortex activation when tracking reward anticipation and outcomes (Forbes et al., 2009). Consistent with past studies employing the MID task in adults, we hypothesized that NAcc activity would be positively correlated with gain anticipation (Abler, Walter, Erk, Kammerer, & Spitzer, 2006; Knutson, Adams, Fong, & Hommer, 2001; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008a; Pizzagalli et al., 2009). The MID data reported in this study bolster the utility of the task to differentiate the neural reactivity to reward signals and related morphology in depressed adolescents and controls.

Using diffusion tensor imaging to probe the morphological markers of depression

Diffusion tensor imaging (DTI) allows investigators to measure the magnitude and directionality of restricted water diffusion in tissue. Use of DTI in the brain enables researchers to examine the amount of restricted diffusion in individual white matter tracts and create neural

tract images. There are two diffusion characteristics commonly measured depending on one's research question: functional anisotropy (FA) and mean diffusivity (MD). Functional anisotropy is a scalar representing the amount of diffusion asymmetry in a voxel. Anisotropic diffusion in a tract is more restricted. Higher FA values are therefore thought to reflect greater coherence or integrity of a tract (Mukherjee, Berman, Chung, Hess, & Henry, 2008). MD is a scalar representing the total free-flowing diffusion in a voxel. Higher MD values (and lower FA values) are thus indicative of lower fiber integrity or coherence (Soares, Marques, Alves, & Sousa, 2013). Although fMRI studies such as the ones mentioned in the previous section suggest that depressed individuals have distinctive patterns of neural response to reward, they do not elucidate possible structural differences between depressed individuals and a normative population.

Recent studies provide evidence of significant differences in white matter integrity in fronto-striatal tracts in depressed adolescents when compared to controls. Moreover, Fronto-striatal fiber integrity has been linked to age-related differences in reward learning and successful temporal or delay discounting (Hulvershorn, Cullen, & Anand, 2011; Peper et al., 2013; Samanez-Larkin, Levens, Perry, Dougherty, & Knutson, 2012; van den Bos, Rodriguez, Schweitzer, & McClure, 2014). Cullen and colleagues also observed lower functional anisotropy in tracts between the amygdala and subgenual ACC (Cullen et al., 2009; 2010; Hulvershorn et al., 2011). This group hypothesizes that these differences in fronto-limbic pathways are relevant to the development of major depressive disorder (MDD) in adolescence. However, other components of the fronto-limbic-striatal network implicated in depression may also be important to examine, specifically the anterior insula.

There are multiple roles ascribed to the anterior insula (AI) in humans with support from rodent and non-human primate models. Craig postulated that the anterior insula's primary role is

in relaying interoceptive information, signals of the physiological state of the body (Craig, 2002; 2003). It is further thought that the AI has an evaluative role of these signals for the purpose of monitoring homeostasis, and thus a form of self-awareness (Paulus & Stein, 2006). Paulus and Stein go further and posit that the AI monitors "interoceptive prediction error" signals such that an individual is able to adjust to mismatches between expected and actual bodily conditions when evaluating the salience of environmental stimuli that may affect the body. This hypothesis is further supported in the rodent literature where rats with insular lesions exhibit a failure to adjust the incentive value for a food reward in response to manipulations in motivational states (i.e hunger versus satiety) (Balleine & Dickinson, 1998). The AI's influence in decision-making is thus thought to be its role in mediating affective states and environmental interactions (Craig, 2002; Paulus & Stein, 2006). These affective states are not limited to physiological conditions.

The anterior insula is also characterized as part of a general "salience network" (Menon & Uddin, 2010). Within a network framework, the AI is thought to be involved in higher level attentional and sensory integration of stimulus evaluation, decision prediction errors, and affective states (Craig, 2003; Gray, Harrison, Wiens, & Critchley, 2007; Menon & Uddin, 2010; Paulus & Stein, 2006). Recent resting state fMRI research also identifies the insula as an area with direct influence on the default mode network (DMN; Menon & Uddin, 2010). The DMN is a resting state network that is implicated in theory of mind, the ability to project one's own mental states onto another, social awareness, and emotional processing (A. O. Cohen et al., 2016; Lamm & Singer, 2010; Menon & Uddin, 2010). The anterior insula is thus a logical target for understanding the multiple cognitive modalities relevant to decision-making and emotional processes in depressed adolescents. For example, Leong and colleagues recently published findings on a previously unexamined anterior insula-NAcc tract in healthy adults, reporting that tract integrity was negatively correlated with preference for positively skewed gambles (Leong,

Pestilli, Wu, Samanez-Larkin, & Knutson, 2016). The present study study thus sought to apply a novel strategy using diffusion tensor imaging (DTI) to compare an anterior insula-nucleus accumbens white matter tract in adolescent patients and controls. Using the same coordinate definitions employed and made available to our group by Leong et al., this study reports data that demonstrate differences in the integrity of this tract in patients and controls (Figure 9).

Contributions of this study

This study explored differences in behavioral and neural features of depressed adolescents and healthy controls. Utilizing DTI and region-based fMRI approaches in combination with behavioral measures, the study sought to further the understanding of the neural mechanisms of depression in adolescence. This paper presents findings addressing the two primary questions we set out to investigate: 1) a morphological comparison of an insula-nucleus accumbens white matter tract in patients and controls, and 2) differential activation of selected brain regions associated with reward anticipation and feedback in a monetary incentive delay task.

MATERIALS AND METHODS

Overview

In addition to DTI and fMRI measurements, this study included self-report inventories and a behavioral task: The Monetary Incentive Delay (MID) task (described below). Patients and controls were recruited from Greater Atlanta by collaborators at the Emory Child and Adolescent Mood Program (CAMP), a mental health clinical research team. The CAMP team screened participants and obtained informed consent according to the study procedures approved

by the Emory University Institutional Review Board. Following their initial visit with the CAMP team, patients and controls came into the laboratory to complete the behavioral tasks and an fMRI scan. Upon arrival, participants first completed MRI safety screening information and a series of self-report questionnaires. Participants were then introduced to the MID task along with 3 other behavioral tasks (listed below) to be performed in the scanner and given the opportunity to practice ahead of the fMRI scan. These practice sessions were used to familiarize the participants with the tasks as well as provide baseline measures for certain tasks. For instance, the MID practice session is used to calibrate the task difficulty in the scanner such that participants succeed on 66% of their responses based on accuracy rates and mean reaction time. In addition to the tasks analyzed in the present study, participants completed a resting-state scan and 3 other behavioral tasks for future analysis: an effort discounting task, a reinforcement learning task designed to evaluate participant's ability to use reward prediction error signals, and the Self-Related Emotional Words Task, which examines a participant's response to viewing positive and negative adjectives that they previously rated as describing themselves (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). During the study, participants were told they would receive $60 for each fMRI scan, plus up to an additional $40 bonus. To encourage enthusiastic participations, they were told successful performance would positively impact the bonus payment they would take home.

Participants

Seventeen unmedicated patients with a current diagnosis of MDD (14 female) and 15 controls (10 female) aged 12 to 18 (at the time of the first scan session) were recruited by the Emory Child and Adolescent Mood Program. All participants were right-handed. Following exclusion due to excessive movement during the scanning sessions, the present analyses include

16 participants (8 patients, 8 controls) with usable data for both behavioral questionnaire scores and DTI measures and 12 participants (6 patients, 6 controls) with usable data for both DTI and the MID task.

Imaging Acquisition

Scans were acquired at the Emory Facility for Education & Research in Neuroscience using a 3T Siemens Magnetom Trio scanner (Siemens Medical Solutions, Malvern, P.A.). Each run of the MID fMRI task (TR 1000; TE 30; Orientation -18) lasted approximately 6 minutes. A T1 anatomical scan was also acquired (TR 1900; TE 2.27). The DTI scan (TR 6400; TE 79) lasted approximately 5 minutes. The scan session including all tasks totaled approximately 1.5 hours.

fMRI Analyses

fMRI data were pre-processed and analyzed in SPM 12 (University College London). Motion correction, slice-timing correction, coregistration, normalization, and spatial smoothing were performed. Main effects were reported using small volume correction.

DTI Analyses

DTI data were analyzed using the FMRIB Software Library (FSL) (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Tract analyses were performed through the probabilistic tractography (PROBTRACKX) interface.

Self-Report Questionnaires

Several paper and pencil self-report inventories were administered during the study and by our clinical collaborators throughout treatment. These include the Beck Depression Inventory (BDI-II; Beck, A.T., Steer, R.A., & Brown, G.K. 1996), the Behavioral Activation for

Depression Scale (BADS; Martell, Addis & Jacobson, 2001), and the Children's Depression Rating Scale (CDRS; Poznanski & Mokros, 1996). We also administered several questionnaires by computer, which include the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006), the Perceived Stress Scale (PSS; Cohen 1994), the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988), the Apathy Evaluation Scale (Marin, 1996), and the Appetitive Motivation Scale (AMS; Cooper, Smillie, Jackson, 2008). All inventories have been age-validated for use in this study sample.

Behavioral Task Descriptions

Monetary Incentive Delay Task

The Monetary Incentive Delay Task (MID) seeks to probe neural mechanisms related to anticipation of monetary reward and loss as well as an individual's reaction to work associated with gaining reward or avoiding loss (Knutson et al., 2001). The task permits the observation of various stages of reward processing including anticipating a result (in this case a monetary outcome of gain or loss) and processing the actual outcome (Lutz & Widmer, 2014). The participants' goal was to hit a button when a red square flashed on the screen and before it disappeared (Figure 1). Success in hitting the red square determined whether a participant gained or avoided losing money. Participants were informed that there were three types of trials indicated by a cue on the screen: "Gain" trials, where they could win between $0.20 and $5.00, "Loss" trials where the goal was to avoid losing between $0.20 and $5.00, and "No Change" trials where success did not result in gains or losses. Participants were informed of outcomes following each trial. A practice session ahead of the scan calibrated the task difficulty in the scanner such that participants succeeded on 66% of their responses based on accuracy rates and mean reaction time. Trial type order (gain, loss, and no change) was randomized.

RESULTS

This study included analyses on DTI measures and behavioral questionnaire scores for 16 participants (8 patients, 8 controls) and of MID in conjunction with DTI data for 12 participants (6 patients, 6 controls). Exclusion of data was typically due to individuals not completing a scan or excessive motion. A summary of demographic information along with mean BDI and BADS scores for all participants can be found in Table 1. A Chi-Square test indicated that there was no statistically significant relationship between gender and diagnostic group in the present sample ($X^2(1, N = 32) = 1.046, p > .05$). Although a higher prevalence of depression in females over males is well established, only a trend towards this gender difference was reflected in our participant pool. This difference is likely due to the small sample size of this study and the disproportionate number of female participants **(**Pratt & Brody, 2014**)**. As expected, linear regressions confirmed a strong relationship between diagnosis and BDI total scores (R^2=.749, β = -.883, p<0.0005), as well as diagnosis and BADS total scores (R^2=.790, β = .907, p<0.0005) when controlling for age and gender.

DTI

We examined an anterior-insula to NAcc tract using coordinate definitions made available to our group by Leong and colleagues (Leong et al., 2016). Our findings indicate a group effect approaching significance for fractional anisotropy (FA), an indicator of tract integrity, in a model controlling for gender and age (R^2=.176, β = -.423, p=0.037; Figure 2). Gender and age were also significantly related to FA (β=0.829, p=0.007; β=0.789, p=0.010 respectively) where females were more likely to exhibit higher FA values than males and FA trended positively with age. The relationship between FA and behavioral inventories was

examined using linear regression. All regressions included controls for age and gender. A significant positive relationship was observed between FA and BDI total score (R^2=.379, β = .821, p=0.015; Figure 3). A negative relationship between FA and BADS total score was observed but did not reach significance (R^2=.198, β = -0.593, p=0.103; Figure 4). However, isolating the Avoidance/Rumination subscale of the BADS questionnaire *did* reveal a significant relationship (R^2=.432, β = 0.876, p=0.010; Figure 5). The relationship between the BADS subscale scores and FA presumably reflects the higher FA values observed in patients, a population expected to exhibit higher Avoidance/Rumination scores.

MID Feedback and Anticipation Findings

There were two primary fMRI contrasts examined in this study for the MID task: reward anticipation (win trial>neutral trial) and reward feedback (won > lost). In addition to reporting the main effects of the MID anticipation and feedback contrasts, we were interested in the possible interactions between the MID findings and DTI results as well as relationships between the MID feedback contrast (won>lost feedback), BDI, and BADS Avoidance/Rumination scores. Linear regressions controlling for age and gender revealed significant relationships between the anticipation phase contrast in bilateral NAcc activity and total BDI score as well as the contrast in bilateral NAcc activity and BADS Avoidance/Rumination scores. Significant bilateral group effects were also present (Table 3). Right NAcc activity exhibited a near-significant negative relationship with FA in the won>lost feedback contrast (R^2=.286, β = -0.631, p=0.072; Figure 6).

Main effects for activity in left and right NAcc ROIs are reported in Table 4. Greater signal increases were observed in both left NAcc (t=4.10; $p_{FWE\text{-}corrr}$=0.015; small volume) and right NAcc (t=4.16; $p_{FWE\text{-}corr}$=0.019; small volume) in anticipation of potential gain over

anticipation of a neutral outcome. There was a significant main effect in right ($t=3.85$; $p_{FWE-corr}=0.034$; small volume) but not left NAcc in response to feedback of a win greater than feedback of a loss (Table 4). We were subsequently interested in the contrast of win trial hits greater than win trial misses (i.e. winning > failing to win). Similarly, there was a significant main effect in right ($t=3.95$; $p_{FWE-corr}=0.016$; small volume), but not left NAcc. Other contrasts for possible future analysis include win feedback > hit on neutral trials, loss feedback > miss on neutral trials, loss anticipation > neutral anticipation, and win anticipation > loss anticipation. ROIs for left and right NAcc are based on the same masks employed in creating the DTI tract used in this study (Figure 7 & 8).

DISCUSSION

Adolescence is the time of peak onset of mental disorders including depression (Kessler et al., 2005). It is thus crucial to advance our understanding of adolescent-onset depression and develop translational methods of evaluating treatments. We aimed to contribute to the literature by addressing two primary questions, focusing on a specific circuit: 1) Does DTI reveal differences in white matter connectivity between regions implicated in reward processing and mood? 2) Are there different patterns of neural activity involved in reward anticipation and feedback in patients and controls? The results outlined contribute to the understanding of the functional mechanisms and morphological markers of depression in adolescence and may have implications for the evaluation of treatment.

Morphological changes in the developing brain may influence our DTI data and must be considered when interpreting the results. Healthy development of fiber tracts may affect developmental changes in reward response. Age-related differences in reward learning have been linked to developmental changes resulting in increased fronto-striatal fiber integrity as measured

by DTI (Hulvershorn et al., 2011; Peper et al., 2013; Samanez-Larkin et al., 2012; van den Bos et al., 2014). It is possible that relationships between the integrity of the right anterior insula-NAcc tract observed in this study are expected individual differences due to working with a developing population in general and not the effects of depression per se. The greater structural integrity of this tract in depressed individuals in the study may thus be interpreted as reflecting a more mature brain and not a sign of pathology. Longitudinal study would be required to parse whether age-related changes in the integrity of this tract affect reward response regardless of diagnosis.

Our DTI measures indicated a trend towards greater structural integrity in the right anterior insula-NAcc tract (i.e. higher FA values) in patients over controls. This trend was further supported by the significant positive relationships of BDI and BADS Avoidance/Rumination scores and FA in this tract. Both behavioral measurements are indicators of depressive symptomatology. This result is especially interesting within the context of Leong and colleagues' findings on this tract in a healthy adult population. Integrity of this tract was inversely correlated with preference for positively skewed gambles, instances where one is attracted to having even a small chance of winning a large amount of money (Leong et al., 2016). This is a way of formalizing absence of a tendency to avoid risk. Risk averseness is of particular relevance to adolescence, a period when neurotypical individuals are most likely to engage in rewarding risk-taking behaviors, such as drug use and unprotected sex, but also positive risk-taking behaviors, such as participation in new social interactions (Cauffman, Shulman, Steinberg, Claus, Banich, Graham, & Woolard, 2010b; Somerville et al., 2010; Steinberg et al., 2009). We posit that the depressed adolescents' tendency to be more avoidant, as measured by the BADS inventory, is indicative of risk averseness in a population that more commonly embraces risk. Avoidant behavior is also a possible marker of behavioral inhibition, a risk factor for depression (Kasch, Rottenberg, & Arnow, 2002). As the anterior insula-NAcc is not a tract that has been extensively

studied, it is not possible to speak to the generalizability of this result based on *a posteriori* knowledge. Furthermore, in adults, Leong and colleagues did not find an association between an MPFC-NAcc tract and gambling conditions. However, this connection may differ in a developing population and would thus be another avenue to explore in future DTI analyses (Leong et al., 2016). To our knowledge, this is the first study examining the AIns-NAcc white matter tract in depressed individuals, either adults or adolescents.

The MID task is considered to probe the brain's preparatory signals in anticipation of making a rewarding action, a process hampered in anhedonic individuals. If the task does indeed tap into processes involving emotion and mood, it should be particularly useful for assessing depressive traits. The anticipation phases of the task reliably recruit bilateral NAcc activity and thus the task is an established tool for assessing activity in this structure (Abler et al., 2006; Knutson et al., 2000; 2001). Recent findings in studies utilizing the task also indicate that in depressed individuals, diminished NAcc activity is more consistently observed in response to reward outcome rather than anticipation (Knutson & Heinz, 2015; Vartanian & Mandel, 2011). Pizzagalli and colleagues used a modified version of the task to increase prediction error signaling during the feedback phase, which may account for their effects (Pizzagalli et al., 2009). We did not observe differences in prediction error signaling. However, we did observe expected significant bilateral NAcc activation in anticipation of potential gain over anticipation of neutral outcomes in the task. We additionally built contrasts of the feedback onsets of the MID task. Significant activity was observed in right but not left NAcc in the won>lost feedback contrast; however, this activity only approached significance with FA of the anterior insula-NAcc tract.

Limitations

This study is challenged by several limitations. The sample size was small and underpowered, largely due to data lost to motion and scans cut during visits (commonly due to patients reporting discomfort). Age and sex effect evaluations were limited by an uneven representation of gender and a small age distribution of the subjects. DTI results are also particularly susceptible to age effects. On one hand, DTI is extremely useful in developmental studies of decision-making because of the distinct patterns one can observe in white matter development. These age-related changes have been linked to changes in decision-making behavior in childhood and adolescence (Karlsgodt et al., 2015). On the other, cortical-striatal tracts have also been linked to age-related differences in reward processing in general (Hulvershorn et al., 2011; Peper et al., 2013; Samanez-Larkin et al., 2012; van den Bos et al., 2014). It is important to note that, in addition to the relationships reported between FA and indicators of depression, our group also observed a significant relationship between FA and age. It is possible that some of the observed individual differences in FA, a proxy for white matter integrity, are due to developmental differences and not pathology. Any attempt to identify changes in white matter integrity in relation to symptomatology thus comes with the caveat of chronological age not necessarily reflecting individual differences in brain development. Thus, including other covariates of developmental status such as pubertal status (physical and hormonal) may help parse these findings. Ultimately, however, longitudinal methods would be the most valuable approach to control for individual developmental differences and for seeking early markers of depression. There are also multiple fundamental limits to the technology to consider. As DTI scans detect the motion of water, the scan quality itself is highly susceptible to subject movement (hence the number of scans that could not be considered due to participant motion). Furthermore, DTI measurements allow researchers to infer neuroanatomy and reconstruct fiber tracts but do not provide information regarding the directionality of axons (Mori

& Zhang, 2006). Although we can comment on the organization of the AIns-NAcc tract examined in this study, we cannot determine the directionality of the projections between these two areas (i.e. we cannot use the technology to determine the information flow in the AIns-NAcc tract).

Future Directions

In addition to strengthening this study by increasing the sample size, future investigation will explore the larger implications of this research. There are tasks unaddressed in this study that may be valuable to examine in future research and with a larger subject pool. These include the Effort-Expenditure for Rewards Task, a reinforcement learning task, the Self-Related Emotional Words Task, and resting-state fMRI. As aforementioned, the present study is also part of a larger investigation evaluating two behavioral therapies for depression in adolescents according to neurobiological and task measures. Following the studies reported here, patients underwent 16 weeks of 1 hour individual therapy sessions of either behavioral activation (BA) or cognitive behavioral therapy (CBT). Monthly "booster sessions" were then offered throughout a 6-month follow-up period after completion of the study. Participants were randomly assigned to either BA or CBT. CBT, the most widely used behavioral therapy for a variety of brain disorders including depression, is designed to address unwanted behavior by modifying negative patterns of thought (Craske, 2010). BA, in contrast, is a situation-focused intervention based on a conditioning model. Patients learn to identify the environmental sources of their depression and target behavior that affects their depression rather than their thinking. Patients are asked to participate in pleasing activities, thus learning to actively mediate their depressive symptoms, particularly anhedonia (Cuijpers, van Straten, & Warmerdam, 2007; Jacobson, Martell, & Dimidjian, 2001). BA thus helps patients counteract common inactivity observed in depressed

individuals by manipulating the contextual factors that may reinforce depression (Jacobson et al., 2001). Although the general efficacy of these treatments is established, little is known about the underlying neural changes that may occur in treatment.

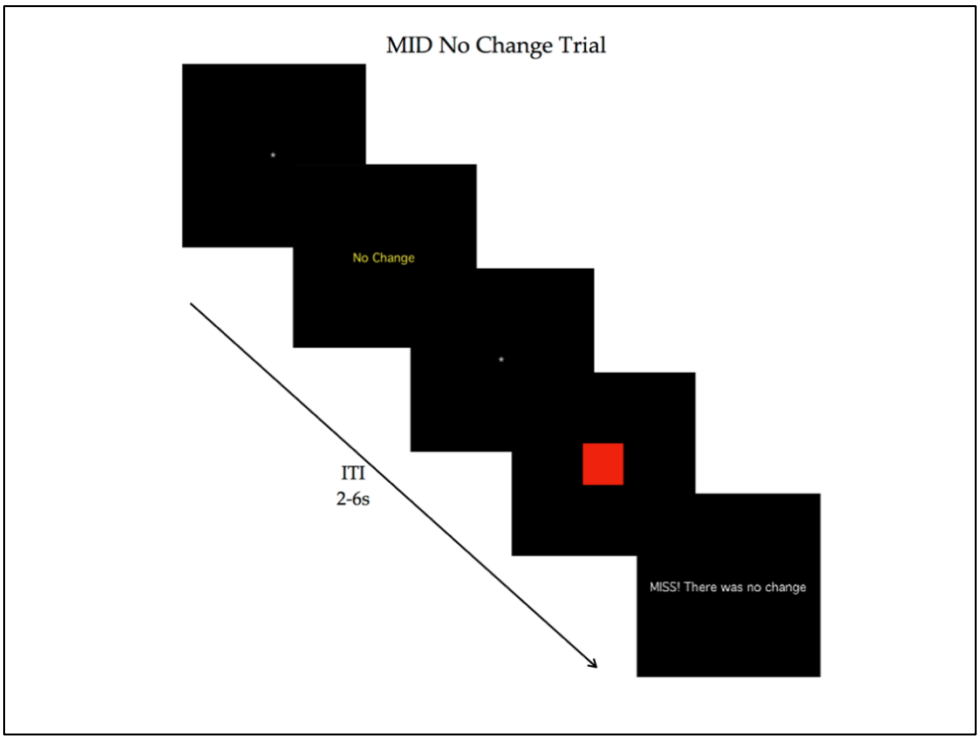
Among the possible mechanistic changes following treatment is convergence of the differences in functional activation and morphology between patients and controls. In theory, if positive response to treatment results in normalizing behavior, these changes should be reflected in the neural mechanisms associated with healthy cognition. In other words, if patients experience greater reward post-treatment, activity and morphology probed by these tasks should look more like those of controls (e.g. an increase in bilateral NAcc activation in patients when anticipating a reward). For example, if neurotypical adolescents are indeed predisposed to prefer immediate gains due to a disproportionate activation in the accumbens relative to areas crucial for cognitive control, then the neural response to successful treatment in adolescents could theoretically normalize to reflect higher activation in the accumbens typical of adolescents and *not* the activity expected of a healthy adult (Galvan et al., 2006).

Previous research revealed functional and physiological responses to treatment in regions other than those we examined that would be worth exploring in future works, particularly the amygdala and VMPFC. These two regions are pertinent to the discussion of adolescent brain development and thought to be involved in forming depressive phenotypes. The VMPFC and amygdala are also highly interconnected and linked to emotional appraisal mechanisms that exhibit differential response in depression (Ochsner, Bunge, Gross, & Gabrieli, 2002). The amygdala, commonly linked to emotional reactivity and regulation, is thought to be hyperactive in adolescents in general. This general hyperactivity in adolescents further complicates the disentanglement of amygdala activity indicative of depression and amygdala activity typical of healthy adolescents (Davey, Allen, Harrison, & Yücel, 2011; Yang et al., 2010). Patients with

the greatest improvement following CBT have been found to exhibit amygdala reactivity more similar to those of healthy individuals in response to negatively valenced emotional stimuli (Siegle, Carter, & Thase, 2006). Reduced activity in the VMPFC, one of the slowest developing brain regions, may also normalize post-CBT treatment. Ritchey and colleagues reported that patients showing improvement following CBT exhibited increased overall VMPFC activity and heightened arousal responses in the amygdala. They posit that these apparent improvements to areas involved in emotion processing reflects the improved emotion regulation in treatment responders (Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011).

It is important to note that the abovementioned studies of neural correlates of treatment outcomes may not be indicative of our future findings because of the heavy focus on CBT in those studies. Although the end goal of BA and CBT is the same, their strategies differ. It is possible that the type of behavioral treatment will result in different changes. Unlike CBT, BA approaches treatment by asking patients to place themselves in rewarding situations, not learn how to respond to the presentation of reward. Since BA does not feature the same active reframing of reward response as CBT it is possible that changes in immediate reactivity to presented rewards does not occur following treatment. Despite changes in outward behavior, BA patients may not exhibit normalized VMPFC and amygdala activity. Although it is possible that the length of the treatments in the current study (16 weeks) will not reveal robust changes, especially in DTI measurements, further study will elucidate the usefulness of assessing the treatment of adolescent-onset depression through the methodology employed in this study.

FIGURES


MID No Change Trial
No Change
ITI
2-6s
MISS! There was no change


MID Loss Trial
Lose $1
ITI
2-6s
MISS! You lost $1

Figure 1. Examples of MID "no change" and "loss" trials. Participants saw a fixation point and then were prompted with information on the trial type and the amount of money at stake for that trial. A red square flashed on the screen followed by feedback on if the participant successfully hit the red square and if they lost money, gained money, or there was no change.

Diagnosis	n	Min Age (years)	Max Age	Mean BDI	Mean BADS	Mean BADS AR Subscale
Patients	17 (3 male)	13.17	18.42	29.35	63.20	24.76
Controls	15 (5 male)	13.00	17.75	2.40	127.73	5.27

Table 1. Demographics and Questionnaire Data for Patients and Controls. Beck Depression Inventory (BDI), Behavioral Activation for Depression Scale (BADS), and BADS Avoidance/Rumination Subscale (BADS AR). Age ranges were comparable. As expected, mean BDI scores were significantly higher in patients than controls. BADS total scores were significantly higher in controls and reflect population means (Kanter, Rusch, Busch, & Sedivy, 2008).

Ind. Variable	LNAcc R-Square	LNAcc Beta	LNAcc Sig.	RNAcc R-Square	RNAcc Beta	RNAcc Sig.
BDI	0.258	-0.557	0.024	0.362	-0.637	0.005
BADS AR	0.216	-0.51	0.05	0.287	-0.567	0.021
Group	0.212	0.494	0.033	0.258	0.546	0.021

Table 2. BDI, BADS, and Group Linear Regressions with Bilateral NAcc activity. Patients coded as "1" and controls as "2".

Anticipation and Feedback-Elicited Activations -- Small Volume Correction using R and L NAcc MASKS

	CLUSTER-LEVEL			PEAK-LEVEL				MNI COORDINATES		
Region	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T-value	p_{uncorr}	x	y	z
R NAcc Win>Neu Anticipation	0.020	0.802	0.446	0.019	0.837	4.16	0.000	12	4	-8
R NAcc Win>Neu Anticipation	0.036	0.802	0.802	0.038	0.837	3.75	0.001	8	10	-12
L NAcc Win>Neu Anticipation	0.015	0.314	0.314	0.022	0.471	4.10	0.000	-10	4	-6
R NAcc Won>Lost Feedback	0.034	0.820	0.820	0.029	0.713	3.85	0.001	6	20	-4

Table 3. Peak feedback and anticipation-elicited activations in left and right NAcc ROIs. Main effects, small volume corrected.

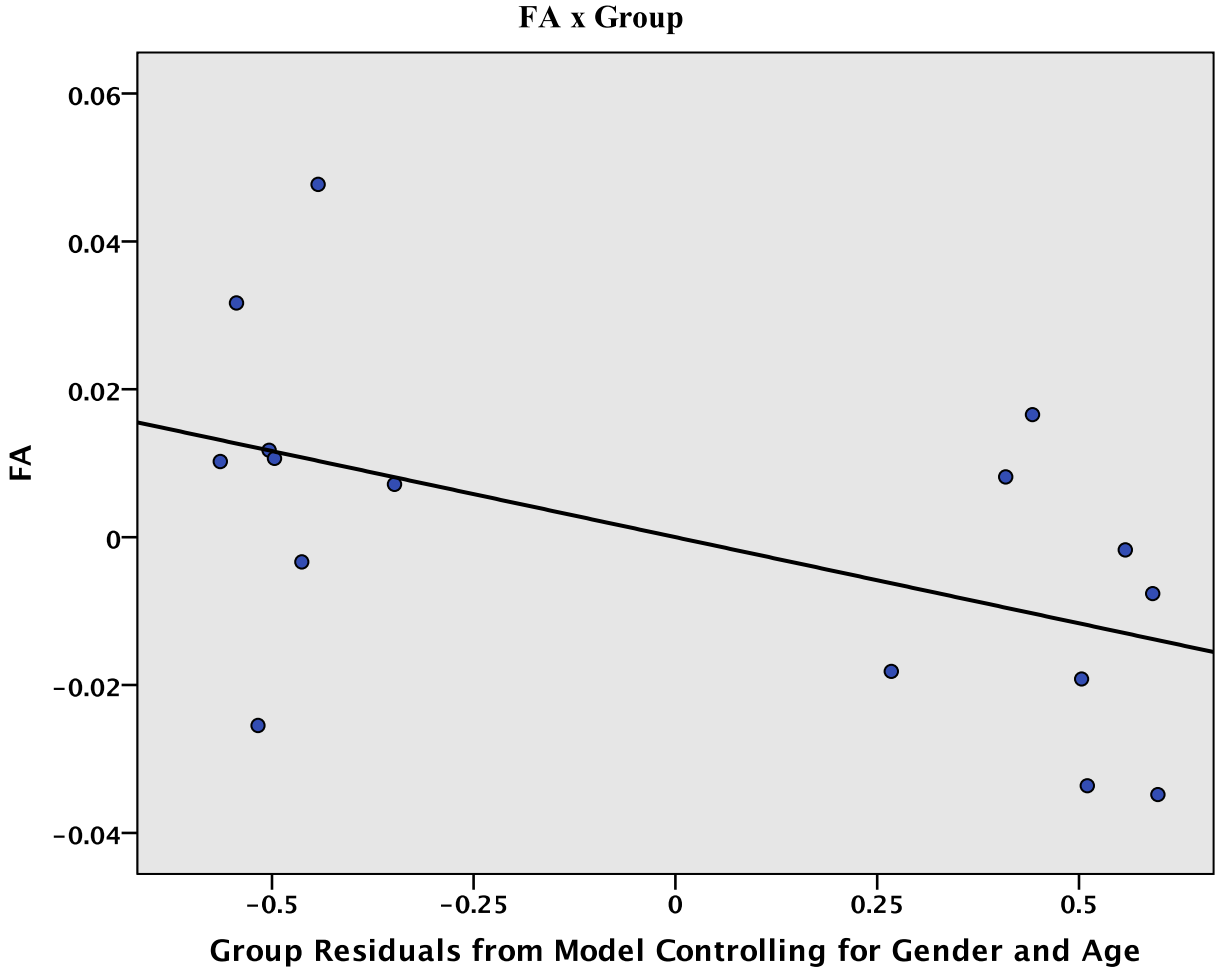


Figure 2. Partial regression scatterplot showing the effect of group when controlling for age and sex. As age increases, FA values in the anterior insula-right nucleus accumbens tract decrease, indicating that structural coherence in this tract decreases with age in our sample.

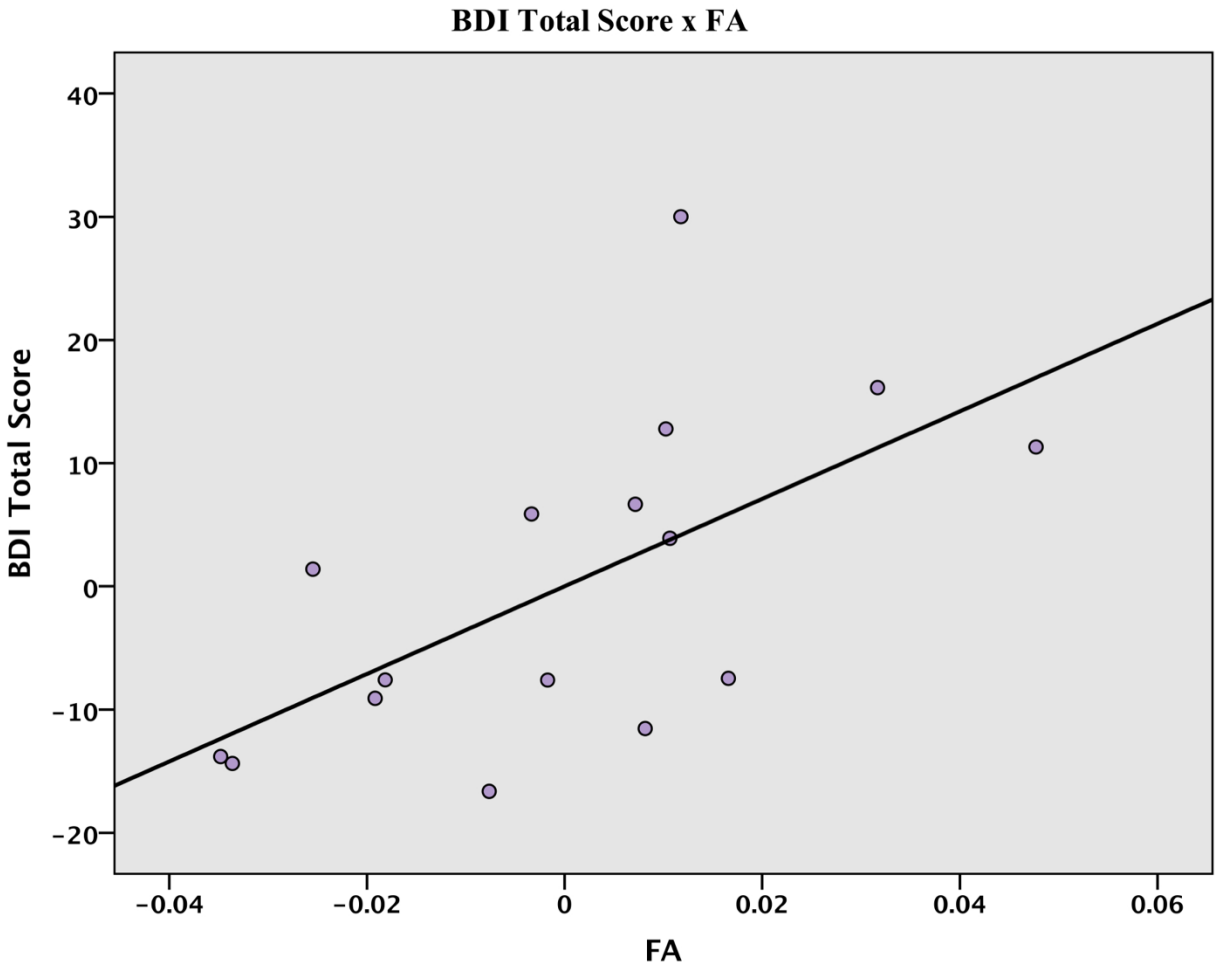


Figure 3. Partial regression scatterplot of residuals for Beck's Depression Inventory Total Scores x FA (a scalar value). BDI total scores trend up as FA increases. The trend suggests that depressed individuals are more likely than non-depressed individuals to have higher FA values in the right anterior insula-NAcc tract.

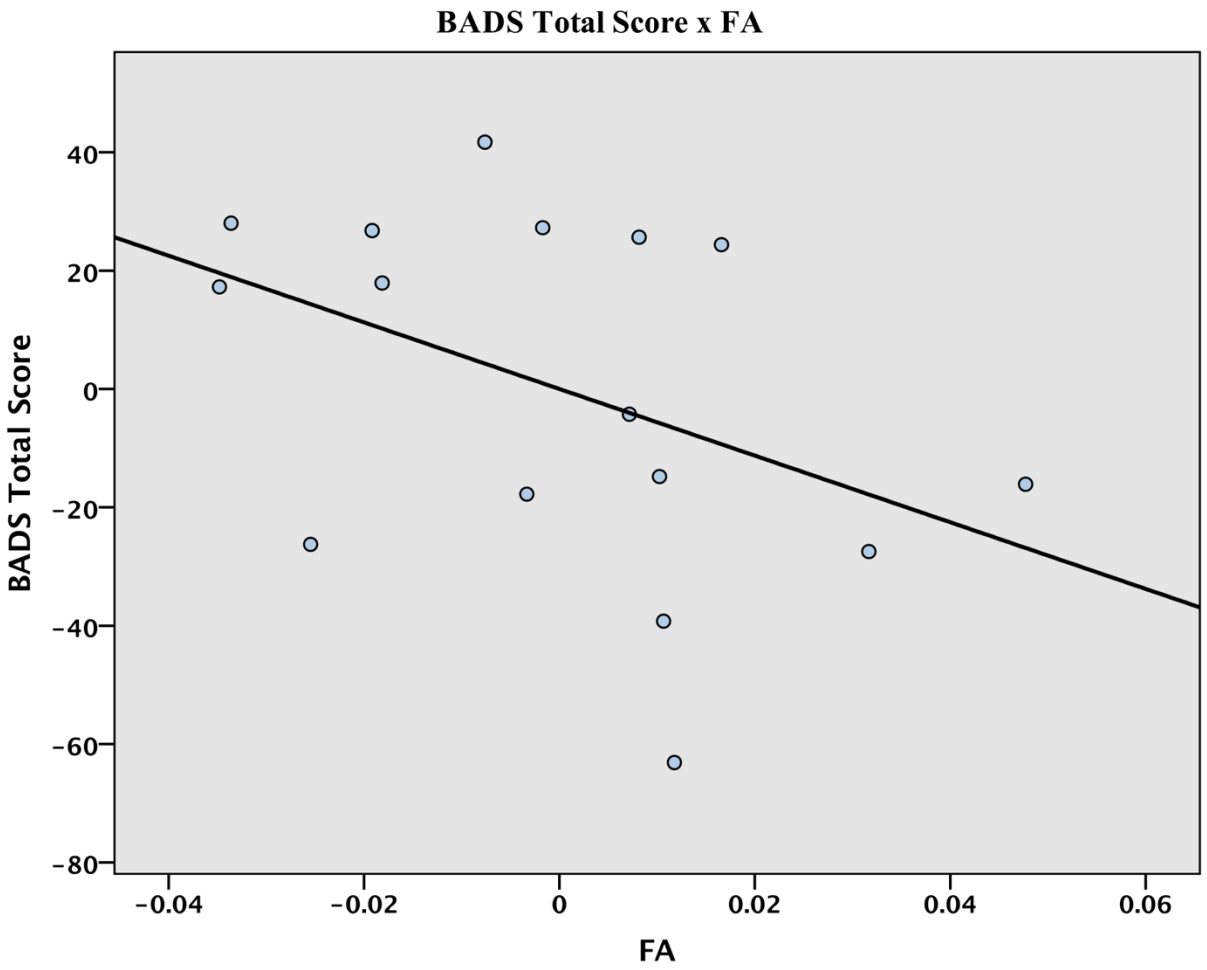


Figure 4. Partial regression scatterplot of residuals for Behavioral Activation for Depression Scale Total Score x FA. BADS total scores trend down as FA increases. Higher BADS scores are associated with greater behavioral activation and are therefore more commonly seen in controls. The BADS x FA trend is consistent with the relationship between BDI scores and FA depicted in Figure 3.

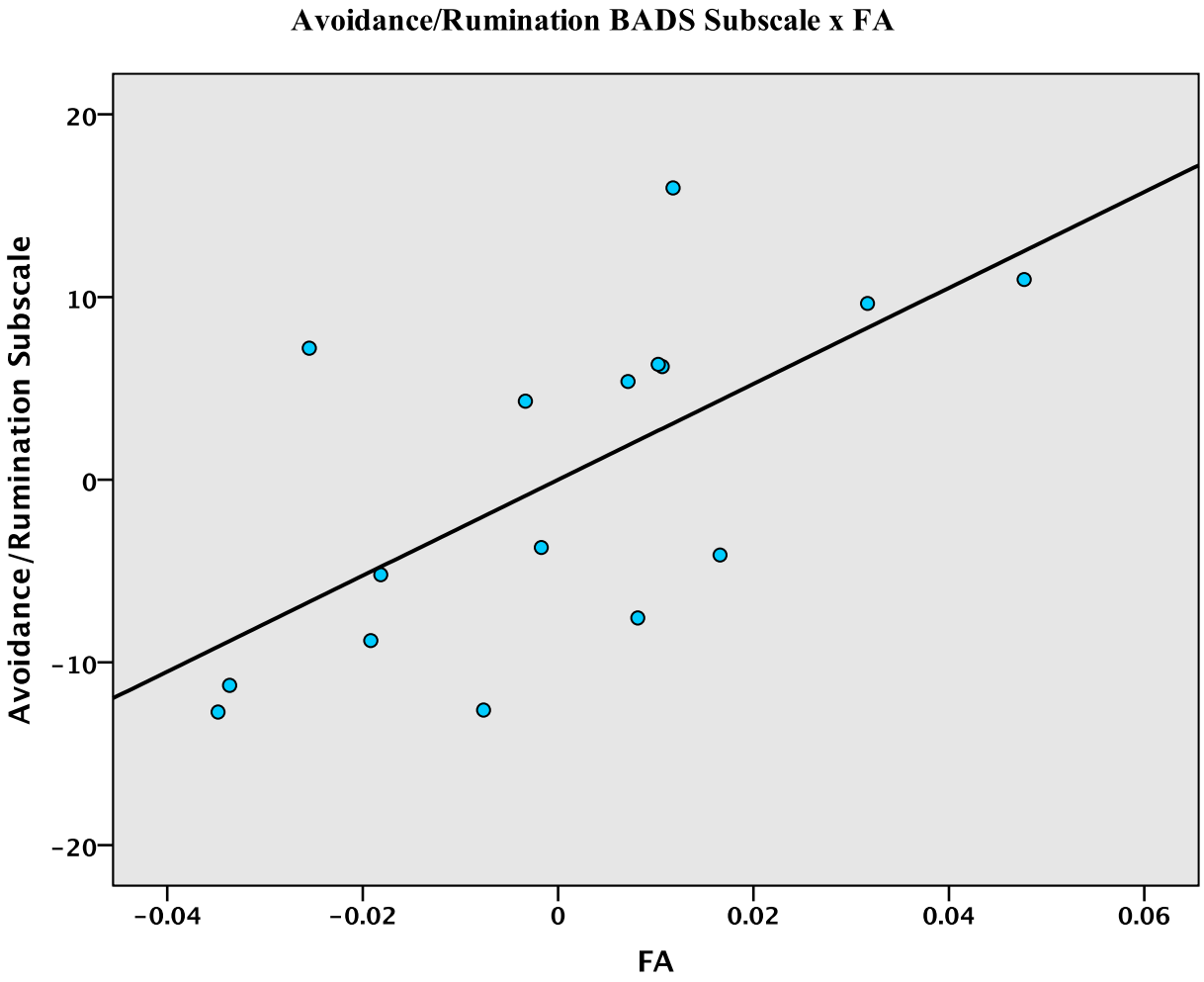


Figure 5. Partial regression scatterplot of residuals for Behavioral Activation for Depression Scale avoidance/rumination subscale x FA. Higher subscale scores correspond to greater avoidance and rumination behavior. Avoidance/rumination scores trend up as FA increases indicating further consistency with the observation that depressed individuals exhibit higher coherence in the right anterior insula-NAcc tract examined in this study.

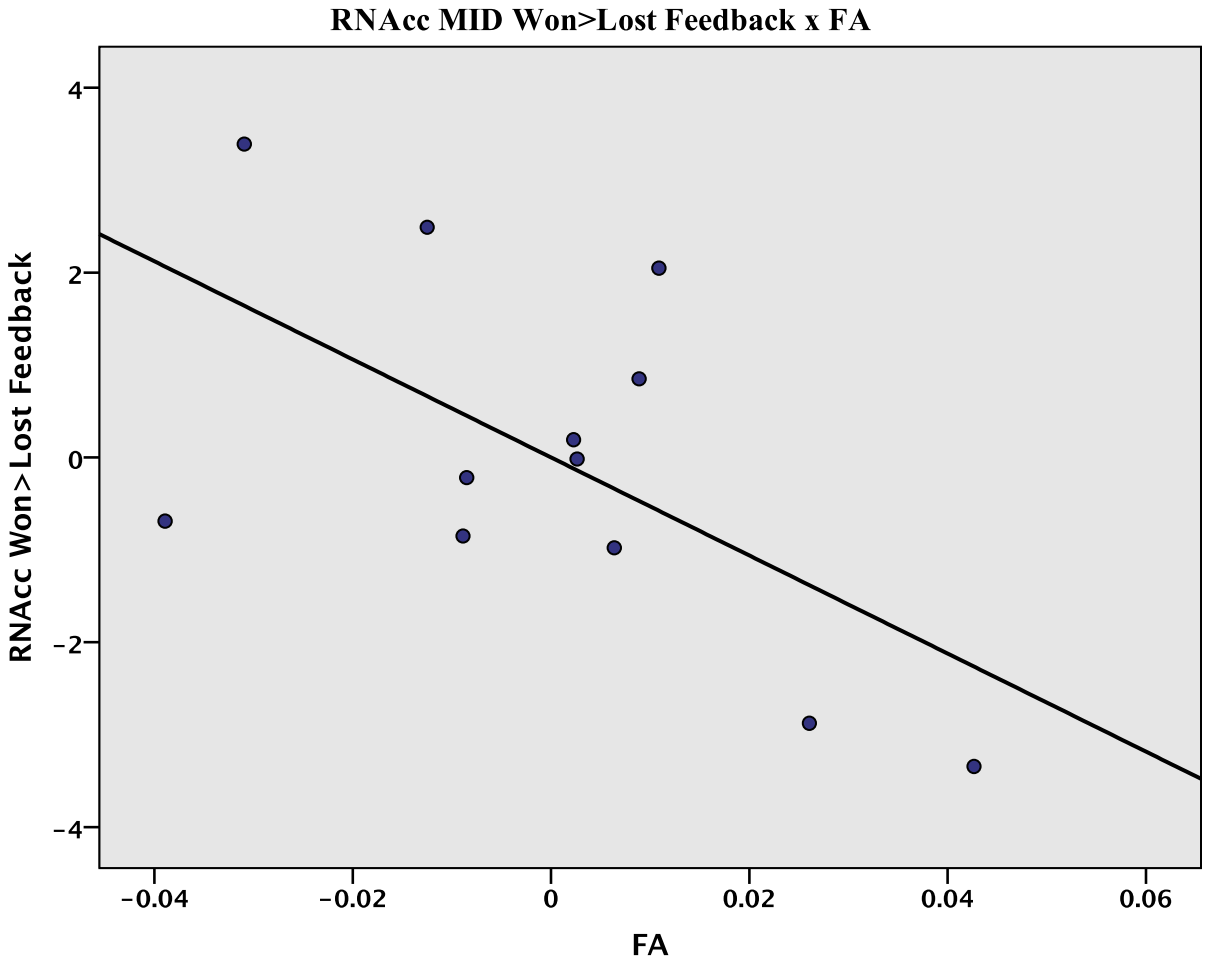


Figure 6. Partial regression scatterplot of residuals for right NAcc activation for the MID won>lost feedback contrast x FA. RNAcc activity trends down as FA increases.

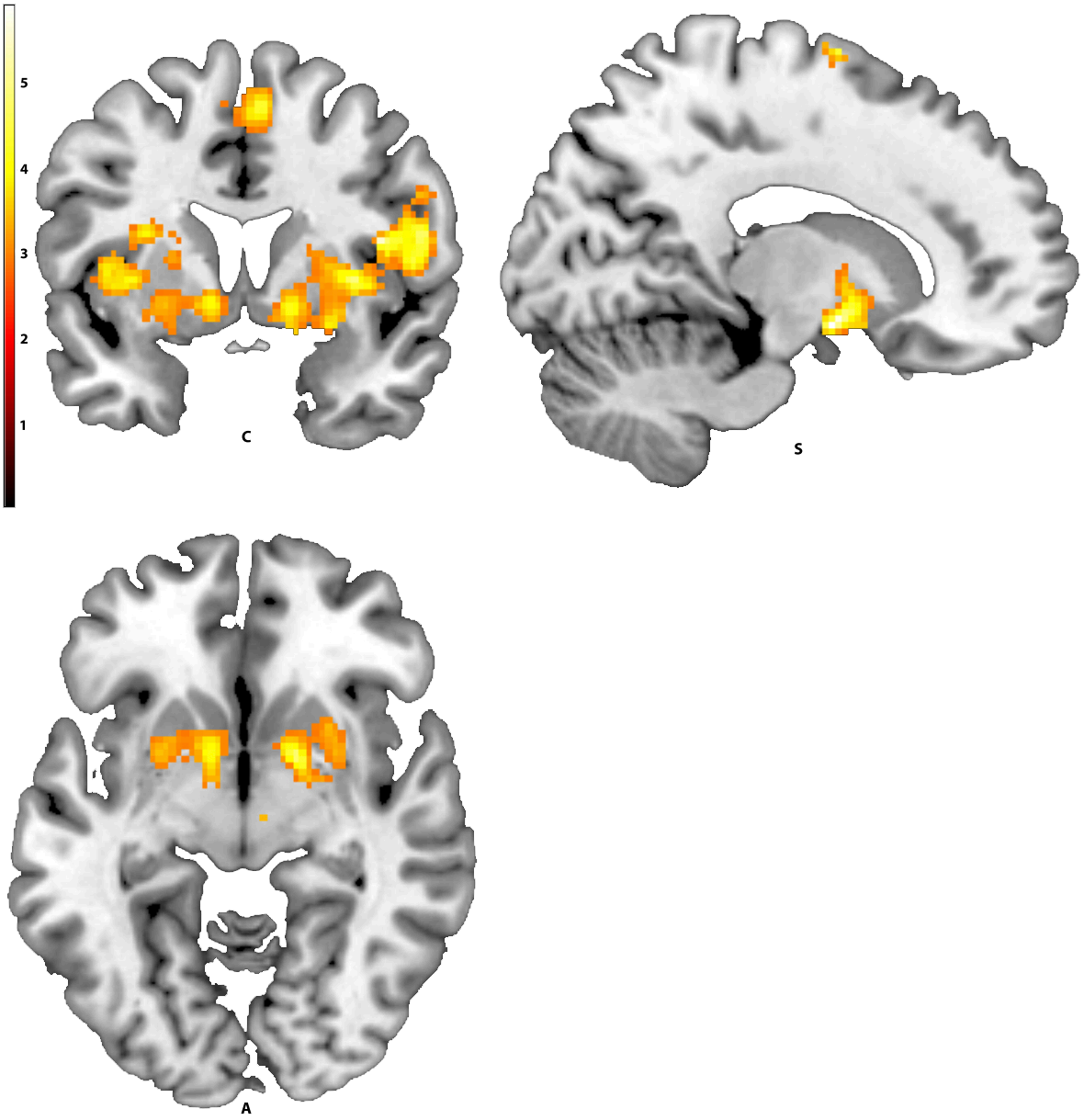


Figure 7. Whole brain map of MID win>neutral anticipation activity, highlighting bilateral NAcc activation. p<0.005, k=300. See Table 3 for specific values. The bar indicates t-values for activations. C, S, and A refer to coronal, sagittal, and axial views respectively.

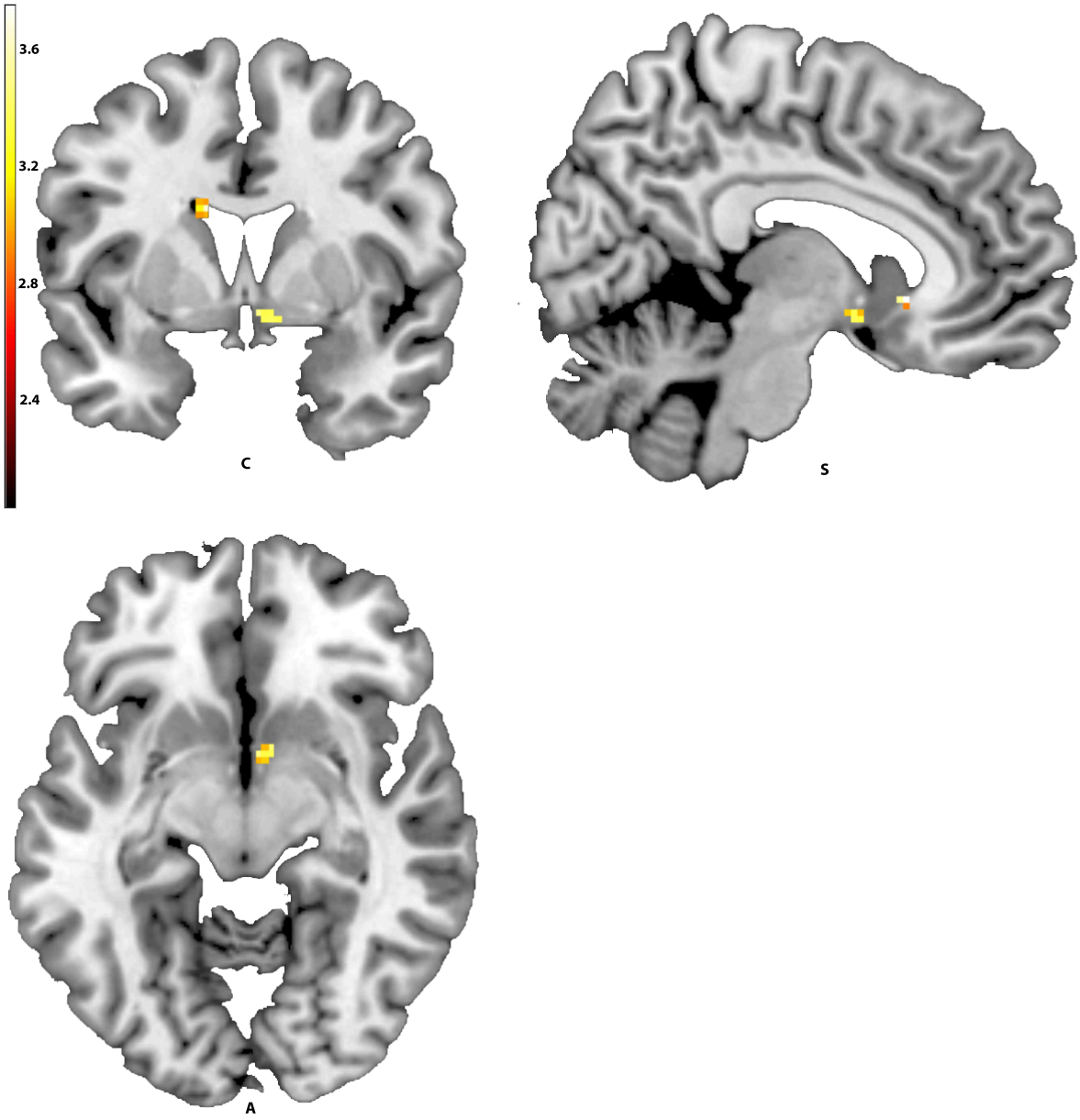


Figure 8. Whole brain map of MID won>lost feedback activity, highlighting RNAcc activation. p<0.005, k=10. See Table 3 for specific values. The bar indicates t-values for activations. C, S, and A refer to coronal, sagittal, and axial views respectively.

FIGURE REMOVED FOR THE PURPOSES OF SUBMISSION TO THE EMORY ELECTRONIC THESIS AND DISSERTATION REPOSITORY

Figure 9. Tract connecting the anterior insula and nucleus accumbens used by Leong et al., 2016. The masks used to create the tract in this study are based on coordinates provided to us by Leong and colleagues. Image reproduced with permission from the author.

REFERENCES

Abler, B., Walter, H., Erk, S., Kammerer, H., & Spitzer, M. (2006). Prediction error as a linear function of reward probability is coded in human nucleus accumbens. *NeuroImage*, *31*(2), 790–795. http://doi.org/10.1016/j.neuroimage.2006.01.001

American Psychological Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.

Arnett, J. (1994). Sensation seeking: A new conceptualization and a new scale. *Personality and Individual Differences*, *16*(2), 289–296. http://doi.org/10.1016/0191-8869(94)90165-1

Arnett, J. J. (1999). Adolescent storm and stress, reconsidered. *American Psychologist*, *54*(5), 317–326. http://doi.org/10.1037/0003-066X.54.5.317

Balleine, B. W., & Dickinson, A. (1998). Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology*, *37*(4-5), 407–419.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck depression inventory-II. *San Antonio*, *78*(2), 490-8.

Casey, B. J., Jones, R. M., & Somerville, L. H. (2011a). Braking and Accelerating of the Adolescent Brain. *Journal of Research on Adolescence*, *21*(1), 21–33. http://doi.org/10.1111/j.1532-7795.2010.00712.x

Casey, B. J., Somerville, L. H., Gotlib, I. H., Ayduk, O., Franklin, N. T., Askren, M. K., et al. (2011b). Behavioral and neural correlates of delay of gratification 40 years later. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(36), 14998–15003. http://doi.org/10.1073/pnas.1108561108

Cauffman, E., Shulman, E. P., Steinberg, L., Claus, E., Banich, M. T., Graham, S., & Woolard, J. (2010a). Age differences in affective decision making as indexed by performance on the Iowa Gambling Task. *Developmental Psychology*, *46*(1), 193–207. http://doi.org/10.1037/a0016128

Cauffman, E., Shulman, E. P., Steinberg, L., Claus, E., Banich, M. T., Graham, S., & Woolard, J. (2010b). Age differences in affective decision making as indexed by performance on the Iowa Gambling Task. *Developmental Psychology*, *46*(1), 193–207. http://doi.org/10.1037/a0016128

Cohen, A. O., Dellarco, D. V., Breiner, K., Helion, C., Heller, A. S., Rahdar, A., et al. (2016). The Impact of Emotional States on Cognitive Control Circuitry and Function. *Cognitive Neuroscience, Journal of*, *28*(3), 446–459. http://doi.org/10.1162/jocn_a_00906

Cohen, J. R., Asarnow, R. F., Sabb, F. W., Bilder, R. M., Bookheimer, S. Y., Knowlton, B. J., & Poldrack, R. A. (2010). A unique adolescent response to reward prediction errors. *Nature Publishing Group*, *13*(6), 669–671. http://doi.org/10.1038/nn.2558

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*(8), 655–666. http://doi.org/10.1038/nrn894

Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology*, *13*(4), 500–505. http://doi.org/10.1016/S0959-4388(03)00090-4

Craske, M. G. (2010). *Cognitive–behavioral therapy*. Washington, DC, US: American Psychological Association.

Cuijpers, P., van Straten, A., & Warmerdam, L. (2007). Behavioral activation treatments of depression: a meta-analysis. *Clinical Psychology Review*, *27*(3), 318–326. http://doi.org/10.1016/j.cpr.2006.11.001

Cullen, K. R., Gee, D. G., Klimes-Dougan, B., Gabbay, V., Hulvershorn, L., Mueller, B. A., et al. (2009). A preliminary study of functional connectivity in comorbid adolescent depression. *Neuroscience Letters*, *460*(3), 227–231. http://doi.org/10.1016/j.neulet.2009.05.022

Cullen, K. R., Klimes-Dougan, B., Muetzel, R., Mueller, B. A., Camchong, J., Houri, A., et al. (2010). Altered white matter microstructure in adolescents with major depression: a preliminary study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(2), 173–83.e1. http://doi.org/10.1097/00004583-201002000-00011

Davey, C. G., Allen, N. B., Harrison, B. J., & Yücel, M. (2011). Increased amygdala response to positive social feedback in young people with major depressive disorder. *Biological psychiatry*, *69*(8), 734-741.

Ernst, M., Nelson, E. E., Jazbec, S., McCLURE, E. B., Monk, C. S., Leibenluft, E., et al. (2005). Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *NeuroImage*, *25*(4), 1279–1291. http://doi.org/10.1016/j.neuroimage.2004.12.038

Figner, B., Mackinlay, R. J., Wilkening, F., & Weber, E. U. (2009). Affective and Deliberative Processes in Risky Choice: Age Differences in Risk Taking in the Columbia Card Task. *Journal of Experimental Psychology-Learning Memory and Cognition*, *35*(3), 709–730. http://doi.org/10.1037/a0014983

Forbes, E. E., Christopher May, J., Siegle, G. J., Ladouceur, C. D., Ryan, N. D., Carter, C. S., et al. (2006). Reward-related decision-making in pediatric major depressive disorder: an fMRI study. *Journal of Child Psychology and Psychiatry*, *47*(10), 1031–1040. http://doi.org/10.1111/j.1469-7610.2006.01673.x

Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., et al. (2009). Altered Striatal Activation Predicting Real-World Positive Affect in Adolescent Major Depressive Disorder. *American Journal of Psychiatry*, *166*(1), 64–73. http://doi.org/10.1176/appi.ajp.2008.07081336

Forbes, E. E., Ryan, N. D., Phillips, M. L., Manuck, S. B., Worthman, C. M., Moyles, D. L., et al. (2010). Healthy Adolescents' Neural Response to Reward: Associations With Puberty, Positive Affect, and Depressive Symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(2), 162–172. http://doi.org/10.1016/j.jaac.2009.11.006

Galvan, A., Hare, T. A., Davidson, M., Spicer, J., Glover, G., & Casey, B. J. (2005). The role of ventral frontostriatal circuitry in reward-based learning in humans. *Journal of Neuroscience*, *25*(38), 8650–8656. http://doi.org/10.1523/JNEUROSCI.2431-05.2005

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006).

Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience*, *26*(25), 6885–6892. http://doi.org/10.1523/JNEUROSCI.1062-06.2006

Gard, D. E., Gard, M. G., Kring, A. M., & John, O. P. (2006). Anticipatory and consummatory components of the experience of pleasure: a scale development study. *Journal of research in personality*, *40*(6), 1086-1102.

Geier, C. F., Terwilliger, R., Teslovich, T., Velanova, K., & Luna, B. (2010). Immaturities in Reward Processing and Its Influence on Inhibitory Control in Adolescence. *Cerebral Cortex (New York, N.Y. : 1991)*, *20*(7), 1613–1629. http://doi.org/10.1093/cercor/bhp225

Gray, M. A., Harrison, N. A., Wiens, S., & Critchley, H. D. (2007). Modulation of Emotional Appraisal by False Physiological Feedback during fMRI. *PLoS ONE*, *2*(6). http://doi.org/10.1371/journal.pone.0000546

Hulvershorn, L. A., Cullen, K., & Anand, A. (2011). Toward dysfunctional connectivity: a review of neuroimaging findings in pediatric major depressive disorder. *Brain Imaging and Behavior*, *5*(4), 307–328. http://doi.org/10.1007/s11682-011-9134-3

Jacobson, N. S., Martell, C. R., & Dimidjian, S. (2001). Behavioral Activation Treatment for Depression: Returning to Contextual Roots. *Clinical Psychology: Science and Practice*, *8*(3), 255–270. http://doi.org/10.1093/clipsy.8.3.255

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *Neuroimage*, *62*(2), 782-790.

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., & Davidson, R. J. (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *Journal of Neuroscience*, *27*(33), 8877–8884. http://doi.org/10.1523/JNEUROSCI.2063-07.2007

Kable, J. W., & Glimcher, P. W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience*, *10*(12), 1625–1633. http://doi.org/10.1038/nn2007

Kanter, J. W., Mulick, P. S., Busch, A. M., Berlin, K. S., & Martell, C. R. (2007). The Behavioral Activation for Depression Scale (BADS): psychometric properties and factor structure. *Journal of Psychopathology and Behavioral Assessment*, *29*(3), 191.

Kanter, J. W., Rusch, L. C., Busch, A. M., & Sedivy, S. K. (2008). Validation of the Behavioral Activation for Depression Scale (BADS) in a Community Sample with Elevated Depressive Symptoms. *Journal of Psychopathology and Behavioral Assessment*, *31*(1), 36–42. http://doi.org/10.1007/s10862-008-9088-y

Karlsgodt, K. H., John, M., Ikuta, T., Rigoard, P., Peters, B. D., Derosse, P., et al. (2015). The accumbofrontal tract: Diffusion tensor imaging characterization and developmental change from childhood to adulthood. *Human Brain Mapping*, *36*(12), 4954–4963. http://doi.org/10.1002/hbm.22989

Kasch, K. L., Rottenberg, J., & Arnow, B. A. (2002). Behavioral activation and inhibition systems and the severity and course of depression. *Journal of Abnormal …*. http://doi.org/10.2307/43279223?ref=search-gateway:250cbb40d0a0caf71c7cde928c0cc9c1

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593–602. http://doi.org/10.1001/archpsyc.62.6.593

Knutson, B., & Heinz, A. (2015). Probing psychiatric symptoms with the monetary incentive delay task. *Biological Psychiatry*, *77*(5), 418–420.

http://doi.org/10.1016/j.biopsych.2014.12.022
Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*.
Knutson, B., Bhanji, J. P., Cooney, R. E., Atlas, L. Y., & Gotlib, I. H. (2008a). Neural Responses to Monetary Incentives in Major Depression. *Biological Psychiatry*, *63*(7), 686–692. http://doi.org/10.1016/j.biopsych.2007.07.023
Knutson, B., Bhanji, J. P., Cooney, R. E., Atlas, L. Y., & Gotlib, I. H. (2008b). Neural responses to monetary incentives in major depression. *Biological Psychiatry*, *63*(7), 686–692. http://doi.org/10.1016/j.biopsych.2007.07.023
Knutson, B., Westdorp, A., Kaiser, E., & Hommer, D. (2000). FMRI Visualization of Brain Activity during a Monetary Incentive Delay Task. *NeuroImage*, *12*(1), 20–27. http://doi.org/10.1006/nimg.2000.0593
Lamm, C., & Singer, T. (2010). The role of anterior insular cortex in social emotions. *Brain Structure & Function*, *214*(5-6), 579–591. http://doi.org/10.1007/s00429-010-0251-3
Larson, R. W., Moneta, G., Richards, M. H., & Wilson, S. (2002). Continuity, Stability, and Change in Daily Emotional Experience across Adolescence. *Child Development*, *73*(4), 1151–1165. http://doi.org/10.1111/1467-8624.00464
Leong, J. K., Pestilli, F., Wu, C. C., Samanez-Larkin, G. R., & Knutson, B. (2016). White-Matter Tract Connecting Anterior Insula to Nucleus Accumbens Correlates with Reduced Preference for Positively Skewed Gambles. *Neuron*, *89*(1), 63–69. http://doi.org/10.1016/j.neuron.2015.12.015
Liston, C., Watts, R., Tottenham, N., Davidson, M. C., Niogi, S., Ulug, A. M., & Casey, B. J. (2006). Frontostriatal Microstructure Modulates Efficient Recruitment of Cognitive Control. *Cerebral Cortex (New York, N.Y. : 1991)*, *16*(4), 553–560. http://doi.org/10.1093/cercor/bhj003
Lutz, K., & Widmer, M. (2014). What can the monetary incentive delay task tell us about the neural processing of reward and punishment? *Neuroscience Neuroeconomics*. http://doi.org/10.2307/j.ctt1q1crjg?ref=search-gateway:412c2e73e4058ff19066d844ad84390d
Marin, R. S. (1996, October). Apathy: Concept, Syndrome, Neural Mechanisms, and Treatment. In *Seminars in clinical neuropsychiatry* (Vol. 1, No. 4, pp. 304-314).
Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*, *214*(5-6), 655–667. http://doi.org/10.1007/s00429-010-0262-0
Miniño, A. M. (2010). Mortality Among Teenagers Aged 12-19 Years: United States, 1999-2006. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.
Mischel, W., Shoda, Y., & Rodriguez, M. I. (1989). Delay of gratification in children. *Science*, *244*(4907), 933–938.
Mori, S., & Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron*, *51*(5), 527–539. http://doi.org/10.1016/j.neuron.2006.08.012
Mukherjee, P., Berman, J. I., Chung, S. W., Hess, C. P., & Henry, R. G. (2008). Diffusion tensor MR imaging and fiber tractography: Theoretic underpinnings. *American Journal of Neuroradiology*, *29*(4), 632–641. http://doi.org/10.3174/ajnr.A1051
Mulye, T. P., Park, M. J., Nelson, C. D., Adams, S. H., Irwin, C. E., Jr., & Brindis, C. D. (2009). Trends in Adolescent and Young Adult Health in the United States. *Journal of Adolescent Health*, *45*(1), 8–24. http://doi.org/10.1016/j.jadohealth.2009.03.013

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences*, *9*(5), 242–249. http://doi.org/10.1016/j.tics.2005.03.010

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. (2002). Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *Cognitive Neuroscience, Journal of*, *14*(8), 1215–1229. http://doi.org/10.1162/089892902760807212

Paulus, M. P., & Stein, M. B. (2006). An insular view of anxiety. *Biological Psychiatry*, *60*(4), 383–387. http://doi.org/10.1016/j.biopsych.2006.03.042

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, *9*(12), 947–957. http://doi.org/10.1038/nrn2513

Peper, J. S., Mandl, R. C. W., Braams, B. R., de Water, E., Heijboer, A. C., Koolschijn, P. C. M. P., & Crone, E. A. (2013). Delay Discounting and Frontostriatal Fiber Tracts: A Combined DTI and MTR Study on Impulsive Choices in Healthy Young Adults. *Cerebral Cortex (New York, N.Y. : 1991)*, *23*(7), 1695–1702. http://doi.org/10.1093/cercor/bhs163

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*, *442*(7106), 1042–1045. http://doi.org/10.1038/nature05051

Pizzagalli, D. A., Holmes, A. J., Dillon, D. G., Goetz, E. L., Birk, J. L., Bogdan, R., et al. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *American Journal of Psychiatry*, *166*(6), 702–710. http://doi.org/10.1176/appi.ajp.2008.08081201

Poznanski, E. O., & Mokros, H. B. (1996). *Children's depression rating scale, revised (CDRS-R)*. Los Angeles: Western Psychological Services.

Pratt, L. A., & Brody, D. J. (2014). Depression in the U.S. Household Population, 2005-2010. *Women*, *20*(39), 7.

Ritchey, M., Dolcos, F., Eddington, K. M., Strauman, T. J., & Cabeza, R. (2011). Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response. *Journal of psychiatric research*, *45*(5), 577-587.

Roth, M., Schumacher, J., & Brähler, E. (2005). Sensation seeking in the community: Sex, age and sociodemographic comparisons on a representative German population sample. *Personality and Individual Differences*, *39*(7), 1261–1271. http://doi.org/10.1016/j.paid.2005.05.003

Samanez-Larkin, G. R., Levens, S. M., Perry, L. M., Dougherty, R. F., & Knutson, B. (2012). Frontostriatal White Matter Integrity Mediates Adult Age Differences in Probabilistic Reward Learning. *Journal of Neuroscience*, *32*(15), 5333–5337. http://doi.org/10.1523/JNEUROSCI.5756-11.2012

Siegle, G. J., Carter, C. S., & Thase, M. E. (2006). Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. *American Journal of Psychiatry*, *163*(4), 735-738.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., ... & Niazy, R. K. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23*, S208-S219.

Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Frontiers in Neuroscience*, *7*. http://doi.org/10.3389/fnins.2013.00031

Somerville, L. H., Jones, R. M., & Casey, B. J. (2010). A time of change: Behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain and*

Cognition, *72*(1), 124–133. http://doi.org/10.1016/j.bandc.2009.07.003
Steinberg, L. (2010). A dual systems model of adolescent risk-taking. *Developmental Psychobiology*, *44*(1-3), n/a–n/a. http://doi.org/10.1002/dev.20445
Steinberg, L., Albert, D., Cauffman, E., Banich, M., Graham, S., & Woolard, J. (2008). Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: evidence for a dual systems model. *Developmental Psychology*, *44*(6), 1764–1778. http://doi.org/10.1037/a0012955
Steinberg, L., Graham, S., O'Brien, L., Woolard, J., Cauffman, E., & Banich, M. (2009). Age differences in future orientation and delay discounting. *Child Development*, *80*(1), 28–44. http://doi.org/10.1111/j.1467-8624.2008.01244.x
van den Bos, W., Rodriguez, C. A., Schweitzer, J. B., & McClure, S. M. (2014). Connectivity Strength of Dissociable Striatal Tracts Predict Individual Differences in Temporal Discounting. *Journal of Neuroscience*, *34*(31), 10298–10310. http://doi.org/10.1523/JNEUROSCI.4105-13.2014
Vartanian, O., & Mandel, D. R. (2011). Neuroscience of Decision Making. Psychology Press.
Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology*, *54*(6), 1063.
Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., ... & Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *Neuroimage*, *45*(1), S173-S186.
Yang, T. T., Simmons, A. N., Matthews, S. C., Tapert, S. F., Frank, G. K., Max, J. E., ... & Wu, J. (2010). Adolescents with major depression demonstrate increased amygdala activation. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(1), 42-51.
Zuckerman, M., Eysenck, S., & Eysenck, H. J. (1978). Sensation seeking in England and America: cross-cultural, age, and sex comparisons. *Journal of Consulting and Clinical Psychology*, *46*(1), 139–149.